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Race in Cancer Health Disparities Theme Issue

REVIEW

Triple-Negative Breast Cancer, Stem Cells, and African Ancestry



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Accepted for publication
June 26, 2017.

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Triple-negative breast cancers (TNBCs) are more common among African-ancestry populations, such as African Americans and western, sub-Saharan Africans, compared with European-ancestry populations. This phenotype prevalence contributes to disparities in breast cancer outcomes between African Americans and White Americans. Breast cancer stem cells represent the tumor subpopulation involved in metastatic virulence, and ongoing research seeks to characterize the extent to which TNBC versus non-TNBC stem cells may differ. This review summarizes the existing literature regarding TNBCs and stem cells as they pertain to the burden of breast cancer among African-ancestry populations. Additional research related to variations in somatic tumor genomics between the African-American and White-American populations is also summarized. This review furthermore explores the history of insights regarding breast cancer disparities related to racial/ethnic identity, socioeconomic status, and tumor biology. (*Am J Pathol* 2018, 188: 271–279; <https://doi.org/10.1016/j.ajpath.2017.06.020>)

Triple-negative breast cancer (TNBC) is the term commonly used to describe cancers that are negative for the expression of estrogen and progesterone receptors and that lack over-expression of tyrosine kinase-type cell surface receptor HER2/*Neu*. Approximately 80% of TNBC tumors have the inherently aggressive basal breast cancer subtype as defined by gene-expression studies; the TNBC phenotype is therefore often used as a surrogate to identify patients with the biologically unfavorable basal subtype. The absence of expression of these three biomarkers also carries clinical relevance with regard to the mechanisms of currently available targeted therapies for breast cancer. An array of selective estrogen receptor modulators and aromatase inhibitors can be offered as endocrine therapy for patients with hormone receptor–positive breast cancer, and targeted anti-HER2 agents are effective in managing HER2/*Neu*-over-expressing breast cancers. Systemic therapy is especially important in addressing the virulent nature of most TNBC cases, but general, nontargeted chemotherapy remains the standard-of-care, routine approach.

Recent data suggest that breast cancers are heterogeneous and that only a small and discrete subpopulation of cells

within a tumor, called the *breast cancer stem cells* (BCSCs), possesses self-renewal capacity and the ability to establish metastatic colonies.^{1,2}

Population-based breast cancer mortality rates are higher among women who self-identify as African American compared with White Americans (alias Caucasian Americans). The burden of breast cancer mortality is also elevated among African women residing on the continent of Africa. These two populations will be described as having African ancestry.

TNBCs, BCSCs, and breast cancer patients of African ancestry represent three distinct topics that feature at least one common denominator: an association with increased breast cancer virulence. Each of these topics can be furthermore correlated with one another to varying degrees: i) TNBC is more common among women of western, sub-Saharan African ancestry^{3–6}; ii) TNBC/basal subtype tumors are enriched

Supported in part by Susan G. Komen for the Cure Komen Scholars Leadership grant HFHS F11047 (L.A.N.).

Disclosures: None declared.

This article is part of a review series on understanding the complex role of race in cancer health disparities.

with populations of cells that express BCSC markers^{7–10}; and iii) breast cancer patients of western, sub-Saharan African ancestry have an increased prevalence of tumors that express stem cell markers.^{11–14}

The extent to which the correlations described above represent evidence of genetic/hereditary variation in BCSCs associated with African ancestry versus representing the true, true and unrelated non sequitur remains uncertain. This review will summarize the published literature on TNBC, BCSCs, and their possible relationships with African ancestry. Our group has introduced the term *oncologic anthropology* as a transdisciplinary field of study that combines the expertise of social scientists, geneticists, and translational oncologists in an effort to address these complex issues.¹⁵

Breast Cancer Disparities, TNBC, and African Ancestry

Background: Epidemiology and Socioeconomic Status

Disparities in breast cancer outcomes related to racial/ethnic identity have been well documented for several decades, with the most prominent correlation being higher mortality rates among African-American compared with White-American women.^{16,17} Poverty rates and inadequate health insurance coverage are also more common in the African-American compared with White-American communities, and these socioeconomic disadvantages likely contribute to the disparities in breast cancer outcomes by causing delays in diagnosis, more advanced stage distribution at diagnosis, and inadequate multidisciplinary breast cancer treatment.^{18–20} The downstream effects of impaired health care access do not completely explain the disparities in breast cancer outcomes, as African Americans have worse survival rates even after controlling for stage at diagnosis.^{15,21} An evaluation of race/ethnicity-associated variations in primary tumor biology is therefore warranted, and the presence of such differences is supported by additional epidemiologic data regarding the burden of breast cancer in diverse population subsets.

Historically, population-based incidence rates of breast cancer have been lower in African-American compared with White-American women, and fluctuations in incidence have typically occurred in parallel. Paradoxically, however, population-based breast cancer mortality rates were similar in both groups until the early 1980s, at which point the mortality curves separated as a consequence of declining mortality rates in White Americans contrasted against relatively stable mortality rates in African Americans. The mortality gap that emerged very likely reflected the unmasking of differences in the biology of breast cancer between African-American and White-American women related to the prevalence of biomarker expression and the development of targeted therapy for breast cancer. Tamoxifen became approved as systemic therapy for breast cancer in 1977, and this endocrine agent represents the first targeted therapy for breast cancer,

improving outcomes in hormone receptor–positive disease. Tamoxifen-related reductions in population-based mortality rates became apparent by the early 1980s, but these benefits were predominantly experienced by the White-American patient population, because hormone receptor–positive breast cancer is twice as common among White Americans compared with African Americans.²²

Population-based breast cancer incidence rates have been rising disproportionately among African Americans in recent years, and these rates have now converged with those of White Americans.¹⁶ Rising incidence of breast cancer coupled with the disproportionately high frequency of the biologically aggressive TNBC phenotype in African-American women have resulted in worsening of the breast cancer population–based mortality gap, and this disparity is now a difference of 42%.¹⁶

Disparities: Socioeconomic Status versus Tumor Biology

A variety of epidemiologic and statistical research tools have been utilized in the effort to disentangle the effects of African-American identity from the potentially confounding influences of socioeconomic disadvantage on breast cancer risk and outcome. Two sequential meta-analyses published in 2002²³ and 2006²⁴ pooled the data from publications on breast cancer survival that adjusted for socioeconomic status in African-American compared with White-American patients, with both demonstrating that African-American identity remained a statistically significant risk factor for adverse outcomes. The latter report featured data represented by >14,000 African-American and 76,000 White-American patients, revealing a statistically significant mortality hazard ratio of 1.27 (95% CI, 1.18–1.38).²⁴

Another approach to evaluating breast cancer disparities related to racial/ethnic identity involves the evaluation of data from clinical trials. The bedrock principle of the cancer clinical trials mechanism is that highest-level evidence regarding optimal oncology care is provided through monitoring outcomes in patients receiving tightly regulated and standardized treatment regimens. Albain et al²⁵ attempted to address the question of whether equal treatment in the context of clinical trial participation resulted in equal outcomes (regardless of racial/ethnic identity) by evaluating data from prospective, randomized trials from the Southwest Oncology Group. This robust pooled analysis of data from nearly 20,000 cancer patients (approximately 12% African Americans) treated in 35 trials between 1974 and 2001 found that racial/ethnic identity did not affect outcomes in the majority of malignancies, but results differed in the hormonally driven, sex-specific cancers. Outcome disparities related to African-American identity were observed in breast, prostate, and ovarian cancers, but not in lung or colon cancer, or in lymphoma, leukemia, or myeloma. Ten-year overall survival in premenopausal African-American women with early-stage breast cancer was 68% compared

with 77% in comparable patients with other racial/ethnic identities, and 52% versus 62%, respectively, in those with early-stage, postmenopausal breast cancer.²⁵

The Women's Health Initiative is a massive prospective study of postmenopausal women's health that includes data on the incidence of breast cancer among >150,000 participants. After a median follow-up of 6.3 years, nearly 4000 breast cancers were diagnosed, and among this entire cohort of carefully screened women, the African-American participants were nearly five times as likely as the White Americans to develop high-grade, receptor-negative breast cancers, and the group had a significantly higher mortality hazard ratio of 1.79 (95% CI, 1.05 to 3.05).²⁶ The expression of the HER2/*Neu* biomarker was not included in this analysis.

The approximately twofold increased risk for TNBC in African-American women has been confirmed by population-based incidence rates regionally²⁷ as well as nationally,³ and across all age intervals. Compared with non-TNBC, triple-negative disease has been confirmed to be an adverse prognostic feature in African-American patients.²⁸ It is also noteworthy that data from the Surveillance, Epidemiology, and End Results Program linked to the American Community Survey failed to demonstrate an association between TNBC and socioeconomic status.²⁹

International patterns of breast cancer biomarker expression have prompted additional hypothesis-generating observations regarding a possible hereditary link between African ancestry and the triple-negative phenotype. Population-based data on breast cancer burden in Africa are sparse, but several studies have revealed notably higher frequencies of estrogen receptor-negative disease and TNBC among African patients.^{6,30,31} The highest prevalence rates are observed in western, sub-Saharan Africa, where triple-negative disease has accounted for 27% to 61% of cases.^{32–37} In contrast, the frequency of TNBC is <20% in many studies in patients from northern and eastern Africa.^{5,38–41} The colonial-era trans-Atlantic slave trade resulted in the forced migration of Africans from the continent's gold coast to the Americas, resulting in shared ancestry between African Americans and western, sub-Saharan Africans⁴² and potentially explaining similarities in breast cancer patterns in these two population subsets.

Biology and Genetics of TNBC

TNBCs have morphologic growth patterns illustrating heterogeneity and highlighting distinctive biological features, clinical presentations, responses to therapy, and outcomes. There are several morphologic variants, with the high histologic grade invasive ductal carcinoma being the most common, associated with high mitotic rates, central necrotic or fibrotic zones, pushing borders, and conspicuous lymphocytic infiltrate. Other morphologies that are typically triple negative include medullary, secretory, and apocrine carcinomas—all of which have relatively more favorable

biologic behaviors—and metaplastic carcinomas, which tend to be biologically more aggressive. This heterogeneous morphologic spectrum of subtypes is further supported and defined by diverse genetic pathways. Lehmann et al⁴³ were among the early investigators identifying these triple-negative subtypes, and their efforts were based on analyses of gene-expression profiles from 21 publicly available data sets that included 587 TNBC cases. They identified six different subtypes—two basal-like subtypes, an immunomodulatory subtype, a mesenchymal subtype, a mesenchymal stem-like subtype, and a luminal androgen receptor subtype. Similarly, Burstein et al⁴⁴ identified four TNBC subtypes based on the gene-expression profiles of 198 cases from the Baylor College of Medicine (Houston, TX): i) a luminal androgen receptor subtype; ii) a mesenchymal subtype; iii) a basal-like immune-suppressed subtype; and iv) a basal-like immune-activated subtype. These different patterns have been shown to be associated with prognostic as well as predictive therapeutic value; the luminal androgen receptor subtype tends to respond poorly to neoadjuvant chemotherapy^{45,46} and may be amenable to endocrine manipulation through anti-androgen therapy. Unfortunately, however, neither of these data sets included meaningful samples of triple-negative tumors from women of African ancestry.

A few studies have provided limited but important findings with regard to gene-expression profiles of African-American breast cancer patients. Lindner et al⁴⁷ evaluated 136 tumors from the Yale TNBC cohort (including 50 African-American patients) and found basal-like subtypes to be more common among the African-American cases; they also reported differential activation of insulin-like growth factor 1 and a signature of breast cancer 1 susceptibility protein (BRCA1) deficiency in the African-American samples. Keenan et al⁴⁸ utilized The Cancer Genome Atlas to investigate exome sequencing in 663 White-American compared with 105 African-American cases, and gene-expression data in 711 White-American compared with 159 African-American cases. The African Americans had more basal tumors overall, and within the triple-negative category they were also more likely to have the basal-like and mesenchymal triple-negative subtypes. Recently, Ademuyiwa et al⁴⁹ evaluated 1104 Cancer Genome Atlas breast cancers (including 178 triple-negative tumors) and similarly found the triple-negative phenotype as well as the basal subtype to be more frequent in African Americans compared with White Americans (33.3% vs 14.9% and 34.8% vs 16.1%, respectively). TNBC-specific subtyping was not reported, but these investigators did not identify significant differences in gene-expression patterns between African-American and White-American TNBC cases in the genes that were selected for analysis. Huo et al⁵⁰ also reported on the increased frequency of basal subtype tumors among African-American compared with White-American cases from The Cancer Genome Atlas, and their The Cancer Genome Atlas interrogation furthermore suggested that >40% of differences in frequencies of breast cancer subtypes

Table 1 Studies Reporting on the Landscape of Somatic Mutations in Breast Cancers of African-American and White-American Patients

Study	Cases studied	Selected findings
Martin et al ⁵¹	Baltimore, MD 18 AA (72% ER-negative) 17 WA (29% ER-negative)	<ul style="list-style-type: none"> • Prominent interferon signal in tumors of AA patients • Phosphoserine phosphatase-like expressed more highly in tumor epithelium and stroma of AA patients • Thymopoietin expressed more highly in stroma of AA patients • Chemokine ligands 10 and 11 expressed more strongly in tumor stroma of AA patients
Field et al ⁵²	Clinical Breast Care Project 26 AA (38% TNBC) 26 WA (35% TNBC)	<ul style="list-style-type: none"> • βB2-crystallin; lactotransferrin; and L-3-phosphoserine-phosphatase homologue expressed more strongly in AA patients
Grunda et al ⁵³	Birmingham, AL 11 AA (45% ER-negative) 11 WA (9% ER-negative)	<ul style="list-style-type: none"> • AA patients more likely to have aberrant G1/S cell-cycle regulatory genes • AA patients more likely to have decreased expression of cell adhesion genes • AA patients more likely to have low or no expression of ESR1, PR, c-ErbB2 and estrogen pathway genes
Stewart et al ⁵⁴	The Cancer Genome Atlas 53 AA (19% TNBC) 574 WA (12% TNBC)	<ul style="list-style-type: none"> • Increase in number of differentially expressed genes between AA and WA patients with each stage of tumor progression • Resistin (a gene that is linked to obesity, insulin resistance, and breast cancer) was expressed more than four times higher in AA cases, but was lowest in AA TNBC tumors • Increased expression of p53 and BRCA1 subnetwork components in AA tumors
Lindner et al ⁴⁷	Yale TNBC Cohort 50 AA 69 WA	<ul style="list-style-type: none"> • Major transcriptional signature of proliferation found to be up-regulated in AA cases • Differential activation of insulin-like growth factor 1 and a signature of BRCA1 deficiency in AA cases • TNBC subtyping revealed AA cases more likely to have basal subtype compared with WA cases
Kroenke et al ⁵⁵	Pathways and Life after Cancer Epidemiology Cohorts 128 AA (30% TNBC) 1176 WA (11% TNBC)	<ul style="list-style-type: none"> • PAM50 subtyping revealed increased frequency of basal subtype among AA compared with WA cases (41% vs 17%)
Sweeney et al ⁵⁶	Pathways and Life after Cancer Epidemiology Cohorts 115 AA* 913 WA* 12% of entire cohort with TNBC; frequencies not reported by race/ethnicity	<ul style="list-style-type: none"> • PAM50 subtyping revealed increased frequency of basal subtype among AA cases; odds ratio for having basal vs luminal A subtype (with WA as referent group) 4.38 (95% CI, 2.29–8.39)
Keenan et al ⁴⁸	The Cancer Genome Atlas 159 AA (17% TNBC) 711 WA (8% TNBC)	<ul style="list-style-type: none"> • PAM50 subtyping revealed increased frequency of basal subtype in AA cases (39% vs 19%) and fewer luminal A tumors (17% vs 35%) • TNBC subtyping revealed increased frequency of basal-like 1 and mesenchymal stem-like tumors in AA vs WA cases; no LAR tumors in the AA cases
Ademuyiwa et al ⁴⁹	The Cancer Genome Atlas 183 AA (33% TNBC) 764 WA (15% TNBC)	<ul style="list-style-type: none"> • PAM50 subtyping revealed increased frequency of basal subtype in AA cases (35% vs 16%) • Median counts of somatic tumor mutations higher in AA vs WA cases overall • No significant differences in median mutation counts for AA TNBC compared with WA TNBC cases
Huo et al ⁵⁰	The Cancer Genome Atlas 154 AA 776 WA	<ul style="list-style-type: none"> • PAM50 subtyping revealed increased frequency of basal subtype in AA cases (36% vs 15%; $P < 0.0001$) • AA cases with more TP53 and fewer <i>PIK3CA</i> mutations compared with WA [52% vs 31% ($P = 2.5 \times 10^{-5}$) and 24% vs 36%; ($P = 0.012$), respectively]; African ancestry vs European ancestry cases defined by Ancestry Informative Markers

*Estimated from percentage distributions provided.

AA, African American; BRCA, breast cancer susceptibility protein; c-ErbB2, receptor tyrosine-protein kinase erbB-2; ER, estrogen receptor; ESR1, estrogen receptor 1; LAR, leukocyte common antigen related; PAM50, Prosigna Breast Cancer Prognostic Gene Signature Assay (NanoString Technologies, Inc, Seattle, WA); PR, progesterone receptor; TNBC, triple-negative breast cancer; WA, white American.

may be explained by genetic variants. [Table 1](#) summarizes some key findings from gene-expression studies reported on cases of breast cancer in African-American compared with White-American patients.^{51–56}

The disproportionately high rates of triple-negative and basal breast cancer subtypes among African-American patients undoubtedly contributes to outcome disparities. Available data thus far are inconsistent in determining whether African-American identity and/or African ancestry remains a significant risk factor for adverse breast cancer outcomes within the subsets of patients documented as having these biologically aggressive (and often overlapping) patterns of disease.^{57–60} TNBC subtyping in patients with African ancestry may further inform the discussion of whether disparities in breast cancer outcomes persist after accounting for conventional breast cancer phenotype. Furthermore, additional studies of germline genetics correlating African ancestry with breast cancer risk are also imperative in answering the underlying question of why these virulent patterns of breast cancer are more common in this population subset.

Breast Cancer Stem Cells and TNBC

The hallmark feature of stem cells is the ability to self-renew and to produce diverse progeny. Mammary stem cells (MaSCs) were identified several decades ago and are distinguished by the capacity to regenerate a fully developed mammary gland after individual implantation of these multipotent cells into specially prepared recipient mice.^{61,62} Theoretically, any cell produced along the pathway from the parent MaSC through a multipotent progenitor, to a committed progenitor, and ultimately to a differentiated mammary gland cell can experience some aberrant oncogenic activity and transform into a mammary cancer stem cell, hereafter called a BCSC. Differentiated epithelial cells are expected to interact with their microenvironment in a well-regulated fashion, but they will occasionally be triggered to assume mesenchymal

properties featuring the capacity to migrate and avoid apoptosis. This process is called *epithelial-to-mesenchymal transition*, and *plasticity* refers to the ability of cells to transition between these patterns. The stem cell theory therefore describes both normal mammary tissue and malignancies as featuring a hierarchical structure, with the noncancerous and cancerous stem cells both located at the apices of their respective organizations, but with the normal MaSCs producing differentiated progeny that include luminal (ductal and lobular-alveolar) as well as myoepithelial cells; in contrast, the BCSCs (alias breast cancer–initiating cells) produce neoplastic progeny that possess varying degrees of de-differentiation and tumor-initiating traits. The MaSCs and BCSCs are the only components that have the abilities to both self-renew and regenerate the full spectrum of diverse tissues within the overall mammary gland or mammary cancer, respectively. A detailed discussion of these complex processes is beyond the scope of this article, but some of the key elements are depicted in [Figure 1](#) and have been explored more comprehensively by others.^{63–69}

As described in the previous paragraph, BCSCs represent the subpopulation of tumor cells that can self-renew and recapitulate the parent tumor (as demonstrated by xenotransplantation studies), whereas the cancer cells lacking the BCSC properties do not have this capacity. The latter non-BCSCs tend to comprise the bulk of the detected tumor and its metastases, whereas the minority-subpopulation BCSCs account for the metastatic virulence. Conventional (non-targeted) chemotherapy regimens typically focus on exterminating the hyperproliferative and abundant non-BCSC population. Efforts to identify MaSCs as well as BCSCs, to correlate breast cancer phenotypes with BCSC activity, and to develop therapies that disrupt the BCSC metastatic progression therefore represent exciting prospects in precision-medicine research.^{63,70}

Reliable, accurate strategies to identify and isolate BCSCs have been elusive. Flow cytometry and fluorescence-activated cell sorting to detect surface-marker signatures $CD44^{+}/CD24^{low/-}$ and epithelial cell adhesion

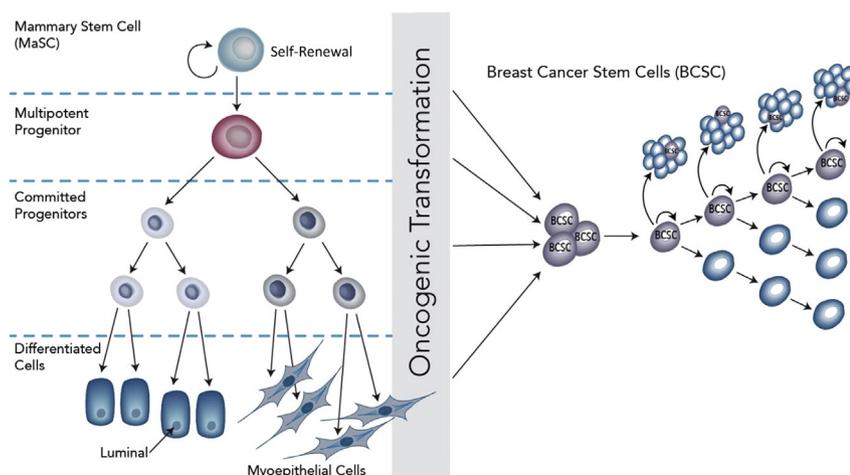


Figure 1 Breast cancer arises from cells harboring dysregulated self-renewal capability resulting from tumorigenic mutations and/or epigenetic modifications. Mammary stem cells and breast cancer stem cells both have the dual abilities to self-renew and differentiate. In the breast cancer stem cells, the capacity for self-renewal enables tumor initiation and growth; the capacity for differentiation allows for generating the bulk tumor cells and tumor cell heterogeneity. Modified and adapted with permission from Lin et al⁶³ and Reya et al.⁶⁹

molecule/epithelial-specific antigen positivity have been among the most popular strategies. The Aldefluor assay (Stem Cell Technologies, Inc., Vancouver, BC, Canada) is also widely used to detect intracellular aldehyde dehydrogenase (ALDH) activity. Immunohistochemistry (IHC) analysis to detect these markers has also been utilized. These same proteins have been considered as putative markers of the MaSC in normal breast tissue. Although the prognostic value of these markers has not been definitively determined, findings from several studies have shown that tumors with higher proportions of cancerous stem cells indicated by any of these markers are associated with a worse prognosis.^{63,71–73}

In malignant breast tissue, studies have indicated minimal overlap between the CD44⁺/CD24^{low/-} and ALDH populations (suggesting that they represent distinct and separate BCSCs) but tumors that are enriched with both BCSC types are especially virulent. The CD44⁺/CD24^{low/-} cells have been associated with an enhanced capacity for detaching from the primary tumor and metastasizing (supported by a dominant epithelial-to-mesenchymal transition gene-expression profile), whereas the ALDH BCSCs appear to feature a stronger predisposition for replicating and thereby possibly yielding more of the non-BCSC progeny that account for the bulk of the tumor (supported by their dominant mesenchymal-to-epithelial transition gene-expression profile).^{63,68,74}

It is unknown at present whether a direct link exists between specific BCSCs and individual breast cancer subtypes. The CD44⁺/CD24^{low/-} and the ALDH BCSCs have both been correlated with high-grade, basal-like, and HER2/*Neu*-overexpressing tumors.^{10,63,75–78} Another potentially therapeutically relevant theory is that HER2/*Neu*-related oncogenic activity in BCSCs may be independent of HER2/*Neu* expression as identified by standard IHC analysis, thereby explaining why some patients with HER2/*Neu*-negative breast cancers derive an outcome advantage from targeted anti-HER2/*Neu* therapy.^{79,80}

Breast Cancer Stem Cells and African Ancestry

Triple-negative and basal subtype breast cancers are more common among African-American compared with White-American women, and breast cancer mortality rates are higher among African Americans. Preliminary data suggest that basal breast cancers are enriched with populations of cells that feature BCSC markers, and this feature may account for the metastatic potential of aggressive breast cancer subtypes. Very little is known regarding BCSC patterns in women of African ancestry, as most stem cell research in humans has been based on specimens from White-American, European, and Asian patient populations.

Nakshatri et al¹³ evaluated the distribution of MaSC phenotypes (defined by cell surface markers assessed with flow cytometry) in African-American and White-American women that donated healthy breast tissue specimens to the Susan G.

Komen Tissue Bank (Indianapolis, IN). These investigators found significant elevations in CD44⁺/CD24⁻ and endothelial protein C receptor—positive/epithelial cell adhesion molecule—negative multipotent stem cells in the tissues from African-American compared with White-American donors.

The candidate BCSC marker ALDH1 has been evaluated by a few different data sets of breast tumors in women of African ancestry, with most of these studies using IHC analysis methodology. Although there is no standardized cut point for assigning ALDH1 positivity, most studies in White-American and European breast cancer patients report less than one-third of cases to have ALDH1 overexpression.^{11,71} Nalwoga et al¹² analyzed 192 breast cancers from the Makerere University College of Health Sciences (Kampala, Uganda) by IHC analysis applied to tissue microarrays and found ALDH1 expression in 48% of cases; ALDH1 expression was also associated with high-grade and triple-negative tumors. Schwartz et al¹¹ reported overexpression of ALDH1 in 42% and 17% of the stromal and epithelial compartments, respectively, from 104 Ghanaian breast cancer cases. These investigators also found notably higher expression of ALDH1 in TNBCs as well as in benign breast tissue from Ghanaian patients. An updated and expanded but unpublished series from this group found ALDH1 expression to be increased among specimens from African-American and Ghanaian breast cancer patients (32% and 36%, respectively) compared with White-American and Ethiopian patients (23% and 17%, respectively; $P = 0.007$).

The concept of assessing cancer stem cells as a factor in outcome disparities related to racial/ethnic identity is gaining traction in other, non-breast disease sites. Recent studies by Farhana et al⁸¹ and Goyal et al⁸² have proposed that increased cancer stem cell activity may explain the increase in colorectal cancer prevalence as well as mortality among African Americans compared with White Americans. Broadening the research opportunities related to stem cells and diverse patient populations even further, Chang et al⁸³ recently reported on the generation of xenofree human induced pluripotent stem cell lines from fibroblasts obtained from individuals representing White-American, African-American, Hispanic/Latino, and Asian backgrounds.

Conclusions

Achieving the full potential of precision medicine in cancer by delivering truly personalized care requires that all elements of the oncology pathway be addressed. This complex picture includes germline genetic patterns as well as somatic/tumor genetics. The stem cell model in mammary tissue as well as in breast cancers suggests that it is equally important to identify and characterize the subpopulation of tumor cells that is involved in metastatic virulence. Racial/ethnic identity can be correlated with germline

genetics/hereditary cancer susceptibility and tumor phenotype; it is therefore imperative that stem cell biology be explored in the context of patients of diverse racial and ethnic backgrounds. These issues are especially important in breast cancer, in which women of African ancestry are well known to experience higher mortality from breast cancer, and this disparity is at least partly explained by a disproportionate risk for triple-negative and basal breast cancer subtypes.

Acknowledgments

We thank Jack Butler and Kelly Comerford (Henry Ford Health System) for assistance with creating Figure 1.

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