Race in Cancer Health Disparities Theme Issue

REVIEW

Analysis of Tumor Biology to Advance Cancer Health Disparity Research

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Cancer mortality rates in the United States continue to decline. Reductions in tobacco use, uptake of preventive measures, adoption of early detection methods, and better treatments have resulted in improved cancer outcomes for men and women. Despite this progress, some population groups continue to experience an excessive cancer burden when compared with other population groups. One of the most prominent cancer health disparities exists in prostate cancer. Prostate cancer mortality rates are highest among men of African ancestry when compared with other men, both in the United States and globally. This disparity and other cancer health disparities are largely explained by differences in access to health care, diet, lifestyle, cultural barriers, and disparate exposures to carcinogens and pathogens. Dietary and lifestyle factors, pathogens, and ancestry-related factors can modify tumor biology and induce a more aggressive disease. There are numerous examples of how environmental exposures, like tobacco, chronic stress, or dietary factors, induce an adverse tumor biology, leading to a more aggressive disease and decreased patient survival. Because of population differences in the exposure to these risk factors, they can be the cause of cancer disparities. In this review, we will summarize recent advances in our understanding of prostate and breast cancer disparities in the United States and discuss how the analysis of tumor biology can advance health disparity research. (Am J Pathol 2018, 188: 304-316; https://doi.org/10.1016/j.ajpath.2017.06.019)

Cancer mortality rates in the United States have been declining since the 1990s because of reduced tobacco use among adults, more widespread cancer screening and testing, and improved cancer therapies. Despite this progress, disparities continue to persist across different racial and ethnic groups. In the United States, African Americans disproportionately bear the cancer burden and have the highest death rates for many cancer types of any racial or ethnic group. Breast cancer and prostate cancer are the two most common invasive cancers in women and men, respectively. Advances in detection and cancer therapy have improved cancer care and disease outcomes for these two cancer types. Although incidence rates for prostate cancer are decreasing in the United States, they are still increasing in many parts of the world. The latter can be attributed to population aging and adaptation of a Western lifestyle. Likewise, breast cancer incidence rates are also increasing globally. In the United States, these rates have been stable for many years; however, for African-American women, breast cancer incidence increased (0.7% per year), whereas the disease incidence decreased (1.0% per year) among European-American women between 2000 and 2009. Although breast cancer mortality has decreased annually by an average of 2%, likely because of improved diagnosis and treatment, African-American women still have the highest mortality when compared with other racial and ethnic groups. The reasons for the observed disparities are multifactorial and include access to health care, socioeconomic status, health literacy, and discrimination.

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This article is part of a review series on understanding the complex role of race in cancer health disparities.
Nonetheless, these socioeconomic and sociobehavioral factors do not fully explain these health disparities. Therefore, health disparity research has begun to explore biological factors. This approach is further supported by the observation that disease characteristics of prostate and breast cancer show significant geographic and ethnic variations. Research efforts have begun to concentrate on molecular mechanisms in tumor biology and ancestry-related aspects that may contribute to cancer disparities (Figure 1). This review will focus on bringing to light the molecular and epidemiologic work that has gone into understanding the tumor biological differences that may contribute to cancer health disparities.

**Survival Health Disparities in Breast and Prostate Cancer in the United States**

**Survival Health Disparities in Prostate Cancer**

Prostate cancer is the second leading cause of cancer-related deaths in US men and exhibits a pronounced racial disparity. Well-established risk factors for the disease are age, family history of the disease, race/ethnicity, and inherited genetic factors that include approximately 100 disease susceptibility loci that are known. African-American men have a mortality rate more than double that of European-American men, in part because of their increased risk of developing the disease. Surveillance, epidemiology, and end results data for the period from 1975 to 2012 show that African-American men have an earlier mean age of a prostate cancer diagnosis (69.1 versus 71.1 years) and a shorter mean survival period (44.4 versus 48.4 months) when compared with European-American men. This survival disparity has been observed for >20 years, despite the approximately equal prevalence of prostate-specific antigen testing among African-American and European-American men. The higher disease mortality of African-American men is caused by multiple factors, including access to care, biological/genetic differences, geography, and patient characteristics and behaviors. Interestingly, men of West-African ancestry from the Caribbean and South America exhibit incidence and mortality rates similar to African-American men, suggesting a possible ancestral basis for some of these common outcomes.

The higher mortality rates among African-American men may also occur because these men are prone to a more aggressive type of prostate cancer. A study conducted by Tyson and Castle examined racial disparities in survival for patients with clinically localized prostate cancer. Even though the investigators adjusted for clinical and socioeconomic factors, African-American men still had the worst survival compared with European-American, Hispanic, or Asian men. Powell et al analyzed prostate autopsy material from 1056 African-American and European-American men who did not have a prior diagnosis of prostate cancer. They compared autopsy findings with results from the analysis of resected tumors. Although the disease presentation was similar between the two patient groups at the subclinical stage, among the patients with clinically detected prostate tumors, African-American men tended to have a more aggressive disease than European-American men. This finding is consistent with an accelerated disease progression in African-American men, indicating that differences in tumor biology may exist between the two patient groups.

**Survival Health Disparities in Breast Cancer**

The US health disparity in breast cancer presents itself different from the disparity in prostate cancer because it is mostly a survival health disparity, with a disproportionately...
high mortality among African-American, Latina, and Native American women. Although advancements in cancer treatment, screening, and diagnosis are helping women overall, breast cancer incidence rates in African-American women are increasing. Currently, the 5-year relative survival rate is 80% for African-American women compared with 91% among European-American women. It is believed that nonbiological and biological factors play a major role in this survival disparity. Nonbiological factors include socioeconomic factors, access to health care, cultural factors, and comorbidities.

A poorer survival of African-American breast cancer patients has also been observed in equal access health care systems and clinical trial settings. It was thought that the increased prevalence of early-onset estrogen receptor (ER)—negative tumors and basal-like/triple-negative tumors in women of African ancestry is largely responsible for the excessive mortality. Although this argument is plausible, one has to be cautious because the breast cancer survival disparity occurs irrespective of the tumor’s ER status. A study by Hershman et al found that, after controlling for stage, demographics, socioeconomic variables, tumor characteristics, and treatment factors, an excessive mortality remained among both pre and postmenopausal African-American women who were diagnosed with early-stage breast cancer. These findings are consistent with the more recent observations by Silber et al. Therefore, still poorly understood molecular and genetic differences in tumor biology may promote a more aggressive disease in women of African descent. A better understanding of these biological factors is critical for addressing the high disease mortality observed in African-American women.

Biological Determinants of Cancer Health Disparities

Observations from migration studies that immigrants tend to acquire cancer rates of their new home country within two generations indicate the importance of modifiable exposures as major risk factors for common cancers in the United States. Yet, breast and prostate tumors tend to be more aggressive at diagnosis in African Americans than they are in European-Americans. This disparity has not been eliminated with the equal use of cancer screening and has generated a heightened interest in understanding the biology of these tumors. Subsequently, this research led to the discovery of differences in both genetic predisposition to cancer and molecular subtypes between these population groups, which we will discuss later in separate sections. Apart from these observations, additional differences in the tumor biology between African-American and European-American patients were described by investigators who used gene expression, mutational, and immunohistochemical analyses of tumors.

In prostate cancer, the epidermal growth factor receptor was found to be more commonly expressed in tumors from African-American patients when compared with European-American patients. Using a differential display analysis, a novel prostate-specific gene, termed PCGEM1, was identified that encodes a long noncoding RNA with a cell growth—promoting function. This transcript is most highly expressed in prostate tumors of African-American patients. Others described ZBTB33 (alias KAISO) and motor neuron and pancreas homeobox 1 (MNX1) as oncogenically up-regulated genes in tumors of these patients. KAISO is regulated by epidermal growth factor receptor signaling and is a key transcription factor that induces epithelial-to-mesenchymal transition, whereas MNX1 regulates lipid synthesis. Last, a recurrent deletion on chromosome 3q13.31 was found to occur in prostate tumors of African-American patients that associates with the loss of the ZBTB20-LSAMP locus and with an aggressive disease.

Few studies have examined the biology of breast tumors in African-American women beyond the concept of molecular subtypes. Several used gene expression profiling to study the biology. A race/ethnicity-associated gene signature of poor outcome was described for luminal A breast tumors. This signature comprises six genes that are differentially expressed between African-American and European-American patients. Terunuma et al reported a high prevalence of a MYC signaling signature in tumors of African-American patients that was associated with the accumulation of the oncometabolite, 2-hydroxyglutarate. Earlier studies described race/ethnicity differences in the expression of cell cycle regulatory proteins, including p53, which is encoded by the TP53 tumor suppressor gene. These findings were confirmed when it was shown that tumors from African-American patients were more likely to carry a TP53 mutation. The high prevalence of triple-negative tumors in women of African descent accounts for much of this race/ethnicity difference in the TP53 mutation’s frequency because TP53 mutations are most common in this disease subtype. Interestingly, the tumor TP53 status has been associated with socioeconomic deprivation. Thus, an environmental factor related to socioeconomic status may promote the development of TP53 mutations in breast tumors. Alternatively, socioeconomic deprivation may specifically increase the risk of triple-negative breast cancer.

Disparities in Molecular Subtypes of Prostate and Breast Cancer

Disparities in Molecular Subtypes of Prostate Cancer

Prostate cancer evolves as a multistage disease with an accumulation of genomic aberrations during disease progression. Recurrent genomic rearrangements at cancer-related loci define prostate cancer subtypes. TMPRSS2:ERG gene fusion events, which produce fusion transcripts and oncogenic overexpression of ERG, an oncogene that encodes a member
of the E26 transformation–specific (ETS) family of transcription factors, are signature mutations of a subset of prostate tumors and have important biological implications.\textsuperscript{39} Tumors carrying these gene fusions fall into a distinct molecular subtype. Other subtypes are negative for ETS-fusion gene arrangements but may overexpress the \textit{SPINK1} oncogene, or carry a \textit{SPOP} mutation, and have a poor prognosis.\textsuperscript{38,40} Conversely, localized prostate cancer contains few recurrent mutations in oncogenes or tumor suppressor.\textsuperscript{41} Instead, local prostate cancer is characterized by ETS-fusion gene arrangements and allelic gains of the \textit{MYC} (alias \textit{c-myc}) gene and deletions of the \textit{PTEN}, \textit{TP53}, and \textit{NKK3-1} tumor suppressors, with additional common changes in DNA methylation that increase aggressiveness.\textsuperscript{42,43} In stark contrast, nearly half of the metastatic castration-resistant prostate cancers harbor mutations in the androgen receptor, \textit{TP53}, and \textit{PTEN} genes and additional mutations in \textit{BRCA1}, \textit{BRCA2}, and \textit{ATM}, among others.\textsuperscript{44} However, because most studies included only patients of European descent, the mutational landscape of prostate cancer may not have been fully captured.

Multiple reports have shown that prostate tumors from patients of either European, African, or Asian descent exhibit notable differences in acquired chromosomal aberrations.\textsuperscript{40,45–47} These studies examined the frequency of recurrent \textit{ERG} gene fusions and \textit{PTEN} loss in diverse patient populations. Although common in European and European-American patients (40% to 50% frequency), \textit{TMPRSS2:ERG} gene fusion events were found to be significantly less frequent in African-American patients (20% to 30%) and were rather uncommon in patients from Asia in these studies (approximately 10%).\textsuperscript{48} A similar pattern was observed for \textit{PTEN} loss, with rates being significantly lower in Asian and African-American patients.\textsuperscript{47,48} These findings indicate robust race/ethnic differences in disease cause and mutational events affecting these patients.

Disparities in Molecular Subtypes of Breast Cancer

Breast cancer is a heterogeneous disease that encompasses at least four major molecular subtypes. Large-scale gene expression studies showed that breast tumors can be classified into subtypes with distinct gene expression.\textsuperscript{34} Molecular signatures characterize two luminal subtypes (A and B), the HER2 signaling-enriched tumors, and basal-like tumors. Among the subtypes, basal-like and HER2-positive tumors that are ER negative tend to yield the most aggressive disease. Basal-like tumors overlap largely with a group of tumors referred to as triple negative, which are negative for ER, HER2, and progesterone receptor expression. Research into novel therapies of breast cancer has focused on triple-negative tumors because these tumors are not treatable by current endocrine therapies, such as tamoxifen and aromatase inhibitors, or by HER2-targeting therapies, such as trastuzumab (Herceptin; Genentech/ Roche, South San Francisco, CA). It was recognized starting in 2006 that the prevalence of these subtypes varies among women in the United States, with the greatest difference observed between women of African and European descent.\textsuperscript{33,40} Investigations in West and Central Africa have provided further corroboration that women of African descent tend to develop early-onset, high-grade, ER-negative tumors more frequently than women of European descent.\textsuperscript{8} Early-onset ER-negative tumors also develop more frequently in women from India and Pakistan.\textsuperscript{49} Finally, cancer epidemiology showed that the rates of ER-negative breast tumors can change in a population over time, pointing to an influence of environmental and reproductive factors in the development of these tumors.\textsuperscript{51}

Immune-Inflammation Signatures in Breast and Prostate Tumors of African-American Patients

Immune-Inflammation Signatures in Prostate Cancer

Inflammation and neoangiogenesis are key biological processes in cancer biology.\textsuperscript{52} Inflammation is also a putative risk factor for prostate cancer and has been associated with aggressive disease.\textsuperscript{53,54} We and others have previously described a distinct immune-inflammation signature in prostate tumors of African-American patients,\textsuperscript{55–58} which is absent in most European-American patients (Table 1). Moreover, race/ethnicity differences in prostatic inflammation have been described in benign prostate tissues\textsuperscript{59,60} (Table 1), but their relationship to disease risk and aggressiveness remains unclear, because the findings in these two studies were not consistent. Because of the observations that tumors of African-American men commonly contain an immune-inflammation signature, we investigated the link between the regular use of aspirin, a nonsteroidal anti-inflammatory drug, and prostate cancer. Regular aspirin use significantly reduces the risk of both advanced prostate cancer and disease recurrence in African-American men.\textsuperscript{61} Our observation that regular aspirin use increases disease-free survival among these men confirms a similar observation in a previous study.\textsuperscript{62}

Currently, no study has assessed whether men of African descent are affected by a systemic inflammatory process that increases the risk of lethal prostate cancer. However, there is evidence from the measurement of blood C-reactive protein levels that African Americans tend to have higher levels of this inflammation marker than European-Americans,\textsuperscript{61,63} indicating increased systemic inflammation. Although environmental exposures, including infections, promote systemic inflammation, ancestral factors may also influence inflammatory processes. For example, allele frequencies of genetic variants in inflammation-related genes can markedly differ among population groups.\textsuperscript{64} Therefore, ancestral factors may be a cause of the immune-inflammation signature in African-American prostate cancer patients.
In summary, there is evidence that prostate cancer patients of African descent experience an increased occurrence of a low-grade chronic inflammation in their tumors. These observations suggest that disease progression and recurrence can be prevented, at least to some extent, with regular use of anti-inflammatory drugs, such as aspirin, in this high-risk group of patients.

Immune-Inflammation Signatures in Breast Cancer

In breast cancer, an immune-inflammation signature describes a subset of triple-negative breast tumors. Notably, their numbers were found to be elevated in breast tumors of African and African-American women by several investigators (Table 2), suggesting an opportunity of targeting this immune environment as a therapeutic intervention. Moreover, Martin et al. observed an increased microvessel density in these tumors. An elevated tumor vascularization in African-American breast cancer patients was also reported by Lindner et al. Tumor angiogenesis correlates with breast cancer metastasis and poor survival. Several mediators of inflammation contribute to increased angiogenesis and breast cancer progression. Aberrant expression of inflammation mediators, such as cyclooxygenase-2 and inducible nitric oxide synthase, occurs in breast tumors. The significance of TAMs and an altered tumor microenvironment in the promotion of breast cancer progression is well documented. Thus, chronic inflammatory stimuli may have a crucial role in disease progression through inflammation-induced angiogenesis and tissue remodeling. Although solid evidence is still missing, current data suggest that inflammation-induced breast cancer progression may be more prevalent in patients of African descent and may relate to increased inflammatory cytokine levels in these women.

Differences in Cancer Epigenetics among Population Groups

DNA methylation regulates gene expression and cell differentiation and is partly inherited. Environmental exposures and obesity can modify DNA methylation patterns and alter the tumor epigenome, as shown for prostate and breast cancer. Changes to DNA methylation are present in all cancers and cooperate with acquired genetic alterations to promote the cancer phenotype. Alterations in DNA methylation are among the earliest somatic changes that can be detected in cancerous lesions and occur at the stage of proliferative inflammatory atrophy, a precursor lesion in prostate cancer development. An aberrant increase in DNA methylation can lead to numerous downstream effects, including inactivation of PTEN, a bona fide tumor suppressor gene in prostate cancer, or a loss of GSTP1 expression, which is observed in 90% of prostate cancers. Epigenome-wide DNA methylation patterns have been linked to aggressive and lethal prostate cancer and to breast cancer recurrence, metastasis, and survival. Others have described molecular subgroups in breast cancer based on a global DNA methylation pattern. Hence, therapies that target the cancer epigenome are being developed.

Race/ethnicity-related differences in DNA methylation have been observed in peripheral blood mononuclear cells of newborns. This study observed significant differences in DNA methylation affecting cancer-related loci, indicating that early life exposures may induce a DNA methylation

<table>
<thead>
<tr>
<th>Tumor marker</th>
<th>Observation</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Immune-inflammation signatures</td>
<td>Gene expression differences between tumors from AA and EA men related to immune response and inflammation. Prominent immune-inflammation signature and a distinct interferon-related gene signature in AA tumors.</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>Increased expression of cytokines in AA tumors.</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>Distinct DNA copy number alterations in AA tumors. Alterations at the gene expression and DNA copy number levels point to differences in immune response between AA and EA men.</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Increased expression of genes associated with immune response and inflammation in AA tumors. A prominent interferon signature is present.</td>
<td>58</td>
</tr>
<tr>
<td>Tissue inflammation</td>
<td>Pathology-based scoring of inflammation in benign prostate tissue from AA and EA men. Inflammation was more prevalent in AA men.</td>
<td>59</td>
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<tr>
<td></td>
<td>Pathology-based scoring of acute and chronic inflammation in benign prostate tissue from Asian, AA, EA, and Hispanic men, all participants of the REDUCE trial. No race/ethnic differences in chronic inflammation but more acute inflammation in men less in AA men, when compared with EA men. Acute inflammation was associated with a lower prostate cancer risk.</td>
<td>60</td>
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pattern that later associates with disease susceptibility. Others reported a relationship between African ancestry and global DNA hypomethylation in blood leukocytes of cancer patients. Therefore, ancestry-related factors may influence the regulation of DNA methylation. Given the importance of epigenetic alterations in the development and progression of cancer, multiple investigators examined and compared DNA methylation in prostate and breast tumors of African-American, European-American, and Asian patients using targeted and genome-wide approaches.

Race/Ethnic Differences in Prostate Cancer Epigenetics

In the prostate cancer studies, a pattern emerged consistent with an increased prevalence of DNA hypermethylation at several disease-related loci in African-American tumors when compared with similar stage tumors from European-American men (Table 3). Some of these alterations may relate to disease progression. Recently, the transcriptional regulator, KAISO, was found to be overexpressed in prostate tumors from African-American patients. KAISO recognizes clusters of methylated CpG nucleotides and enhances invasion of prostate cancer cells. This suggests that aberrant KAISO expression in tumors from African-American men may enhance disease aggressiveness by mechanisms that include aberrant DNA methylation of cancer-related genomic loci.

Race/Ethnic Differences in Breast Cancer Epigenetics

In breast cancer studies, investigations focused on the differences in DNA methylation between African-American and European-American patients by analyzing tumors with both candidate gene and genome-wide approaches (Table 3). Differences in methylation between the two patient groups were reported for the ER-negative disease, but less so for the ER-positive disease. In general, the observed differences were not widespread but rather restricted to a few loci, and may be partially related to differences in MYC signaling among these patients. There is also evidence that some of the reported DNA methylation differences may not be tumor specific because similar patterns have been found in normal breast tissues and peripheral blood monocytes. To date, the mechanisms that lead to race/ethnicity differences in DNA methylation patterns of tumors are not fully understood. Whether these patterns are induced by ancestral genetic factors, the mutational landscape, environmental exposures, intrinsic differences in tumor biology, including cancer metabolism and metabolism-induced epigenetic alterations, or a combination of these factors also remains unknown. However, population differences in genome-wide DNA methylation have been described by Heyn et al. The study showed that two-thirds of the population-specific CpG sites were directly associated with the underlying genetic background of the populations. This finding indicates that inheritance and genetic ancestry are key drivers of epigenetic differences between populations that not only contribute to physical appearance, but may also contribute to traits, such as behavior, disease susceptibility, and disease aggressiveness.

### Stress Signaling—Mediated Effects in Cancer Biology and Disease Progression

#### Stress Signaling—Mediated Effects in Prostate Cancer

Cancer epidemiology has linked stressful life events and discrimination to poor disease survival. Several investigations into the effects of stress exposures on tumor biology have also focused on prostate cancer. It was discovered that catecholamine signaling increases the metastatic phenotype of prostate cancer cells. Recently, a stress-related signaling signature was found to occur in human prostate tumors, suggesting that environmentally induced stress signaling may adversely affect prostate cancer patients. Although there is no direct evidence that stress exposures affect prostate cancer patients from minority or disadvantaged backgrounds more so than other patients, a functional annotation of copy number and gene expression differences comparing tumors from African-American and European-American patients showed that these differences not only relate to immune function but also to neurotransmitter transport and catecholamine metabolic processes. Although the significance of these findings is unclear, the data suggest that differences in stress-induced catecholamine signaling may exist between the two patient groups.

### Table 2  Reports of Race/Ethnic Differences in Immune Cell Numbers in Breast Tumors

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Observation</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Tumor-associated macrophages</td>
<td>Number of CD68-positive macrophages is higher in breast tumors of AA patients than EA patients. Chemotaxis-related gene signature in AA tumors.</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Proliferating cellular nuclear antigen—positive macrophages are increased in breast tumors of Latina and AA women when compared with EA women.</td>
<td>66</td>
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<tr>
<td></td>
<td>High numbers of tumor-associated macrophages in breast tumors of Nigerian women.</td>
<td>67</td>
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<tr>
<td></td>
<td>High immune cell infiltration, including CD163-positive macrophages, in breast tumors of Kenyan women.</td>
<td>68</td>
</tr>
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</table>

Stress Signaling—Mediated Effects in Breast Cancer

Stressful life events and perceived experiences of racism have a significant association with adverse health behaviors and breast cancer.\textsuperscript{95,96} whereas stress because of a cancer diagnosis may disproportionately affect minority populations.\textsuperscript{97} Social class, social isolation, and related stress affect immune cell function and tumor biology. In mice, chronic restraint stress decreased levels and function of p53 and promoted tumorigenesis.\textsuperscript{98} In women, Baker et al,\textsuperscript{35} and Starks et al\textsuperscript{36} observed a relationship between socioeconomic deprivation and an increased frequency of TP53 mutations in breast tumors. Other studies reported that social adversity in early life leads to resistance in glucocorticoid signaling and increased proinflammatory signaling.\textsuperscript{99} Social stress also affects the response to infections, telomere length, and immune cell function, and elevates the tumor catecholamine content.\textsuperscript{100,101} Thus, stress exposures have a potentially oncogenic function in tumor biology and may have a disproportionately high adverse impact in socially deprived and minority populations. Specifically, in breast cancer biology, social isolation can lead to reprogramming of tumor biology.\textsuperscript{102,103}

Chronic stress influences tumor biology through two major pathways involving catecholamines and glucocorticoids.\textsuperscript{104} Stress-induced β-adrenergic signaling has been shown to promote cancer progression and metastasis in animal models of breast cancer.\textsuperscript{105,106} The mechanism by which this pathway promotes metastasis has been described and includes recruitment of TAMs and interactions between TAMs and cancer cells that cause increased tumor angiogenesis and distant metastasis.\textsuperscript{105,106} Recently, social isolation was found to be associated with elevated tumor catecholamine levels in human ovarian tumors and with a tumor gene signature, albeit this study was rather small.\textsuperscript{107} In 2010, it was first reported that β-blocker use after a disease diagnosis reduces disease recurrence and improves cancer-specific survival of breast cancer patients.\textsuperscript{108} In another study, users of the β-blocker, propranolol, were found to be significantly less likely to develop advanced breast cancer and have reduced breast cancer—specific mortality.\textsuperscript{109} β-blocker use has also been associated with improved recurrence-free survival in triple-negative breast cancer.\textsuperscript{110} Jointly, these data indicate that stress may influence human breast cancer biology through activation of the prometastatic catecholamine pathway, leading to a poor outcome phenotype in a subpopulation of patients who would benefit from β-blocker use and stress management.

Our group observed that breast tumors from African-American patients contained a higher microvessel density and more TAMs than tumors from European-American patients, independent of disease stage and tumor ER status.\textsuperscript{28} Because the phenotype is consistent with characteristics that are induced by catecholamine signaling in experimental models,\textsuperscript{105} our findings may indicate that increased signaling by this pathway occurs in tumors of these patients. Thus, inhibitors of catecholamine signaling may improve outcomes specifically among African-American patients, which has not been examined thus far.

### Contribution of Population Genetics and Ancestry to Health Disparities

Genetic ancestral factors not only characterize population groups but also participate in selection and can define phenotypic traits within populations.\textsuperscript{111} Several studies have shown that gene expression differences exist among...
populations that are attributable to common genetic variations and ancestral background. Two of these studies investigated gene expression variations between individuals of European and African ancestry (Nigeria) using lymphoblastoid cell lines. The researchers observed that these variations can cluster in disease-related pathways, raising the possibility that differences in common genetic variations among population groups cause population-specific susceptibilities for common diseases, like cancer, because of their effect on the transcriptome.

Contribution of Ancestry to Prostate Cancer Health Disparities

Prostate cancer is a genetically heterogeneous disease, in which inherited factors may account for approximately 40% to 50% of the cases. Several familial susceptibility genes have been described, including RNASEL, BRCA1, BRCA2, and HOXB13. Germline mutations in these genes account for 5% to 10% of all prostate cancer cases. Most of the inherited risk for prostate cancer arises from common genetic variants. Approximately 100 disease susceptibility loci are currently known, but not all of them confer risk in men of African ancestry. Numerous studies have examined the possibility of low-penetrance genes contributing to the excessive burden of prostate cancer in men of African ancestry. To date, the best characterized risk locus for prostate cancer is located at 8q24. This locus likely affects tumor biology because it encodes an enhancer region that regulates MYC in an allele-specific manner. Multiple common variants within this locus increase the risk of prostate cancer in diverse populations. As shown by admixture mapping and genome-wide association studies, 8q24 confers an even higher risk for prostate cancer in men of West African ancestry, when compared with men of European and Asian ancestry, partly explained by variants that were only found in men of African ancestry. Thus, the 8q24 region accounts for at least some of the excessive disease risk among men of African ancestry. A susceptibility locus at 17q21 has been identified as another genetic risk factor that appears to be restricted to men of African ancestry. However, few common genetic variations have been associated with prostate cancer aggressiveness, mortality, or response to therapy, and none has been associated with increased mortality among men of African ancestry.

Contribution of Ancestry to Breast Cancer Health Disparities

Genome-wide association studies and admixture mapping have also been used to examine the contribution of inherited risk to breast cancer and to the excessive risk of breast cancer mortality among women of African and Latina descent. Numerous genome-wide association studies showed that a large set of common genetic variants defines the risk of breast cancer, the ER- and triple-negative disease, and breast cancer survival. The most strongly associated risk locus has been mapped to the region containing fibroblast growth factor receptor 2. However, an analysis within the Multiethnic Cohort Study observed significant population heterogeneity for the association of 12 highly replicated single-nucleotide polymorphisms with breast cancer and did not find an association of these single-nucleotide polymorphisms with breast cancer in African Americans. Additional studies did not replicate genome-wide association study findings from European populations in populations of African ancestry. Instead, different low-penetrance risk loci for breast cancer may exist in populations of African ancestry. One study suggested that a common variant at the TERT-CLPTM1L locus may be an underlying cause for the high prevalence of ER-negative tumors among women of African ancestry. Admixture scans in African-American and Latina women with breast cancer further support the concept of ancestry-related risk factors in breast cancer. Two studies of Latina women found that European and indigenous American ancestry are significantly associated with breast cancer risk and survival, respectively, in this population. Admixture mapping of African-American women identified new breast cancer risk loci for this population.

Together, these data show that population genetics and ancestry likely contribute to existing health disparities and partly explain the increased risk of prostate cancer among men of African ancestry, whereas these factors may also promote an excessive breast cancer mortality among African-American and Latina women.

Conclusions

Not all segments of the US population have equally benefited from the advances in our knowledge and treatment of cancer. Minority, immigrant, and disadvantaged populations continue to experience an excessive cancer burden. This burden is not only attributable to barriers in access to health care and cultural obstacles, but is also attributable to distinct carcinogen and pathogen exposures, environmentally induced stress, comorbidities, and ancestry-related risk factors. These factors, singularly or in combination, are the likely causes of the existing cancer health disparities in the United States and globally. There is strong evidence from migration studies that the environment defines cancer risk, but there is also evidence that population differences in genetic ancestry can lead to population differences in cancer susceptibility. One mechanism by which environmental and ancestry-related factors affect health outcomes is by inducing an adverse tumor biology. Multiple studies have identified differences in tumor biology and epigenetic factors among diverse patient populations. For example, the analysis of tumor markers revealed the existence of tumor biological and mutational differences in prostate cancer among patients of African, European, and Asian descent. These differences indicate disparities in disease cause and
may arise from pathogenic mechanisms that are different between population groups. Environmental factors have also been shown to define the cause of many cancer types, and both environmentally induced stress and toxins from tobacco smoke can induce a tumor biology that increases the odds of a metastatic disease. Changes in tumor biology attributable to modifiable risk factors may also affect early disease detection and the response to therapy. These changes may contribute to a distinct disease presentation of prostate cancer among men of African descent, including the excessive mortality in this patient group in the United States and globally. Thus, gaining an understanding of tumor biology in diverse patient populations can advance cancer health disparity research and provide new insights that can be harnessed to improve cancer prevention and care and to reduce or eliminate outcome disparities in cancer.

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