



Understanding breast cancer disparities—a multi-scale challenge

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Abstract: Despite convergence of overall breast cancer incidence rates between European American (EA) and African American (AA) women, disparities in mortality persist. The factors contributing to differences in mortality rates across population groups remain controversial and range from population genetics to sociodemographic influences. This review explores the complex multi-factorial nature of tumor-intrinsic and -extrinsic factors that impact the biology and clinical outcomes of breast cancer patients. In addition to summarizing the current state of breast cancer disparities research, we also motivate the development of integrative multi-scale approaches involving interdisciplinary teams to tackle this complex clinical challenge.

Keywords: African American (AA); breast cancer; health disparities; multi-omics; radiomics; pathomics; systems biology; integrative modeling

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Introduction

The past few decades have witnessed a steady decline in breast cancer mortality in the United States despite largely stable rates of diagnoses, a feat that is largely due to improved screening and treatment strategies in this disease (1). However, the benefits of this overall trend towards improved breast cancer-specific mortality is not equitably distributed across populations groups within the United States. Indeed, despite convergence of overall breast cancer incidence rates between European American (EA) and African American (AA) women, disparities in mortality still persist (2). While mortality hazard rates among AA women vary by breast cancer subtypes, AA women in general exhibit about 20% to 150% higher mortality relative to EA women (3). AA women are more likely to present at an earlier age, with higher-grade tumors and higher rates of triple-negative breast cancer (TNBC) (4). Accounting for age, AA women are at least 2-times more likely than

their EA counterparts to be diagnosed with TNBC (3,5,6), a subtype known to be heterogeneous, aggressive and difficult to treat (7). Several studies have suggested that the racial disparities observed in mortality are due to this higher rate of TNBC in AA women (4,8,9). However, the mere increased incidence of the aggressive TNBC subtype in AA women fails to fully explain the observed disparities in outcomes, since AA women face poorer overall survival even after accounting for age and stage at diagnosis within other breast cancer subtypes as well (10,11). These results pose differing but important questions regarding the potential determinants of observed breast cancer incidence and outcome disparities across population groups.

In this review, we explore the multi-factorial nature of cancer health disparities (*Figure 1*). Over the course of a patient's disease from the time of diagnosis, therapy selection to survivorship, a variety of factors potentially contribute to overall outcomes, including socioeconomic circumstance, access to care, behavioral factors, and

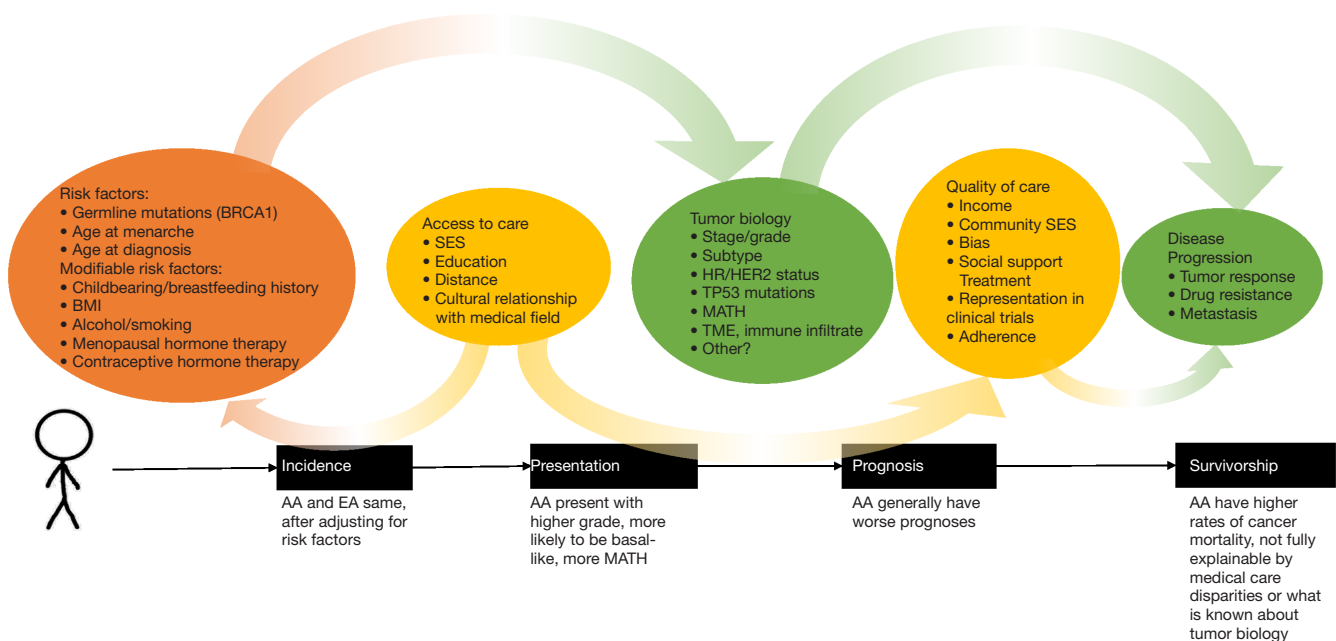


Figure 1 The multi-factorial nature of cancer health disparities. This model depicts the various factors that impact cancer incidence, presentation, prognosis, and survivorship as well as the codependence and influence of these factors on each other. AA, African American; EA, European American; SES, socioeconomic status; BMI, body mass index.

tumor biology. While incidence rates of breast cancer are similar between AA and EA population groups (5,6), we nevertheless observe disparities between AA and EA breast cancers at the time of clinical presentation and prognosis (*Figure 1*) where AA women generally present with higher grade, basal-like tumors (5,6). This gap expands during the course of treatment, with AA women exhibiting higher rates of mortality that are not fully explained by medical care disparities or what is known about tumor biology. Here, we summarize current data regarding how the interplay between non-modifiable and behavioral risk factors, access to quality care, equal treatment and tumor biology may contribute to differences in breast cancer mortality rates across population groups.

Modifiable factors that influence breast cancer risk

One of the early hypotheses proposed to explain the differential risk of TNBC in AA versus EA women involved breastfeeding practices [*Figure 1*, (4)]. This was motivated by the general understanding that breastfeeding, or lack thereof, was associated with increased risk of developing TNBC (12-16). Indeed, the Nurses' Health Study found

that among women with invasive breast cancer, higher parity and the absence or short duration of breastfeeding were independently associated with TNBC (17). Epidemiologic studies have noted differences in breastfeeding rates between EA and AA women, with 62% and 45%, respectively, breastfeeding at 6 months (18), thus raising the question as to whether these differences may contribute to higher incidence rates of TNBC among AA women. Indeed, the American Breast Cancer Epidemiology and Risk Consortium (AMBER) explored this association in AA women, identifying an increased risk of estrogen receptor (ER)-negative breast cancer with each additional childbirth in AA women who had not breastfed (19). Further investigating the likely biologic mechanism underlying these epidemiologic observations, Basree *et al.* (20) showed in mouse models and human breast tissue that abrupt involution of mammary glands following pregnancy and limited breast feeding (<6 months) results in expansion of the luminal progenitor cell compartment associated with development of basal-like tumors. Taken together, these studies suggest that the lower rates of breastfeeding by AA women may potentially contribute to higher TNBC disease burden among this group, a supposition whose validity awaits the performance of large well-

controlled epidemiologic and in-depth mechanistic studies to determine the relative importance of breastfeeding as a determinant of TNBC incidence disparities across population groups.

The ability of adipocytes in obese states to secrete proinflammatory cytokines and exhibit poorer metabolic control (21) led to the hypothesis that obesity may be a major driver of aggressive TNBC biology (7) (*Figure 1*). Indeed, the Carolina Breast Cancer study found that women with a higher waist-to-hip ratio (WHR) had increased risk for developing TNBC (14). Likewise, a meta-analysis of eleven original articles found a significant association between obesity and TNBC in both case-case and case-control analyses (22). However, it is worth noting that this association, even across racial groups, is not definitive. The Women's Circle of Health Study observed a significant inverse relationship between high body mass index (BMI) and hormone receptor negative breast cancer among postmenopausal women (23). Moreover, these findings were also substantiated by The Premenopausal Breast Cancer Collaborative Group who found an inverse association between BMI and cancer risk in young (18 to 24 years) women and no association across ages with TNBC (24). Regardless, the combination of a possible association between obesity and TNBC, together with a higher prevalence of obesity in AA women compared to EA women, led several groups to investigate whether increased body mass could contribute to higher rates of TNBC among AA women. The AMBER consortium showed varied trends associating obesity with breast cancer in AA women depending on the metric used, but none of which specifically linked body mass in AA women to TNBC. In fact, higher BMI correlated with increased risk for ER-positive breast cancer and decreased risk for TNBC in postmenopausal women. Additionally, high WHR in postmenopausal women was associated with increased risk of all breast cancer subtypes whereas in premenopausal women, high WHR was associated with an increased probability of ER+ tumors but not others (25). Interestingly, a study by Capers *et al.* (26) explored the importance of body shape in EA and AA women to predict disease associations, and found that obese AA and EA women exhibit differences in distribution of adipose tissue, insulin resistance, and lipoprotein subclasses. These results suggest that obesity in AA women might influence disease progression differently than in EA women, potentially contributing to disparities in mortality, but not to differences in TNBC incidence rates.

Smoking and alcohol consumption are mild risk factors

for breast cancer incidence (27,28). However, considering that the rates of heavy smoking (29) or drinking (30) are not particularly high in the AA population compared to the EA population, and that both exposures are associated with ER-positive BC and not TNBC (31,32), it is unlikely that these behavioral risk factors have much influence on breast cancer disparities.

Biologic factors related to breast cancer incidence

One of the major areas of research in breast cancer risk is in the heritability of the disease. The first germline mutations found to be associated with increased risk of TNBC were *BRCA1/BRCA2* (33). *BRCA1* is a tumor suppressor gene that plays a key role in homology-directed repair of DNA double-stranded breaks (34-36). The majority of breast cancers in women with *BRCA1* mutations are TNBC (37), but despite the higher incidence rate of TNBC in AA women, several studies show the frequency of germline *BRCA1* mutations is relatively low compared to the observed mutation rate in EA women (38,39). A study of 155 high-risk families evaluated at the University of Chicago found germline *BRCA1* mutations in 50% of EA women with TNBC and fewer than 20% of AA women with TNBC (40), suggesting that other mechanisms may promote TNBC in AA women. For example, SNP rs8170 on the *BABAM1* gene was found to be linked to TNBC in a mixed population of patients (41,42), and was associated with increased risk of TNBC in an AA population (43). This higher prevalence of a pathogenic SNP in women of African ancestry may contribute to the higher incidence rate of TNBC in AA women (*Figure 2*). Because these genes are insufficient to explain all inherited breast cancer risk, researchers have hypothesized that variations in combinations of several genes, known as polygenic risk models, may more accurately predict breast cancer risk (44). However, it is important to develop population-specific polygenic risk models in order to better understand the extent to which population-specific genetic factors influence racial disparities in cancer incidence (45).

Impact of access and quality of care on breast cancer outcomes

It is conceivable that in a society still recovering from hundreds of years of institutionalized discrimination, access to quality health care could be a major contributor of

outcome disparities. Supporting this notion, a meta-analysis of 23 studies that examined racial patterns of care for breast cancer concluded that AA women less frequently receive radiation therapy after breast-conserving surgery, thereby suggesting that disparities in access and quality of treatment may be an underlying factor (46). Further supporting this, Pacheco *et al.* (9) found that race was not significantly associated with outcomes of TNBC in a single center study where patients received similar therapy and follow-up, suggesting that the observed disparities in cancer mortality may be the result of inequalities of disease management. In contrast, studies conducted in presumably equal-access health care systems such as the military health system in the United States (47) or the National Health Service in the UK (48) observed significant disparities in breast cancer outcomes between women of African versus European ancestry. Furthermore, several studies in controlled care settings have still reported differences in outcomes between racial groups. Woodward *et al.* (49) report that race is independently associated with overall survival in locally advanced, nonmetastatic breast cancer treated with mastectomy and doxorubicin-based chemotherapy, with AA women exhibiting poorer survival than their EA counterparts. Likewise, an analysis of 35 randomized phase III clinical trials conducted by the Southwest Oncology Group (SWOG) found that AA patients had worse survival than EA patients, despite enrollment with uniform stage, treatment and follow-up (50). Therefore, while reducing barriers to care is fundamentally important and has, in some settings, resulted in at least a 20% reduction in racial disparities in breast cancer outcomes (51), it remains unclear whether equalizing access to care alone would suffice to eradicate outcome disparities.

There is significant debate on the role of socioeconomic status (SES) in the context of cancer outcomes (52), as outlined in *Table 1*. Indeed, while some studies show that biological/clinical factors do not fully explain racial disparities (10,11,61–63), controlling for SES and other factors related to healthcare access do not always explain all of the racial disparities in breast cancer (53–60) (*Table 1*). For example, Curtis *et al.* (56) found that adjusting for mammography screening, tumor characteristics, biologic markers, treatment, comorbidity and SES demographics derived from the Surveillance, Epidemiology, and End Results (SEER)-Medicare data reduced the mortality difference between AA and EA women in all stages of breast cancer [HR: 1.08 (0.97–1.20)]. However, controlling for these variables did not eliminate these mortality differences

in women with stage II/III disease [HR: 1.30 (1.10–1.54)]. Indeed, this study used median income by zip code and “type of community”, defined as rural, less rural, urban, metropolitan, and big metropolitan, as markers of SES. A similar analysis of the SEER data by Chu *et al.* (64) found a significant association between race and stage-specific survival rates in younger breast cancer patients (<50 years old), a disparity that was no longer significant for patients 65 years or older due in part to access to Medicare in the older population. This suggested that uniform access to medical insurance may help to alleviate racial disparities in access to care (64). While this study did not consider SES directly, these findings still point toward discrepancies in external factors as likely being partially responsible for disparities in cancer mortality.

Given that racial disparities in breast cancer are not fully explained by access to care, lifestyle and socioeconomic factors alone, there has been a growing interest in exploring potential molecular differences in breast cancers across population groups to gain insights into likely biologic factors underpinning outcome disparities.

Impact of tumor biology on breast cancer disparities

While the external factors contributing to higher rates of TNBC in AA women remain uncertain, deciphering the molecular and biological drivers at the tumor level is a key step to developing treatments for aggressive disease. Multiple studies have reported relatively modest differences in somatic mutations, associated copy-number profiles, gene expression levels, tumor mutation burden and intratumor heterogeneity between breast tumor lesions from AA and EA women (*Figure 2*).

In an analysis of 930 patients with breast cancer, Huo *et al.* (42) found that tumors from women with African ancestry had a higher proportion of *TP53* mutations, *MYC* amplifications and a lower proportion of *PIK3CA* mutations as compared to tumors from women of European descent; however, these molecular differences were accounted for after adjusting for intrinsic subtype (*Figure 2*). Keenan *et al.* (65) similarly studied samples from The Cancer Genome Atlas (TCGA) and found higher rates of *TP53* mutations, lower rates of *PIK3CA* mutations and higher prevalence of the basal-like PAM50 subtype in breast cancers in AA women as compared to their EA counterparts. They also observed higher levels of intratumor heterogeneity in

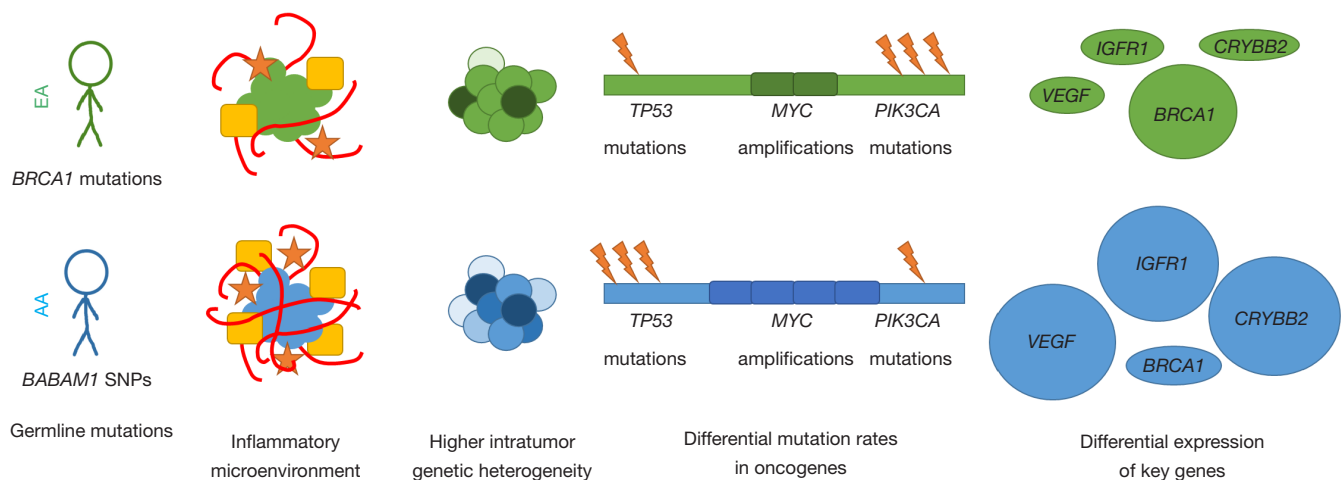


Figure 2 Molecular and biological differences in tumors from AA vs. EA women. Variations on several biological levels differentiate tumors from AA women from EA counterparts. These groups exhibit different frequencies of germline mutations associated with TNBC; while *BRCA1* mutations are more common in EA women, recent studies have shown that SNP rs8170 on the *BABAM1* gene was linked to TNBC in an AA population. TMEs in AA women were found to have elevated levels of proinflammatory cytokines (orange stars), higher blood vessel density (red curves), and increased macrophage recruitment (yellow boxes). Intratumor genetic heterogeneity is generally higher in tumors from AA women and these cancers have a higher proportion of *TP53* mutations, *MYC* amplifications and a lower proportion of *PIK3CA* mutations, consistent with higher rates of TNBC. A few studies have defined gene expression signatures that differ between tumors from AA women and tumors for EA women, including an increased expression of *IGFR1*, *VEGF* activated genes, *CRYBB2* and decreased *BRCA1* expression. AA, African American; EA, European American; TNBC, triple-negative breast cancer; TME, tumor microenvironment.

breast cancers in AA versus EA women, but this difference did not significantly contribute to the racial disparity in tumor recurrence (Figure 2). However, upon adjusting for *TP53* mutation status, *PIK3CA* mutation status, as well as expression-based subtypes (PAM50) of breast cancer, almost no differences were observed in tumor recurrence hazard between AA and EA (65), thus suggesting that differences in the molecular makeup of breast cancer across populations may contribute to disparities in outcomes.

In a study focused on TNBC, comparing a total of 128 tumor samples from EA women (54%) and AA women (39%), Lindner *et al.* (66) found the transcriptional profiles of tumors from AA women to exhibit gene expression signatures consistent with the Basal 1 (BL1) TNBC subtype, decreased *BRCA1* expression, increased activation of insulin-like growth factor 1 receptor (*IGF1R*) and increased expression of vascular endothelial growth factor (*VEGF*) activated genes (Figure 2). However, given that differential expression of *IGF1R* could also be associated with differences in the rates of obesity and metabolic syndrome between the AA and EA patients in this cohort, additional studies are warranted to determine whether

differences in tumor molecular profiles in AA and EA patients are intrinsic to tumor biology, or merely reflective of patient comorbidities.

Another intriguing proposition entails the existence of novel subtypes of breast cancers that are unique to specific population groups considering that canonical breast cancer subtyping was derived from majority EA cohorts. Exploring this possibility, a study of 147 Ghanaian women found a counter-intuitive correlation of androgen receptor and aldehyde dehydrogenase (*ALDH1*) expression among TNBCs from AA women, suggesting that novel TNBC subtypes may exist among populations with African ancestry. The discovery of these novel subtypes will require large-scale profiling of AA TNBCs followed by molecular subtyping similar to the TNBC subtypes (67).

Role of the tumor microenvironment (TME) in cancer health disparities

The past decade has resulted in dramatic new advances in our understanding of the role of the TME in carcinogenesis and tumor progression. Therefore, when exploring factors

Table 1 Summary of findings from multiple studies on SES factors and racial breast cancer disparities

Category	Publication	Adjusted factors	Effect
Biological/clinical + SES factors do not fully explain breast cancer disparities	Field <i>et al.</i> (53)	Age, stage, grade, tumor size, HR status; patients limited to those with insurance	Controlling for these characteristics did not fully explain the higher risk of breast cancer death [OR: 1.34 (1.22–1.46)]
	Adams <i>et al.</i> (54)	Age, Elston pathology grade, ER status, HER2 status, insurance	Controlling for these characteristics, AA women had significantly higher breast-cancer specific mortality than EA women [HR: 3.45 (1.79–6.65)]
	Lund <i>et al.</i> (55)	Age, stage, grade, poverty index, treatment, comorbidities	Within TNBC subtype, racial disparities in mortality persisted after adjustment [HR: 2.0 (1.0–3.7)]
	Curtis <i>et al.</i> (56)	Age, stage, mammography screening, tumor size, lymph node status, stage, ER status, comorbidities, demographics (type of community, median income by zip code)	In stage II/III patients, controlling for these characteristics did not fully explain the higher risk of breast cancer death [OR: 1.30 (1.10–1.54)]
	Bauer <i>et al.</i> (57)	Age, SES (based on PCA from US Census), stage, grade	AA women more likely to be diagnosed with TNBC after adjusting for these factors
Biological/clinical + SES factors sufficiently explain breast cancer disparities	Jatoi <i>et al.</i> (58)	Age, stage; all patients limited to a single healthcare system (DOD)	Survival of AA women compared with EA women was poorer in the 1980's (HR: 1.269) and worsened in the 1990's (HR: 1.849), in the DOD healthcare system
	Gordon (59)	Lymph node status, tumor size, ER status, SES	Controlling for these factors accounted for the difference in survival. A log-linear analysis demonstrated that association of race with ER status is mediated by SES
	Bradley <i>et al.</i> (60)	Age, stage, SES (census tract poverty), insurance	Breast cancer stage at diagnosis, treatment and survival in AA women was not statistically significantly different from EA women after controlling for covariates

All of the following studies found SES factors, such as insurance status, neighborhood income and community demographics, accounted for at least some of the racial disparities in TNBC incidence, or breast cancer mortality. However, those in the top section found that disparities were not entirely explained after adjustment for known biological/clinical factors and SES indicators. SES, socioeconomic status; ER, estrogen receptor; AA, African American; EA, European American; TNBC, triple-negative breast cancer.

contributing to aggressive cancer phenotypes in AA women and poorer outcomes, it is essential to characterize not only tumor intrinsic molecular profiles but also the TME to get a fuller picture of the disease.

Broadly, TME, which provides a favorable niche for the growth of tumor cells, is comprised of several types of stromal cells (e.g., fibroblasts, endothelial, and immune cells) and the various proteins secreted as a consequence of bi-directional tumor-stromal cross-talk. Emerging evidence suggests inherent biological differences in the TME of breast cancer patients from different racial backgrounds. Indeed, elevated levels of cytokines, including Resistin and *IL-6* (68), higher vessel density (69) and increased macrophage recruitment (70) characterize the TME of breast cancers in AA women (Figure 2). These TME components render patients more susceptible to the development of aggressive tumors, faster progression of disease, and poorer patient survival (71).

It is possible that molecular drivers for higher rates of TNBC observed in AA women are differences in immune signaling. In a study of the AMBER consortium data, Hong *et al.* (72) chronicled genetic variations and differential activation of key immune response pathways among AA women with breast cancer. SNPs in genes involved in regulation of immune system processes, immune activation, and inflammation were associated with higher risk of breast cancer. Specifically, SNPs in the NF- κ B pathway were found to associate with innate immunity and activation of the inflammatory response, leading to an increased risk of ER-positive breast cancers. Likewise, pathways associated with *MAP3K1* activation were also linked to an increased risk of ER-negative cancers (72). In addition to contributing to breast cancer risk, certain variations in immune components may regulate tumor response to treatment. For example, Jenkins *et al.* (73) found that infiltrating carcinomas in AA women have a higher proportion of tumors that are negative for the atypical chemokine receptor 1 (*DARC/ACKR1*) as compared to EA women, a difference likely driven by sub-Saharan African-specific alleles in this gene. *DARC/ACKR1* expression not only plays a significant role in immune regulation, but also promotes significantly enhanced survival in individuals with *DARC/ACKR1*-high tumors across all molecular tumor subtypes (73).

Collectively, these data suggest that genetic variations in key immune regulatory genes may underlie racial disparities in breast cancer susceptibility, as well as mortality. Nonetheless, the extent to which cancer health disparities are influenced by ancestry-related differences in

the innate and adaptive immune systems remains unclear. Indeed, while germline variations could modulate immune responses across population groups, there is a growing recognition of the potential immunomodulatory role of allostatic load and/or chronic stress (74-78). As such, well-controlled longitudinal studies are warranted to explore the relative influence of germline factors or external stressors on individual patient immune responses, which in turn may contribute to outcome disparities (Figure 3).

Future directions in population scale exploration of cancer health disparities

Despite the rapid drop in cost of sequencing over the past few years, large-scale molecular profiling of tumors is still an expensive proposition, thus limiting our ability to assess for differences in tumor biology at the population scale. However, recent developments in computational imaging approaches applied to routinely collected radiologic images and pathology slides have revealed previously underappreciated insights into tumor biology. Indeed, we and others have shown that tumor profiles at the radiomic and pathomic scales are associated with molecular subtypes and clinical outcomes across cancers (36,79,80). As these radiogenomic and pathomic approaches continue to be developed and validated, they will enable population-level assessments of variations in tumor biology, thus allowing the exploration of mechanisms underlying cancer health disparities at scale.

Yet another challenge in population-scale explorations of social determinants of cancer health disparities involves the assessment of SES of individual patients. Epidemiologic studies in cancer health disparities often incorporate SES status measured by education, occupation, wealth or income, but the availability and reliability of many of these measures remains a key challenge in the field (81). However, recent advancements in social science methodologies that incorporate geospatial analytics to assess economic disadvantage have enabled large-scale studies in cancer health disparities. For example, after analyzing data on Louisiana TNBC patients diagnosed in 2010–2012 with a robust measure of physical and social environment called neighborhood concentrated disadvantage index (CDI), Hossain *et al.* (82) found that CDI was associated with more advanced stages of TNBC at diagnosis and poor stage-specific survival. Similarly, by combining data from the US Centers for Disease Control and Prevention and the Home Mortgage Disclosure Act database, Beyer *et al.* (83)

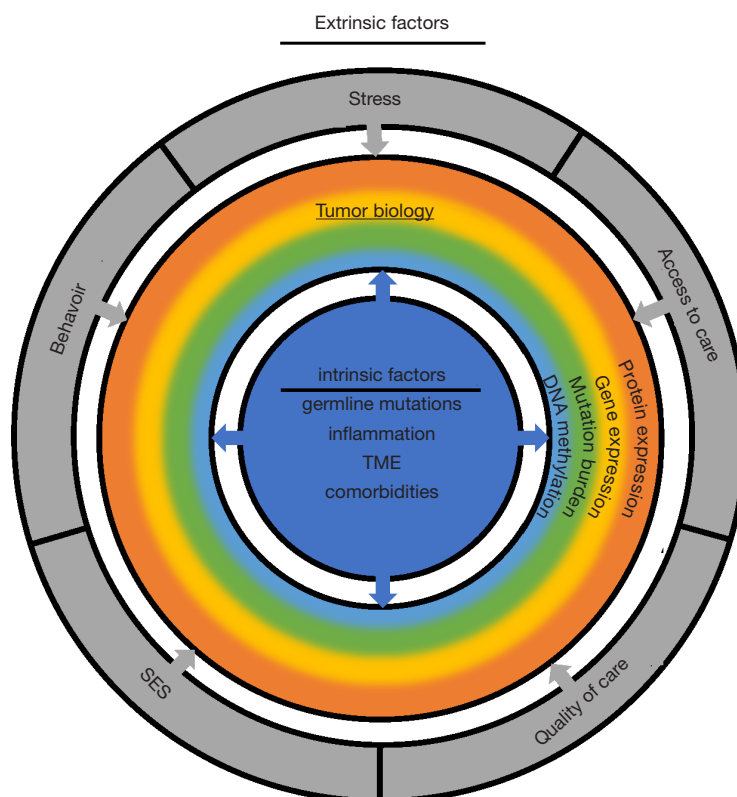


Figure 3 Multi-scale influences on tumor biology and aggressiveness. Intrinsic factors to the patient, such as germline mutations and comorbidities, affect tumor biology. Likewise, patient extrinsic factors including SES and access to care contribute to tumor aggressiveness. Additionally, tumor biology is itself defined on multiple scales such as mutation burden and gene expression. Information on each of these levels is needed to truly decipher the underlying causes of breast cancer disparities. SES, socioeconomic status; TME, tumor microenvironment.

determined that mortgage discrimination was associated with larger racial cancer mortality disparities. In a study of 13,066 female patients, neighborhood SES (education, occupation, employment, household income, poverty, rent, and house value by census tract) and individual SES (insurance and marital status) stably explained one-half of the racial disparities in survival outcomes (84). These studies suggest that novel geospatial indices of disadvantage in combination with traditional demographic measures can provide a more comprehensive assessment of socioeconomic factors likely contributing to cancer health disparities.

Discussion

Our understanding of breast cancer disparities over the past decade has been driven by research conducted by epidemiologists, social scientists, and biologists,

working largely independent of each other. However, these substantial efforts have reinforced the notion that cancer health disparities are driven by a complex interplay of factors spanning the molecular to sociologic scales. Studying differences in medical outcomes between racial groups, a socially-constructed concept, without accounting for the historical and current social environment of those groups can result in missed opportunities to improve health equity in addition to confounding our understanding of the biological factors driving disease aggressiveness. Accordingly, the next phase in breast cancer disparities research will be driven by multi-disciplinary teams of scientists who curate large-scale datasets with comprehensive tumor measurements and sociodemographic data. Indeed, advances in geospatial data collection at the sociodemographic scale coupled with innovations in radiologic/pathologic imaging and molecular profiling

at the biologic scales are poised to enable such large-scale dataset curation. Additionally, recent advances in machine learning and systems biology have begun to provide the necessary methodologic frameworks to analyze such multi-scale datasets. Such a convergence of large-scale dataset curation and big data analytics is expected to better elucidate the sociologic and biologic determinants of patient outcomes, and thus enable the development of more effective interventional strategies to reduce breast cancer disparities.

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