

Health Disparities and Triple-Negative Breast Cancer in African American Women A Review

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IMPORTANCE Variation in cancer incidence and outcome has well-documented correlations with racial/ethnic identity. In the United States, the possible genetic and ancestral hereditary explanations for these associations are confounded by socioeconomic, cultural, and lifestyle patterns. Differences in the breast cancer burden of African American compared with European/white American women represent one of the most notable examples of disparities in oncology related to racial/ethnic identity. Elucidating the source of these associations is imperative in achieving the promise of the national Precision Medicine Initiative.

OBSERVATIONS Population-based breast cancer mortality rates have been higher for African American compared with white American women since the early 1980s, largely reflecting declines in mortality that have been disproportionately experienced among white American patients and at least partly explained by the advent of endocrine therapy that is less effective in African American women because of the higher prevalence of estrogen receptor-negative disease. The increased risk of triple-negative breast cancer in African American women as well as western, sub-Saharan African women compared with white American, European, and east African women furthermore suggests that selected genetic components of geographically defined African ancestry are associated with hereditary susceptibility for specific patterns of mammary carcinogenesis. Disentangling health care access barriers, as well as reproductive, lifestyle, and dietary factors from genetic contributions to breast cancer disparities remains challenging. Epigenetics and experiences of societal inequality (allostatic load) increase the complexity of studying breast cancer risk related to racial/ethnic identity.

CONCLUSIONS AND RELEVANCE Oncologic anthropology represents a transdisciplinary field of research that can combine the expertise of population geneticists, multispecialty oncologists, molecular epidemiologists, and behavioral scientists to eliminate breast cancer disparities related to racial/ethnic identity and advance knowledge related to the pathogenesis of triple-negative breast cancer.

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What Is Oncologic Anthropology?

The robust racial and ethnic diversity of the American population has been a source of tremendous strength as well sensitivity and tension dating back to colonial-era history. The oncology community faces unique challenges in addressing this diversity, since the cancer burden is well known to vary by racial/ethnic identity, and elucidating the cause of these associations will clearly be imperative in the national Precision Medicine Initiative. The concept of race implies identification based on ancestry and is therefore closely associated with population genetics. However, societal groupings and economic patterns that are highly correlated with race have led to the suggestion that racial identity in the United States is a sociopolitical construct.¹⁻³ Ethnic identity implies characterization based on culture. Although race and ethnicity are not interchangeable, they often feature common hereditary, dietary,

environmental, lifestyle, and socioeconomic conditions—all of which can influence the epidemiologic associations with cancer. The complex interplay of these factors is arguably most notable in breast cancer (BC), where differences in disease incidence and outcome are particularly striking between communities of individuals who self-identify as African American and Americans with predominantly European/white descent, often referred to as white Americans. Similarities in BC phenotypes among African American and western sub-Saharan African women contrasted against differences with east African women furthermore suggest that ancestral population migration patterns contribute to BC epidemiology.^{4,5} This review summarizes the socioeconomic and cultural context in which disparities arise; it also explores the expanding volume of studies correlating both germline and somatic BC-related genetics with geographically defined African ancestry. We introduce the

Table 1. Breast Cancer in African American and White American Women^{8,9}

Characteristic	African American	White American
Population-Based Incidence Rates, per 100 000		
Overall, age standardized	122.9	124.4
Age stratified, y		
35-39	70.6	59.9
40-44	118.2	122.2
45-49	180.4	188.1
50-54	231.6	220.3
55-59	270.7	260.4
60-64	332.0	332.4
65-69	399.5	428.7
Population-Based Mortality Rates, per 100 000		
Overall, age standardized, y	28.2	20.3
Age stratified		
35-39	10.2	5.8
40-44	22.1	11.5
45-49	30.7	18.3
50-54	47.3	27.3
55-59	57.4	36.6
60-64	71.3	49.2
65-69	80.4	62.2
Stage Distribution at Diagnosis, %		
Localized	53	64
Regional	35	28
Distant	8	5
Unknown	4	3
5-Year Cause-Specific Survival, %		
All stages	80	89
Localized	93	96
Regional	78	87
Distant	24	34
Population-Based Incidence Rates, TNBC	27.2	14.4

Abbreviation: TNBC, triple-negative breast cancer.

nomenclature *oncologic anthropology* to describe this transdisciplinary field of research.

Breast Cancer Incidence and Mortality Rates in African American and White American Women: Implications for Mammography Screening

The 2015 American Cancer Society review of trends in population-based BC incidence and mortality among African American compared with white American women featured data from the Surveillance, Epidemiology, and End Results (SEER) Program as well as the North American Association of Central Cancer Registries.⁶ Historically, incidence rates were parallel for African American and white American women, but with lower lifetime rates for African American women. However, during the most recent 5-year interval of data collection (2008 through 2012), the incidence of BC rose steadily for African American women (by 0.4% per year) while remaining stable for white American women, and the incidence rates then converged, with 2013 rates

of 122 per 100 000 for African American women and 124 per 100 000 for white American women.⁶⁻⁸ The median age at BC diagnosis for African American women is 58 years compared with 62 years for white American women,⁶ and population-based BC incidence rates for women younger than 40 to 44 years are higher among African American women⁷ (Table 1).

In contrast to these incidence trends, population-based BC mortality rates were comparable for African American and white American women until the early 1980s, at which time a mortality gap developed. This outcome disparity has increased over the past 30 years, and current BC mortality is 42% higher for African American compared with white American women.⁶ As presented in Table 1, the mortality disparity is present for all ages and stages at diagnosis.⁷ Advances in BC risk stratification by biomarker expression provide biologically plausible explanations for the observed mortality trends. The African American patients have an approximately 2-fold higher frequency as well as population-based incidence rate of estrogen receptor (ER)-negative BC that has been documented during the past 2 decades and persists after adjustments for age and stage at diagnosis.¹⁰ Tamoxifen citrate was approved by the US Food and Drug Administration as adjuvant BC systemic therapy in 1977; it is likely that the resulting population-based reductions in BC mortality did not become apparent until the early 1980s. Since African American patients with BC benefit less from adjuvant endocrine therapy, the mortality gap appearing in this time frame may reflect race-related differences in ER-positive disease.¹¹

The terminology *triple-negative breast cancer* (TNBC) identifies invasive tumors that are negative for ER as well as the progesterone receptor (PR) and *ERBB2*. Approximately 80% of TNBC cases have the gene expression profile of the biologically aggressive basal BC intrinsic subtype, and patients with TNBC by definition are not candidates for endocrine therapy or treatment with targeted anti-*ERBB2* agents. Triple-negative BC is therefore an adverse prognostic feature and indicates the likelihood of more limited systemic therapeutic options. Triple-negative BC is also a marker of hereditary susceptibility for BC, regardless of family history; it occurs in a disproportionately high rate among younger women; it is more likely to metastasize to the brain compared with non-TNBC; and, although TNBC responds briskly to neoadjuvant chemotherapy, patients who do not achieve a complete response have a disproportionately high relapse and mortality rate (the "TNBC paradox").¹²

The unique epidemiology and biology of TNBC have resulted in substantial research attention, despite the fact that, overall, only 15% of BCs in the United States have the triple-negative phenotype. In contrast, a landmark report by Carey et al¹³ from the Carolina Breast Cancer Study found that 39% of tumors diagnosed in premenopausal African American patients were TNBC, prompting questions regarding the role of TNBC in BC disparities. Two-fold higher population-based incidence rates of TNBC in African American compared with white American women in all age categories have since been confirmed by others,^{9,14} including the 2015 *Annual Report to the Nation on the Status of Cancer*,⁹ documenting TNBC incidence rates of 27.2 per 100 000 and 14.4 per 100 000 women, respectively. Akinyemiju et al¹⁵ demonstrated from a SEER-based analysis that, as expected, African American patients with TNBC have a worse outcome compared with African American patients with non-TNBC. It is therefore likely that rising BC incidence rates in African American women coupled with the increased risk for TNBC

contribute to the progressively widening BC mortality gap between African American and white American women.⁶

The younger age distribution for BC in African American compared with white American women, as well as the increased risk of TNBC, which is observed in younger as well as older patients, is particularly relevant in the context of mammography screening guidelines. Current screening mammography utilization rates are similar, approximately 81% for African American and approximately 76% for white American women.⁶ The US Preventive Services Task Force recommends that average-risk American women initiate screening mammography at age 50 years. Initiation of screening mammography at 40 years had been the US Preventive Services Task Force recommendation until 2009, and the National Comprehensive Cancer Network continues to recommend initiation at 40 years. The American Cancer Society recommends the availability of screening mammography at 40 years, but suggests that initiation is imperative by 45 years. Screening mammography proponents and disparities researchers express concern that delayed initiation of mammographic screening could have a disproportionately adverse effect on the BC burden of African American women, thereby worsening the mortality disparity.¹⁶

Influence of Socioeconomic Disparities and Race as a Sociopolitical Construct on Breast Cancer Outcome

Breast cancer outcome disparities between African American women and white American women can be attributed to socioeconomic disadvantages that are more prevalent in the African American community. Recent data from the US Census Bureau reveal that poverty rates are more than twice as high in African American compared with white American communities (25.8% vs 11.6%).¹⁷ Furthermore, although overall uninsured rates have declined from 16.0% in 2010 to 11.5% in 2014, disparities in this socioeconomic status metric persist, with 11.9% of the African American population being uninsured compared with 8.2% of the white American population.¹⁸ Differences in BC stage distributions support the theory that mortality disparities are mediated at least in part by diagnostic and treatment delays associated with health care access barriers. African American patients with BC are diagnosed with regional disease in approximately one-third of the cases compared with one-quarter of white American patients, and localized disease is detected in approximately one-half vs two-thirds, respectively.⁷ Ward et al¹⁹ conducted an analysis of 5-year survival from any cancer diagnosis and found that the poorest communities within each racial/ethnic population subset had worse outcomes, confirming that poverty is an adverse prognostic factor regardless of racial/ethnic identity. Correlations between minority racial identity and socioeconomic status have prompted many public health experts to suggest that race is a sociopolitical construct rather than a true biological or genetic characteristic.¹⁻³

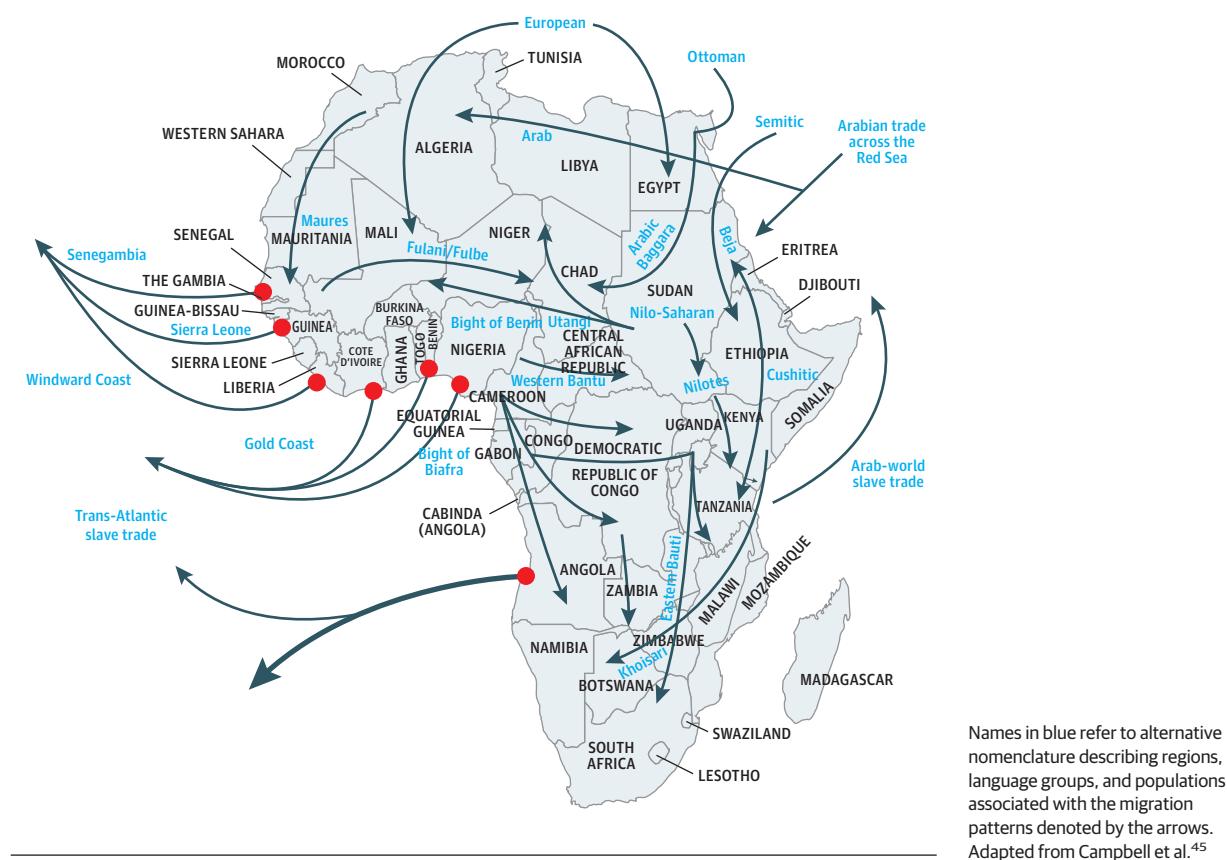
Socioeconomic disadvantages are also reflected by differences in the patterns of cancer care delivered. Inequities have been reported in the frequency of African American patients utilizing each component of comprehensive, multidisciplinary BC care.²⁰ Studies have demonstrated disproportionately low use of guideline-concordant locoregional treatment, adjuvant radiotherapy, lymphatic mapping with sentinel lymph node biopsy, adjuvant systemic therapy, breast reconstruction, and clinical trial participation among African American patients. Tammemagi et al²¹

found that comorbidities (eg, diabetes and hypertension) were important factors in survival differences between African American and white American patients. Hershman et al²² furthermore demonstrated that ethnicity-associated neutropenia (the lower average but clinically irrelevant baseline white blood cell counts seen in African American patients) was significantly associated with inadequate delivery of adjuvant BC chemotherapy in African American patients. Treatment disparities can result from African American patients being more likely to receive care in underresourced public and safety-net hospitals. Flawed communication between patients and health care professionals and biases leading to discriminatory practices in the health care system may also contribute to disparate outcomes.

In contrast to data suggesting that African American identity is a sociopolitical construct acting as a feature that confounds the true causal association between financial hardship and BC outcome disadvantages, other lines of evidence indicate that African American identity is independently associated with outcome. A 2006 meta-analysis of socioeconomic status-adjusted BC survival among more than 14 000 African American patients compared with more than 76 000 white American patients revealed that African American identity was associated with a statistically significant nearly 30% higher mortality hazard.²³ The standardized care delivered through clinical trial participation theoretically represents an effective strategy for disentangling race/ethnic identity from socioeconomic status in oncology outcomes. Nonetheless, a pooled analysis of Southwest Oncology Group adjuvant therapy trials²⁴ found that equal treatments delivered in the context of these clinical trials resulted in equal outcomes, except for hormonally driven diseases, such as breast and prostate cancer, where African American patients had persistent survival disadvantages.

Several features characterizing differences in the BC burden of African American compared with white American population subsets are unlikely to be explained by socioeconomic status, such as the younger age distribution, higher rates of high-grade pathologic findings, and the higher frequency of male BC in the African American population.^{5,6} As noted previously, the incidence of TNBC is also higher in African American women.^{9,14} Although it has been suggested that poverty might be a risk factor for ER-negative tumors and TNBC,^{2,25} a 2015 population-based study from the SEER program demonstrated that socioeconomic status was not associated with hormone receptor-negative tumors or TNBC.²⁶

Established BC risk factors may have a differential effect on phenotype. For example, multiparity tends to reduce the lifetime risk of ER-positive disease, but may increase the likelihood of TNBC.¹² However, international patterns of TNBC fail to consistently demonstrate comparable frequencies of TNBC among populations likely to have similar childbearing patterns.⁵ Lactation appears to protect against TNBC as well as non-TNBC, and utilization varies between population subsets; obesity has an additionally complex interplay with BC disparities.^{2,27} African American women appear to have a disproportionately increased likelihood of ER-negative disease and TNBC among cohorts facing increased BC risk related to hormone replacement therapy and prior benign fibrocystic and/or hyperproliferative breast biopsies.^{28,29} Further research is warranted regarding correlations between reproductive factors and TNBC in women with African ancestry.

Figure 1. The African Diaspora—Population Migration Patterns

Associations between racial/ethnic identity, socioeconomic status, and BC burden are clearly complex. Compounding these interactions is a growing body of literature demonstrating that lifetime stresses related to both racial/ethnic identity and poverty may influence tumor biology. Williams et al³ recently conducted a comprehensive review of these issues, including a provocative discussion of allostatic load, which refers to the biological dysregulation that affects multiple organ systems as a consequence of cumulative lifetime stresses. Poverty and exposure to racial, residential, and/or occupational discrimination contribute to these stresses, prompting speculation that allostatic load may be related to the epidemiology of BC.

Breast cancer disparities may also be mediated by the influence of epigenetics, where an individual's genes are manipulated by environmental factors without affecting the actual DNA sequence. For example, methylation and histone modification of germline DNA can alter gene expression and subsequent BC risk. Studies have revealed that epigenetic patterns vary by racial/ethnic identity, racial admixture, socioeconomic status, and stress pathways.^{3,30}

African Ancestry, Population Genetics, and TNBC

The human genome is a vast collection of genetic material: more than 3 billion bases of DNA and 25 000 to 30 000 protein-coding genes. Although any 2 randomly selected individuals are expected to share 99.9% identical DNA, the remaining 0.1% clearly accounts

for tremendous heterogeneity across several domains of the human experience, including disease risk.³¹ Hereditary susceptibility for BC through generational passage of mutations in genes, such as *BRCA1* and *BRCA2*, is well documented, and selected (founder) mutations cluster within specific communities of shared ancestral heritage. Founder mutations of *BRCA* associated with Ashkenazi Jewish background are prominent examples, but many others exist.³² Furthermore, the TNBC phenotype itself is associated with an increased risk for harboring a *BRCA1* mutation, independent of family history. Founder mutations of *BRCA* have been identified among African American and Bahamian Caribbean individuals,^{33,34} and a study from Nigeria³⁵ reported an elevated frequency of *BRCA1* and *BRCA2* mutations (7.1% and 3.9%, respectively) among a population of Nigerian patients with BC, unselected by age, family history, or BC phenotype. A study from South Africa confirmed an association between TNBC and *BRCA* mutation carrier status in black as well as white South Africans.³⁶ However, the full extent to which as yet uncharacterized founder mutations in the *BRCA* genes or in other genes associated with BC pathways might contribute to the increased risk of TNBC in the African American population remains unclear.

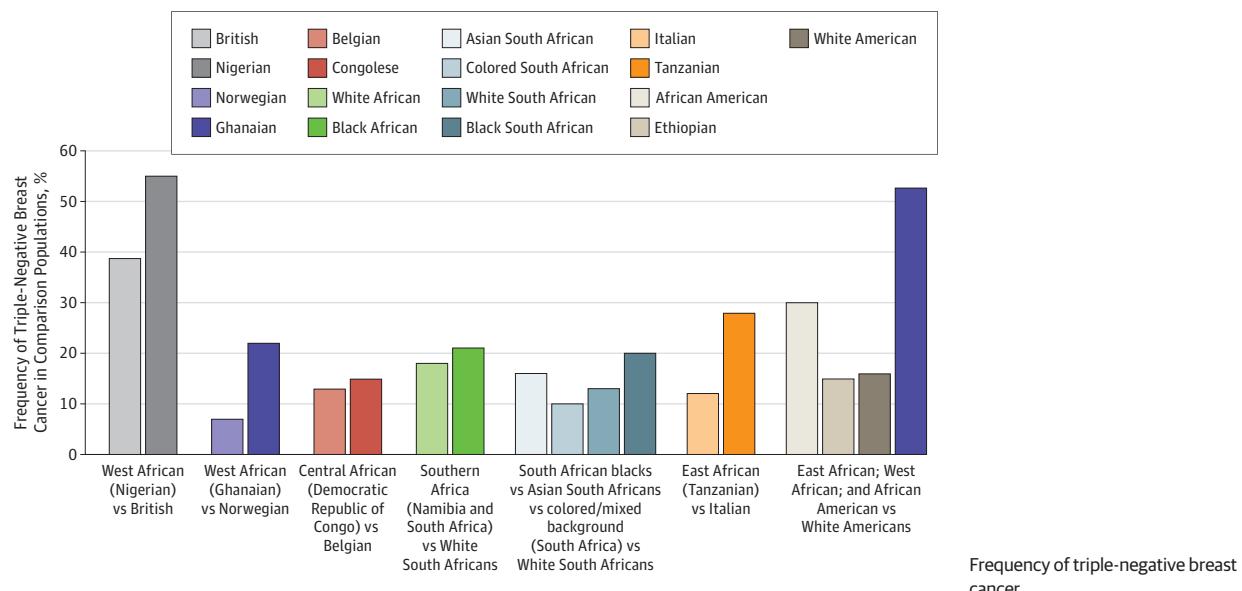
Americans in the contemporary United States represent genetic admixtures from several ancestral populations, including Native Americans predating the colonial era, European settlers, and Africans who arrived largely through forced migration from the trans-Atlantic slave trade. African American identity through

Figure 2. Triple-Negative Breast Cancer in Diverse Populations

A Studies comparing breast cancer phenotype frequencies in internationally diverse patients, including African comparison populations

Source	African Ancestry Comparison Population/Region	Non-African Ancestry Comparison Population
Agboola, ⁴⁷ 2014	West African (Nigerian)	United Kingdom British
Adjei et al, ⁴⁸ 2014	West African (Ghanaian)	Norwegian
Luyeye Mvila, ⁴⁹ 2015	Central African (Democratic Republic of Congo)	Belgian
Dickens et al, ⁵⁰ 2014	Southern African (Namibia and South Africa)	White South Africans
McCormack et al, ⁵¹ 2013	Southern African blacks and colored/mixed background (South Africa)	White South Africans
Amadori et al, ⁵² 2014	East African (Tanzanian)	Italian
Jiagge et al, ⁴ 2016	East African; West African; and African American	White American

B Frequency of triple-negative breast cancer in African vs non-African patient populations



self-report therefore represents a combination of true African ancestral heritage and an individual's societal and community ties. Geographically defined ancestry can be quantified through ancestry informative marker genotyping data. The quantified extent of African ancestry varies substantially among individuals who self-report as being African American. Studies of African American communities throughout the United States estimate that contributions from European ancestry range from 3.5% in the relatively isolated Gullah-speaking South Carolina Sea Islanders to 35% in Seattle, Washington.³¹

The African American community is a minority, accounting for approximately 12% of the US population. Studies of BC genetics related to African ancestry therefore face an immediate disadvantage in terms of sample sizes—a challenge that is magnified by genetic admixture. Single-institution studies and even multicenter partnerships are often underpowered to determine biologically significant genetic features. Nonetheless, a report from the Black Women's Health Study successfully correlated a quantified extent of global African ancestry with a TNBC-associated single-nucleotide polymorphism.³⁷

The African American Breast Cancer Epidemiology and Risk (AMBER) Consortium was established as a strategy to overcome

the sample size obstacle described above.³⁸ The AMBER Consortium is a collaboration of the 4 largest programs of BC research involving African American women: the Carolina Breast Cancer Study, the Women's Circle of Health Study, the Black Women's Health Study, and the Multiethnic Cohort Study. This powerful data set includes epidemiologic data and tissue specimens representing several thousand African American patients with BC and controls. AMBER has published extensively on BC risk factors, demonstrating that obesity, reproductive history, and vitamin D metabolism may have significant interactions related to BC risk in African American women. The AMBER Consortium completed an exome-wide analysis of rare variants in 3629 BC cases in African American individuals (approximately one-third ER-negative) compared with 4658 controls and identified a novel gene (*FBXL22*) as well as a gene previously identified in genome-wide association studies of European ancestry populations (*PDE4D*) as being associated with ER-negative tumors and TNBC.³⁹

The AMBER Consortium investigators collaborated with the Genome-Wide Association Study of Breast Cancer in the African Diaspora—the ROOT Study and the African American Breast Cancer Consortium, with the identification of 3q26.21 as a novel susceptibility locus for ER-negative BC among African American

Table 2. Reported Frequencies of ERN or TNBC in Africa

Region, Source	Country	Phenotype Reported	Frequency, %
EastAfrica			
Trinkaus et al, ⁵³ 2011	Kenya	Basal-like (TNBC and CK 5/6 and/or EGFR)	23
Bird et al, ⁵⁴ 2008	Kenya	TNBC	44
Nyagol et al, ⁵⁵ 2006	Kenya	TNBC	28
Nalwoga et al, ⁵⁶ 2007	Uganda	Basal-like (TNBC and CK 5/6)	34
Roy and Othieno, ⁵⁷ 2011	Uganda	TNBC	36
Mbonde et al, ⁵⁸ 2000	Tanzania	ERN	67
Burson et al, ⁵⁹ 2010	Tanzania	ERN	49
Kantelhardt et al, ⁴³ 2014	Ethiopia	ERN	35
Sayed et al, ⁶⁰ 2014	Kenya	TNBC	20
Galukande et al, ⁶¹ 2014	Uganda	TNBC	34
Rambau et al, ⁶² 2014	Tanzania	TNBC	38
North Africa			
Fourati et al, ⁶³ 2014	Tunisia	TNBC	23
Rais et al, ⁶⁴ 2012	Morocco	TNBC	17
Bennis et al, ⁶⁵ 2012	Morocco	Basal-like (TNBC and CK 5/6)	13
El-Hawary et al, ⁶⁶ 2012	Egypt	TNBC	29
Salthia et al, ⁶⁷ 2011	Egypt	Basal-like (TNBC and CK 5/6)	11
Cherbal et al, ⁶⁸ 2015	Algeria	TNBC	20
Aiad et al, ⁶⁹ 2014	Egypt	TNBC	8
West Africa			
Huo et al, ⁷⁰ 2009	Nigeria, Senegal	Basal-like (TNBC and CK 5/6)	27
Ly et al, ⁷¹ 2012	Mali	TNBC	46
Der et al, ⁷² 2015	Ghana	TNBC	58
Ohene-Yeboah and Adjei, ⁷³ 2012	Ghana	TNBC	43
Nwafor and Keshinro, ⁷⁴ 2015	Nigeria	TNBC	29
Proctor et al, ⁷⁵ 2015	Ghana	TNBC	61

Abbreviations: CK, cytokeratin; EGFR, epidermal growth factor receptor; ERN, estrogen receptor-negative; TNBC, triple-negative breast cancer.

women.⁴⁰ Most recently, a consortium of 18 study cohorts has been funded by the National Institutes of Health to pool resources as the Breast Cancer Genetic Study in African-Ancestry Populations, representing the largest study to date of BC in African American women.⁴¹

Studies of BC among international populations with African heritage have strengthened arguments that geographically defined ancestry influences the risk of TNBC. Accurate population-based data on BC in African countries are sparse, but the BC burden appears to be rising.⁴² Immunohistochemistry resources are limited in the low- and middle-income countries of Africa, and data on biomarker expression are often unavailable. However, investigators from various sites have reported elevated TNBC frequencies in comparison with the 15% prevalence observed in women of European ancestry, ranging from 23% to 82% of all cases.^{5,42}

Deeper probing into the BC burden of Africa, stratified by phenotype as well as region, reveals intriguing and hypothesis-generating patterns. Most studies demonstrating higher frequencies of TNBC in Africa have represented western sub-Saharan Africa with less known about BC in east Africans. However, low frequencies of ER-negative BC have been reported in Ethiopia⁴³ and in Ethiopian patients with BC residing in the United States.⁴⁴ Jiagge et al⁴ recently published the first direct comparison of African American, white American, Ghanaian/West African and

Ethiopian/East African patients with BC. This study found TNBC in 53.2% of Ghanaians and 29.8% of African Americans; the frequency of TNBC was similarly low among white Americans and Ethiopians, at 15.5% and 15.0% respectively ($P < .0001$). Population migration patterns may explain these findings (Figure 1). The European-controlled trans-Atlantic slave trade transported West Africans to North America. In contrast, the slave trade from east Africa was largely controlled by Arab traders, with forced migration to the Mideast and Asia.⁴⁵ African American women therefore are more likely to have shared ancestry with west Africans than east Africans, and this is confirmed by ancestry informative marker genotyping.⁴⁶ Figure 2 summarizes results from studies evaluating TNBC in African vs non-African ancestry populations, revealing that increased TNBC frequencies are generally seen when west African countries comprise the comparison populations.^{4,47-52} Table 2 reveals TNBC frequencies by country as well as region, also demonstrating that western sub-Saharan Africa is the site of increased TNBC prevalence. Regions of Africa with stronger ancestral ties to east Africa (eg, central and south Africa) tend to have relatively lower TNBC frequencies.

The increased frequency of TNBC among women with western sub-Saharan African ancestry becomes particularly relevant as advances are made in the gene expression technology of precision medicine and the heterogeneity of TNBC becomes apparent. Gene expression profiling indicates that several distinct TNBC

subtypes exist, characterized by different prognostic and treatment-predictive profiles.^{76,77} For example, the luminal androgen receptor subtype is less likely to respond to neoadjuvant chemotherapy but may be a candidate for targeted therapy with antiandrogenic agents, such as bicaludamide.¹² Unfortunately, however, few patients with African ancestry contributed to the landmark studies defining TNBC subtypes. We therefore do not know whether the TNBC subtypes of women with European and Asian heritage represent the same TNBC patterns of women with African ancestry.

A recent analysis of The Cancer Genome Atlas compared the genomic landscape of breast tumors from 159 African American and 711 white American women, finding significantly more intratumoral genetic heterogeneity and basal gene expression among African American cases. Subtyping of TNBC furthermore identified no luminal androgen receptor tumors among the African American women, but African American women were more likely to have basal-like 1 and mesenchymal stem cell-like tumors.⁷⁸ An earlier and smaller gene expression study also demonstrated an increased frequency of the basal subtype in African American patients with TNBC.⁷⁹ International collaborative partnerships, such as the Henry Ford Health System International Center for the Study of Breast Cancer Subtypes, have promising research under way to characterize germline as well as somatic

tumors among women with African ancestry throughout the United States and Africa.^{4,80}

Conclusions

Understanding cancer variations associated with racial/ethnic identity requires a transdisciplinary approach that we describe as oncologic anthropology, and this effort is integral to the overarching goals of precision medicine. Many questions remain unanswered regarding the epidemiology of breast cancer in individuals who self-identify as African American or white American; explanations for these differences involve disparities in our health care delivery system as well as race- and ethnicity-related variation in breast tumor biology and genetics. The definitions of race and ethnicity are in transition as patterns of genetic admixture and social groupings evolve and the genotyping technologies that allow us to quantify ancestral heritage advance. It is clear that international collaborations between social scientists, population geneticists, translational oncologists, clinicians, and community-based health care advocates are essential as we strive to eliminate breast cancer outcome disparities and maximize the benefits of personalized therapy. Oncologic anthropology represents a unified, global research effort that will be vital in 21st century medicine.

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REFERENCES

- Freeman HP. Commentary on the meaning of race in science and society. *Cancer Epidemiol Biomarkers Prev*. 2003;12(3):232s-236s.
- Brawley OW. Health disparities in breast cancer. *Obstet Gynecol Clin North Am*. 2013;40(3):513-523.
- Williams DR, Mohammed SA, Shields AE. Understanding and effectively addressing breast cancer in African American women: unpacking the social context. *Cancer*. 2016;122(14):2138-2149.
- Jiagge E, Jibril AS, Chitale D, et al. Comparative analysis of breast cancer phenotypes in African American, white American, and west versus east African patients: correlation between African ancestry and triple-negative breast cancer. *Ann Surg Oncol*. 2016;23(12):3843-3849.
- Newman LA. Disparities in breast cancer and African ancestry: a global perspective. *Breast J*. 2015;21(2):133-139.
- DeSantis CE, Fedewa SA, Goding Sauer A, Kramer JL, Smith RA, Jemal A. Breast cancer statistics, 2015: convergence of incidence rates between black and white women. *CA Cancer J Clin*. 2016;66(1):31-42.
- DeSantis CE, Siegel RL, Sauer AG, et al. Cancer statistics for African Americans, 2016: Progress and opportunities in reducing racial disparities. *CA Cancer J Clin*. 2016;66(4):290-308.
- US Cancer Statistics Working Group. United States Cancer Statistics: 1999-2013 incidence and mortality web-based report. Atlanta: US Dept of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. <http://www.cdc.gov/uscs>. Published 2016. Accessed September 6, 2016.
- Kohler BA, Sherman RL, Howlader N, et al. Annual report to the nation on the status of cancer, 1975-2011, featuring incidence of breast cancer subtypes by race/ethnicity, poverty, and state. *J Natl Cancer Inst*. 2015;107(6):djv048.
- Anderson WF, Chatterjee N, Eshler WB, Brawley OW. Estrogen receptor breast cancer phenotypes in the Surveillance, Epidemiology, and End Results database. *Breast Cancer Res Treat*. 2002;76(1):27-36.
- Newman LA. Parsing the etiology of breast cancer disparities. *J Clin Oncol*. 2016;34(9):1013-1014.
- Newman LA, Reis-Filho JS, Morrow M, Carey LA, King TA. The 2014 Society of Surgical Oncology Susan G. Komen for the Cure Symposium: triple-negative breast cancer. *Ann Surg Oncol*. 2015;22(3):874-882.
- Carey LA, Perou CM, Livasy CA, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. *JAMA*. 2006;295(21):2492-2502.
- Amirkia KC, Mills P, Bush J, Newman LA. Higher population-based incidence rates of triple-negative breast cancer among young African-American women: implications for breast cancer screening recommendations. *Cancer*. 2011;117(12):2747-2753.
- Akinyemiju T, Moore JX, Altekreste SF. Breast cancer survival in African-American women by hormone receptor subtypes. *Breast Cancer Res Treat*. 2015;153(1):211-218.
- Martin N, Wingfield J. USPSTF screening recommendations for breast cancer: the potential impact on the African American community. *J Health Care Poor Underserved*. 2012;23(2)(suppl):91-97.
- Macartney S, Bishaw A, Fontenot K. Poverty rates for selected detailed race and Hispanic groups by state and place: 2007-2011; American Community Survey Briefs. American Community Series Brief/11-17. US Department of Commerce, Economics and Statistics Administration. US Census

- Bureau. <http://www.census.gov/prod/2013pubs/acsbr11-17.pdf>. Published February 2013. Accessed March 3, 2017.
- 18.** Ward BW, Clarke TC, Freeman GJ, Schiller JS. Early release of selected estimates based on data from the 2014 National Health Interview Survey. <https://www.cdc.gov/nchs/data/nhis/earlyrelease/earlyrelease201506.pdf>. Released June 2015. Accessed March 3, 2017.
- 19.** Ward E, Jemal A, Cokkinides V, et al. Cancer disparities by race/ethnicity and socioeconomic status. *CA Cancer J Clin*. 2004;54(2):78-93.
- 20.** Shavers VL, Brown ML. Racial and ethnic disparities in the receipt of cancer treatment. *J Natl Cancer Inst*. 2002;94(5):334-357.
- 21.** Tammemagi CM, Nerenz D, Neslund-Dudas C, Feldkamp C, Nathanson D. Comorbidity and survival disparities among black and white patients with breast cancer. *JAMA*. 2005;294(14):1765-1772.
- 22.** Hershman D, Weinberg M, Rosner Z, et al. Ethnic neutropenia and treatment delay in African American women undergoing chemotherapy for early-stage breast cancer. *J Natl Cancer Inst*. 2003;95(20):1545-1548.
- 23.** Newman LA, Griffith KA, Jatoi I, Simon MS, Crowe JP, Colditz GA. Meta-analysis of survival in African American and white American patients with breast cancer: ethnicity compared with socioeconomic status. *J Clin Oncol*. 2006;24(9):1342-1349.
- 24.** Albain KS, Unger JM, Crowley JJ, Coltman CA Jr, Hershman DL. Racial disparities in cancer survival among randomized clinical trials patients of the Southwest Oncology Group. *J Natl Cancer Inst*. 2009;101(14):984-992.
- 25.** Andaya AA, Enewold L, Horner MJ, Jatoi I, Shriner CD, Zhu K. Socioeconomic disparities and breast cancer hormone receptor status. *Cancer Causes Control*. 2012;23(6):951-958.
- 26.** Akinyemiju TF, Pisu M, Waterbor JW, Altekruze SF. Socioeconomic status and incidence of breast cancer by hormone receptor subtype. *Springerplus*. 2015;4:508.
- 27.** Millikan RC, Newman B, Tse CK, et al. Epidemiology of basal-like breast cancer. *Breast Cancer Res Treat*. 2008;109(1):123-139.
- 28.** Chlebowski RT, Chen Z, Anderson GL, et al. Ethnicity and breast cancer: factors influencing differences in incidence and outcome. *J Natl Cancer Inst*. 2005;97(6):439-448.
- 29.** Newman LA, Stark A, Chitale D, et al. Association between benign breast disease in African American women and white American women and subsequent triple-negative breast cancer [published online December 22, 2016]. *JAMA Oncol*. doi:10.1001/jamaonc.2016.5598
- 30.** Ambrosone CB, Young AC, Sucheston LE, et al. Genome-wide methylation patterns provide insight into differences in breast tumor biology between American women of African and European ancestry. *Oncotarget*. 2014;5(1):237-248.
- 31.** Mersha TB, Abebe T. Self-reported race/ethnicity in the age of genomic research: its potential impact on understanding health disparities. *Hum Genomics*. 2015;9:1.
- 32.** Ferla R, Calò V, Cascio S, et al. Founder mutations in BRCA1 and BRCA2 genes. *Ann Oncol*. 2007;18(suppl 6)(suppl 6):vi93-vi98.
- 33.** Karami F, Mehdipour P. A comprehensive focus on global spectrum of BRCA1 and BRCA2 mutations in breast cancer. *Biomed Res Int*. 2013;2013:928562.
- 34.** Akbari MR, Donenberg T, Lunn J, et al. The spectrum of BRCA1 and BRCA2 mutations in breast cancer patients in the Bahamas. *Clin Genet*. 2014;85(1):64-67.
- 35.** Fackenthal JD, Zhang J, Zhang B, et al. High prevalence of BRCA1 and BRCA2 mutations in unselected Nigerian breast cancer patients. *Int J Cancer*. 2012;131(5):1114-1123.
- 36.** Frances FZ, Wainstein T, De Leeneer K, et al. BRCA1, BRCA2 and PALB2 mutations and CHEK2 c.1100delC in different South African ethnic groups diagnosed with premenopausal and/or triple negative breast cancer. *BMC Cancer*. 2015;15:912.
- 37.** Palmer JR, Ruiz-Narvaez EA, Rotimi CN, et al. Genetic susceptibility loci for subtypes of breast cancer in an African American population. *Cancer Epidemiol Biomarkers Prev*. 2013;22(1):127-134.
- 38.** Palmer JR, Ambrosone CB, Olshan AF. A collaborative study of the etiology of breast cancer subtypes in African American women: the AMBER consortium. *Cancer Causes Control*. 2014;25(3):309-319.
- 39.** Haddad SA, Ruiz-Narváez EA, Haiman CA, et al. An exome-wide analysis of low frequency and rare variants in relation to risk of breast cancer in African American Women: the AMBER Consortium. *Carcinogenesis*. 2016;37(9):870-877.
- 40.** Huo D, Feng Y, Haddad S, et al. Genome-wide association studies in women of African ancestry identified 3q26.21 as a novel susceptibility locus for oestrogen receptor negative breast cancer. *Hum Mol Genet*. 2016;25(21):4835-4846.
- 41.** National Cancer Institute. NCI launches largest-ever study of breast cancer genetics in black women. <http://www.cancer.gov/news-events/press-releases/2016/breast-cancer-genetics-black-women>. Published July 6, 2016. Accessed September 12, 2016.
- 42.** Brewster AM, Chavez-MacGregor M, Brown P. Epidemiology, biology, and treatment of triple-negative breast cancer in women of African ancestry. *Lancet Oncol*. 2014;15(13):e625-e634.
- 43.** Kantelhardt EJ, Mathewos A, Aynalem A, et al. The prevalence of estrogen receptor-negative breast cancer in Ethiopia. *BMC Cancer*. 2014;14:895.
- 44.** Jemal A, Fedewa SA. Is the prevalence of ER-negative breast cancer in the US higher among Africa-born than US-born black women? *Breast Cancer Res Treat*. 2012;135(3):867-873.
- 45.** Campbell MC, Hirbo JB, Townsend JP, Tishkoff SA. The peopling of the African continent and the diaspora into the new world. *Curr Opin Genet Dev*. 2014;29:120-132.
- 46.** Salas A, Carracedo A, Richards M, Macaulay V. Charting the ancestry of African Americans. *Am J Hum Genet*. 2005;77(4):676-680.
- 47.** Agboola AO, Banjo AA, Anunobi CC, et al. Molecular profiling of breast cancer in Nigerian women identifies an altered p53 pathway as a major mechanism underlying its poor prognosis compared with British counterpart. *Malays J Pathol*. 2014;36(1):3-17.
- 48.** Adjei EK, Owusu-Afriyie O, Awuah B, Stalsberg H. Hormone receptors and Her2 expression in breast cancer in sub-Saharan Africa: a comparative study of biopsies from Ghana and Norway. *Breast J*. 2014;20(3):308-311.
- 49.** Luyeye Mvila G, Batalansi D, Praet M, et al. Prognostic features of breast cancer differ between women in the Democratic Republic of Congo and Belgium. *Breast*. 2015;24(5):642-648.
- 50.** Dickens C, Duarte R, Zietsman A, et al. Racial comparison of receptor-defined breast cancer in Southern African women: subtype prevalence and age-incidence analysis of nationwide cancer registry data. *Cancer Epidemiol Biomarkers Prev*. 2014;23(11):2311-2321.
- 51.** McCormack VA, Joffe M, van den Berg E, et al. Breast cancer receptor status and stage at diagnosis in over 1,200 consecutive public hospital patients in Soweto, South Africa: a case series. *Breast Cancer Res*. 2013;15(5):R84.
- 52.** Amadori D, Serra P, Bravaccini S, et al. Differences in biological features of breast cancer between Caucasian (Italian) and African (Tanzanian) populations. *Breast Cancer Res Treat*. 2014;145(1):177-183.
- 53.** Trinkaus ME, Sayed S, Gakinya SM, Moloo Z, Hanna W, Rahim Y. Triple negative and basal-like breast cancer in East Africa. *Breast J*. 2011;17(4):438-440.
- 54.** Bird PA, Hill AG, Houssami N. Poor hormone receptor expression in East African breast cancer: evidence of a biologically different disease? *Ann Surg Oncol*. 2008;15(7):1983-1988.
- 55.** Nyagol J, Nyong'o A, Byakika B, et al. Routine assessment of hormonal receptor and HER-2/neu status underscores the need for more therapeutic targets in Kenyan women with breast cancer. *Anal Quant Cytol Histol*. 2006;28(2):97-103.
- 56.** Nalwoga H, Arnes JB, Wabinga H, Akslen LA. Frequency of the basal-like phenotype in African breast cancer. *APMIS*. 2007;115(12):1391-1399.
- 57.** Roy I, Othieno E. Breast carcinoma in Uganda: microscopic study and receptor profile of 45 cases. *Arch Pathol Lab Med*. 2011;135(2):194-199.
- 58.** Mbondo MP, Amir H, Schwartz-Albiez R, Akslen LA, Kitinya JN. Expression of estrogen and progesterone receptors in carcinomas of the female breast in Tanzania. *Oncol Rep*. 2000;7(2):277-283.
- 59.** Burson AM, Soliman AS, Ngoma TA, et al. Clinical and epidemiologic profile of breast cancer in Tanzania. *Breast Dis*. 2010;31(1):33-41.
- 60.** Sayed S, Moloo Z, Wasike R, et al. Is breast cancer from Sub Saharan Africa truly receptor poor? prevalence of ER/PR/HER2 in breast cancer from Kenya. *Breast*. 2014;23(5):591-596.
- 61.** Galukande M, Wabinga H, Mirembe F, Karamagi C, Asea A. Molecular breast cancer subtypes prevalence in an indigenous Sub Saharan African population. *Pan Afr Med J*. 2014;17:249.
- 62.** Rambau P, Masalu N, Jackson K, Chalya P, Serra P, Bravaccini S. Triple negative breast cancer in a poor resource setting in North-Western Tanzania: a preliminary study of 52 patients. *BMC Res Notes*. 2014;7(1):399.
- 63.** Fourati A, Boussen H, El May MV, et al. Descriptive analysis of molecular subtypes in Tunisian breast cancer. *Asia Pac J Clin Oncol*. 2014;10(2):e69-e74.
- 64.** Rais G, Raissouni S, Aitellaj M, et al. Triple negative breast cancer in Moroccan women:

- clinicopathological and therapeutic study at the National Institute of Oncology. *BMC Womens Health.* 2012;12:35.
- 65.** Bennis S, Abbass F, Akasbi Y, et al. Prevalence of molecular subtypes and prognosis of invasive breast cancer in north-east of Morocco: retrospective study. *BMC Res Notes.* 2012;5:436.
- 66.** El-Hawary AK, Abbas AS, Elsayed AA, Zalata KR. Molecular subtypes of breast carcinoma in Egyptian women: clinicopathological features. *Pathol Res Pract.* 2012;208(7):382-386.
- 67.** Salhia B, Tapia C, Ishak EA, et al. Molecular subtype analysis determines the association of advanced breast cancer in Egypt with favorable biology. *BMC Womens Health.* 2011;11:44.
- 68.** Cherbal F, Gaceb H, Mehemmai C, et al. Distribution of molecular breast cancer subtypes among Algerian women and correlation with clinical and tumor characteristics: a population-based study. *Breast Dis.* 2015;35(2):95-102.
- 69.** Aiad HA, Wahed MM, Asaad NY, El-Tahmody M, Elhosary E. Immunohistochemical expression of GPR30 in breast carcinoma of Egyptian patients: an association with immunohistochemical subtypes. *APMIS.* 2014;122(10):976-984.
- 70.** Huo D, Ikpatt F, Khramtsov A, et al. Population differences in breast cancer: survey in indigenous African women reveals over-representation of triple-negative breast cancer. *J Clin Oncol.* 2009;27(27):4515-4521.
- 71.** Ly M, Antoine M, Dembélé AK, et al. High incidence of triple-negative tumors in sub-Saharan Africa: a prospective study of breast cancer characteristics and risk factors in Malian women seen in a Bamako university hospital. *Oncology.* 2012;83(5):257-263.
- 72.** Der EM, Gyasi RK, Tettey Y, et al. Triple-negative breast cancer in Ghanaian women: the Korle Bu teaching hospital experience. *Breast J.* 2015;21(6):627-633.
- 73.** Ohene-Yeboah M, Adjei E. Breast cancer in Kumasi, Ghana. *Ghana Med J.* 2012;46(1):8-13.
- 74.** Nwafor CC, Keshihiro SO. Pattern of hormone receptors and human epidermal growth factor receptor 2 status in sub-Saharan breast cancer cases: private practice experience. *Niger J Clin Pract.* 2015;18(4):553-558.
- 75.** Proctor E, Kidwell KM, Jiagge E, et al. Characterizing breast cancer in a population with increased prevalence of triple-negative breast cancer: androgen receptor and ALDH1 expression in Ghanaian women. *Ann Surg Oncol.* 2015;22(12):3831-3835.
- 76.** Lehmann BD, Bauer JA, Chen X, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. *J Clin Invest.* 2011;121(7):2750-2767.
- 77.** Burstein MD, Tsimelzon A, Poage GM, et al. Comprehensive genomic analysis identifies novel subtypes and targets of triple-negative breast cancer. *Clin Cancer Res.* 2015;21(7):1688-1698.
- 78.** Keenan T, Moy B, Mroz EA, et al. Comparison of the genomic landscape between primary breast cancer in African American versus white women and the association of racial differences with tumor recurrence. *J Clin Oncol.* 2015;33(31):3621-3627.
- 79.** Lindner R, Sullivan C, Offor O, et al. Molecular phenotypes in triple negative breast cancer from African American patients suggest targets for therapy. *PLoS One.* 2013;8(11):e71915.
- 80.** Jiagge E, Oppong J, Bensenhaver J, et al. Breast Cancer and African Ancestry: lessons learned at the 10-year anniversary of the Ghana-Michigan research partnership and international registry. *J Glob Oncol.* 2016;2(5):302-310.