Linking Structural Racism and Discrimination and Breast Cancer Outcomes: A Social Genomics Approach

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Society to Cells to Outcomes

We live in a society where individuals and communities are marginalized because of their race or ethnicity. This structural inequity extracts enormous health and societal costs, decreasing access to cancer care and increasing health disparities, especially among the most vulnerable. In an effort to identify causes of disparities, we have incorporated individual sociodemographic characteristics (eg, income and education) and other social determinants of health (eg, access to care, insurance, and transportation needs), as well as biologic markers (eg, genetic predisposition to disease) that can serve as therapeutic targets into our research.

Although well intentioned, the use of race as a proxy for genetic predisposition is flawed. There are no genes that are common only within a single racial or ethnic group. In a study of the worldwide geographic distribution of 4,000 alleles,[1] 92% were present in two or more regions and almost 50% were present in all seven major geographic regions (Africa, Europe, Middle East, Central/South Asia, East Asia, Oceania, and America). Intergroup allele similarities were more likely than intragroup similarities. As a biologic construct, ancestry has emerged as a preferred term for the genetic variation reflecting one's geographical origins. Thus, without a viable biologic definition and as a social construct subject to bias, race inadequately captures the complex interaction between ancestry, structural racism[2,3] (eg, higher frequency of hazardous waste producing businesses or food deserts in predominantly Black neighborhoods), and interpersonal and personally mediated racism.

Emerging models of health disparities propose that simply existing in an environment with systematic racial segregation, overt hostility, or heightened vigilance to the threat of hostility induces a level of ambient stress (which has been likened to racial battle fatigue).[4] The potential effects of this stress may manifest in physiologic dysregulation at the cellular and molecular level, such as initiation of the inflammatory cascade and increased expression of inflammatory transcriptomes, predisposing to disease and resulting in outcome disparities traditionally ascribed to race. The objective of this commentary is to outline a novel approach that integrates a Society to Cells to Outcomes framework for a more nuanced understanding of the potential biologic mechanism of structural racism and discrimination on health outcome disparities, using breast cancer to illustrate key principles and pathways.

Breast Cancer in Black Women

The significant improvements in screening, diagnosis, and treatment of breast cancer have not translated into better clinical outcomes for Black women,[5-12] who continue to have up to a 40% higher mortality rate from breast cancer compared with their White counterparts.[13,14] This racial disparity in mortality has been partially attributed to racial differences in stage of presentation,[15,16] molecular subtype,[17-19] and disparities in treatment.[13,20-23] Nevertheless, this mortality disparity persists even in ductal carcinoma in situ,[14] the earliest and curable stage of disease. Black women are more likely to have poor tumor prognostic features such as high-grade, more aggressive breast cancer molecular subtypes (eg, triple-negative breast cancer), and lymph node metastasis at diagnosis.[10,24] Although hypothesized, the effects of the proportion of African (*v* European) ancestry markers on tumor biology and clinical outcomes are inconsistent,[25] with no differences in the prevalence of germline pathogenetic variants in cancer susceptibility genes by race, suggesting that ancestry-related risk insufficiently explains outcome disparities.

Despite breast cancer screening rates that exceed those of White women,[26] Black women are diagnosed with more advanced stages of breast cancer. More worrisome, Black women endure higher rates of false-positive screening results, an unfavorable outcome implicated in an increased risk of breast cancer. Additionally, elevated anxiety, stress, financial burden,[27-32] and paradoxically, reduced breast cancer screening[33]

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from a false-positive diagnosis have been described, but few focused on experiences of Black women.

The National Institute on Minority Health and Health Disparities model of health disparities[34,35] proposed a schema of the inter-relationship between the larger social environment and individual risk modifiers (Fig 1). Applied to breast cancer, disparities traditionally attributed to race result from a complex interplay between upstream social conditions (such as disproportionate rates of racism) and policies (such as structural racism), midstream social and physical stressors (such as the experience of discrimination), and downstream individual risk and biologic and genetic pathways. Therefore, the contribution of structural racism including residential racial segregation[36-39] and the experience of discrimination[40] need to be integrated into any evaluation of disparities in breast cancer outcomes identified by race across the range of clinical outcomes such as molecular subtype, stage at presentation, treatment disparities, and ultimately mortality. However, significant gaps remain in our understanding of this complex relationship between race/racism, genetic and biologic/physiologic factors, false-positive results, and progression from high-risk false-positive lesions to invasive disease.

Linking Structural Racism and Discrimination and Breast Cancer Outcomes: A Social Genomics Approach

We expand on the Society to Cells to Outcomes framework applied to breast cancer using a model where upstream adverse social conditions (eg, structural racism, racial animus, and the experience of discrimination) and the resultant psychologic stress are moderated and/or mediated by genomic/epigenetic changes or allostatic load (physiologic dysregulation) consequently affecting oncogenesis in Black women (Fig 2).

Structural racism can be evaluated using measures of the physical environment, that is, residential racial segregation measures proposed by Massey and Denton,[41,42] which include (1) dissimilarity measuring distribution evenness by race or ethnicity; (2) isolation, the probability that Black individuals will encounter or be exposed to other Black individuals; (3) concentration, the population density of Black neighborhoods within a geographic area; (4) centralization, the degree to which Black neighborhoods are located in urban centers; and (5) clustering, the extent to which Black neighborhoods are surrounded by other Black neighborhoods. Recent systematic reviews[43,44] provide support for the association between higher Black-White segregation and higher breast cancer mortality in Black patients. Landrine et al[44] summarized the effects of segregation on Black women. Only five studies[37,39,45-47] used valid segregation measures.[41,42,48,49] Three of four studies evaluating mortality found that segregation contributed to disparities; one demonstrated associated differences in late-stage breast cancer diagnosis. Segregation contributed to racial disparities in breast cancer screening in some states but not all. Less rigorous studies using the proportion of Black people in the geographic area as a proxy for racial segregation showed that Black women living in neighborhoods with a lower percentage of Black residents are more likely to develop triple-negative breast cancer.[50] Conversely, Black women residing in neighborhoods with at least 20% Black residents have a lower disease specific and all-cause mortality.[39,51] Assessment of the effects of segregation on breast cancer incidence yielded mixed results.[43]

Regarding racial animus as a manifestation of interpersonal racism, Chae et al[52] evaluated the frequency of Black racial slur searches in media markets as an area racism measure, which exerted the greatest association with Black mortality, exceeding other traditional variables such as poverty and urbanicity. The experience of discrimination as a manifestation of interpersonal racism also contributes to health outcomes. In our nationally representative survey, women's experiences of discrimination correlated with increased health service utilization and worse health status,[53] consistent with recent systematic reviews on discrimination and health.[40,54-56] We refer to structural racism, racial animus, and the experience of discrimination collectively as structural racism and discrimination.

Health-related social needs (eg, income, employment, education, insurance, and access to care as well as neighborhood socioeconomic status) and resilience factors (eg, social support and psychologic resourcefulness) can intensify or mitigate structural racism and discrimination risk. We showed that Black women with breast cancer[57,58] were more likely to adhere to endocrine therapy compared with White women controlling for neighborhood socioeconomic status, a composite measure encompassing

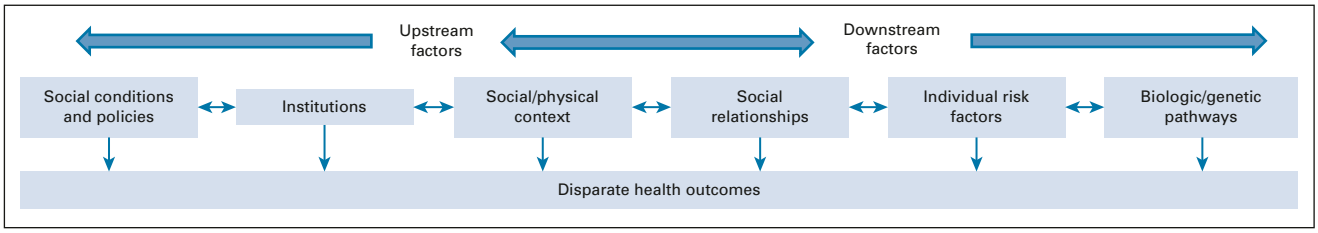

FIG 1. Society → cells → outcomes. Conceptual model of environmental-biologic interactions resulting in health disparities. Adapted from the studies by Alvidrez et al[35] and Agur-Collins et al.[34]

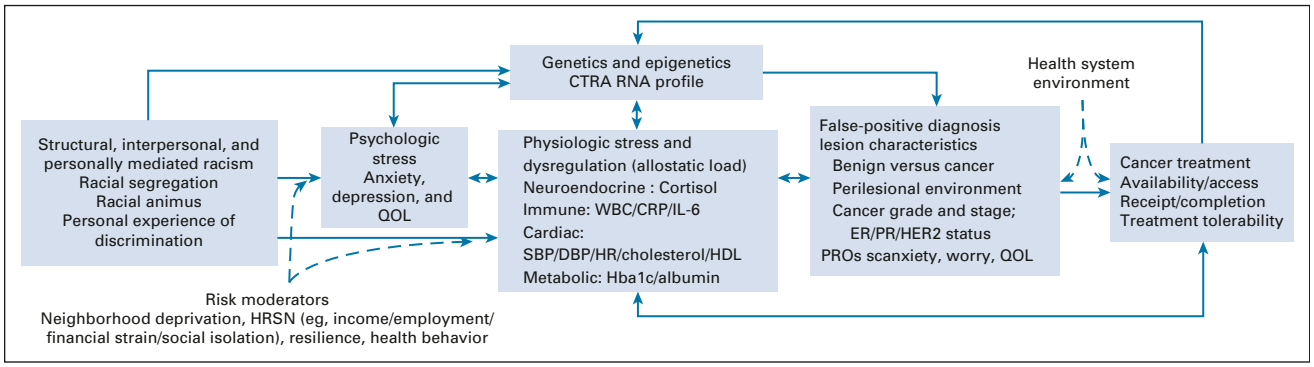

FIG 2. Model of SRD, social genomics, and screening outcomes. CRP, C-reactive protein; CTRA, Conserved Transcriptional Response to Adversity; DBP, diastolic blood pressure; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, heart rate; HRSN, health-related social needs; IL, interleukin; PR, progesterone receptor; PRO, patient-reported outcome; QOL, quality of life; SBP, systolic blood pressure.

area characteristics such as poverty, crowding, and transportation access. Yet, after controlling for neighborhood socioeconomic status, insurance, and endocrine therapy adherence, higher risk for breast cancer recurrence and mortality persisted among Black women.

Despite the significant research on breast cancer and segregation, there are no studies have evaluated the effects of segregation on unfavorable screening outcomes, nor racial animus effects on breast cancer screening, incidence, or mortality disparities. The separate effects of health-related social needs require further quantification.

Translating Social Constructs into Biologic Effects

Unfortunately, published research on racial disparities in breast cancer continue to conflate race, a social construct[59] and ancestry, the genomic variation between populations.[60] Black race as a broad grouping for individuals of African ancestry may not be uniformly endorsed by all who have African ancestry, further adding to the complexity. Emerging research suggests that although race is a social construct, it has biologic implications, which subsequently affects comorbidity and mortality because of SRD. Evidence-based frameworks such as weathering and allostatic load suggest chronic exposure to adverse social determinants of health have implications for physiology and consequently, disease initiation and progression. In the weathering framework, Geronimus[61] postulates that poor health outcomes experienced by Black women such as higher infant and maternal mortality rates, increased comorbidities, and higher overall mortality rates are attributable to the cumulative effects of social and economic marginalization. In this framework, structural racism and discrimination act as environmental stressors and challenges that activate a physiologic stress response.

The weathering framework closely aligns with allostatic load theory, which describes the activation of the hypothalamic-pituitary-adrenal axis and the autonomic nervous system from psychosocial stressors. Allostatic load describes the cumulative physiologic wear and tear because of exposure to adverse social determinants of health.[62] Elevated allostatic load has been associated with low educational achievement, low socioeconomic status, and high work-related stress.[63] Additionally, higher allostatic load has been noted in historically marginalized groups such as women, Black people, and individuals who identify as lesbian, gay, or bisexual.[64]

Social Genomics: A Potential Biologic Pathway for Structural Racism and Discrimination on Breast Cancer

We have previously proposed the effects of social determinants of health and health-related social needs (eg, poverty, low educational attainment, and social isolation) on health.[3] We expand our previous model of health-related social needs including resulting psychologic stress and their potential biologic effects to explicitly account for structural racism and discrimination. The cumulative effects of structural racism and discrimination, health-related social needs, and psychologic stress are hypothesized to result in a biologic stress response with both epigenetic changes and physiologic dysregulation. To this end, a plausible mechanistic pathway for how structural racism and discrimination affects biology can be understood through the lens of social genomics and social epigenomics. Social genomics examines how psychologic (eg, meaning attribution) and social factors (eg, low socioeconomic status and social isolation) influence gene expression. Concomitantly, social epigenomics evaluates how DNA methylation, microRNA expression, and histone modification alter gene expression and consequently affect disease initiation and progression. Social genomics and epigenomics provide an avenue to further evaluate the intersection between race, epigenetics, and health-related social needs.

One proposed potential pathway for linking adverse socioenvironmental factors with poor clinical outcomes is the Conserved Transcriptional Response to Adversity (CTRA) RNA profile. Initially identified as the loneliness gene signature for its association with measures of perceived social isolation, the CTRA is a neurobiologically mediated alteration in immune

cell gene regulation involving increased expression of proinflammatory genes (eg, *IL1B*, *IL6*, *IL8/CXCL8*, and *TNF*) and decreased expression of genes involved in innate antiviral responses (eg, *IFI-*, *MX-*, and *OAS*-family genes). The CTRA profile can be measured by genome-wide transcriptional profiling of circulating blood cells (eg, by RNA sequencing), using either prespecified composites of inflammatory and antiviral gene transcripts (eg, a 53-gene composite used in many studies) or by bioinformatic measures of transcription factor activity mediating inflammatory and antiviral gene regulation.[65] Contributors to poor outcomes among patients with breast cancer have identified African ancestry, increased CTRA expression, higher allostatic load, and elevated interleukin-6 as factors associated with higher morbidity and mortality among Black patients with breast cancer.[50,65-68] Cole et al showed CTRA expression in breast tumors to be associated with socioenvironmental risk factors, such as social isolation and low socioeconomic status.[69] For Black patients with breast cancer in particular, allostatic load has been implicated in negative prognostic features such as larger tumor sizes, poorly differentiated tumors, and estrogen-negative subtypes.[70] Moreover, among noncancer populations, Black women have a higher allostatic load than their White counterparts.[71] Taken together, these studies suggest that breast cancer screening outcomes, tumorigenesis, and disease progression among Black women are a complex interplay between socioenvironmental factors in conjunction with ancestry and their combined effects on physiology through the stress response, DNA modification, and transcription.

We suggest social genomics as a potential biologic pathway including stress-related transcriptional changes (ie, CTRA gene regulation by the sympathetic nervous system) and physiologic dysregulation (ie, allostatic load) through which the social environment mechanistically influences cancer development and progression[69,72-75] (Fig 2). Several studies have linked socioeconomic disadvantage and experienced racial discrimination to elevated inflammatory gene expression and CTRA.[69-71] Exploratory studies of mindfulness and cognitive behavioral stress management interventions have found that CTRA downregulation is associated with improved well-being and disease-free survival among breast cancer survivors.[72]

Relatedly, we hypothesize that structural racism and discrimination may induce psychologic and physiologic stress, DNA modification, and changes to DNA transcription, which has implications for oncogenesis in Black women. Prior studies suggest the deleterious effects of elevated allostatic load on breast cancer risk, unfavorable breast cancer clinicopathology, and overall survival, mirroring our results in patients with multiple myeloma[66] and breast cancer. Similar to CTRA, stress reduction interventions have demonstrated allostatic load reduction in conjunction with improved resilience and quality of life in patients with metastatic breast cancer.[76] Together, these studies implicate CTRA expression and allostatic load as pathways mediating social disparities in breast cancer outcomes.

Summary

Several studies have documented CTRA gene regulation and associated alterations in upstream signal transduction processes in patients with breast cancer.[51,69,75,77-83] Scant evidence exists on the potential biologic pathway that structural racism and discrimination, that is, structural racism, racial animus, and the experience of discrimination, has on exerting effects that lead to disparities in breast cancer screening outcomes. Superimposed over the effects of structural racism and discrimination, other domains of health-related social needs including poverty, social isolation, and health care access have also been implicated in poor clinical outcomes among Black patients with breast cancer. Although it is known that health outcomes are improved among persons of all races who have adequate support networks and psychologic resourcefulness,[84-86] health-related social needs risk and resilience factors have not routinely been evaluated in breast cancer screening.

We call for both mechanistic and intervention trials to better delineate the effects of structural racism and discrimination specifically on breast cancer screening outcomes, including disparities in false-positive diagnoses and aggressive tumor diagnoses. These studies will provide currently unavailable data that will advance our understanding of breast cancer risk and risk-stratified screening strategies on the basis of multilevel factors including SRD. Improved understanding of the biologic underpinnings of SRD could highlight new biologic and molecular targets for interventions. System or individual interventions that target a molecular signaling pathway that mediates deleterious outcomes could be deployed to potentially reduce the negative effects of SRD, social isolation, or other health-related social needs on breast cancer tumor biology to ultimately help enhance clinical outcomes and close persistent disparities gaps.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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