Breast Cancer Disparities

How Can We Leverage Genomics to Improve Outcomes?

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KEYWORDS

• Disparities • Genetics • Genomics • African ancestry

KEY POINTS

- Advances in breast cancer genomics will provide important insights regarding explanations for variations in incidence, as well as disparate outcomes, between African American and white American breast cancer patients.
- Germline genomics are essential in genetic counseling and risk assessment programs; somatic or tumor-based genomics will be critical in defining prognostic and therapeutic algorithms.
- It is imperative that the oncology community be prepared to apply these technologies equitably to diverse patient populations.

BACKGROUND

Disparities in breast cancer risk and outcome related to racial-ethnic identity in the United States have been documented by population-based statistics from the Surveillance, Epidemiology, and End Results (SEER) Program over the past several decades. These patterns are further supported by data from a variety of health care systems and oncology programs. Variations in the breast cancer burden of African Americans (AA) women compared with white American (WA) women have been the subject of rigorous study[1] because of the magnitude of the observed differences and are the focus of this article. **Table 1** summarizes these divergent patterns.

Breast cancer mortality rates are higher for AA compared with WA women, and this is at least partly explained by a more advanced stage distribution, with AA women being diagnosed more frequently with larger, node-positive disease. Breast cancer incidence

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Table 1
Breast cancer in African Americans and European or White Americans

			African American	White American
Population-based incidence rates (per 100,000), female breast cancer	Overall, age-standardized		122.9	124.4
	Age-stratified	35–39 y	70.6	59.9
		40–44 y	118.2	122.2
		45–49 y	180.4	188.1
		50–54 y	231.6	220.3
		55–59 y	270.7	260.4
		60–64 y	332.0	332.4
		65–69 y	399.5	428.7
Population-based mortality rates (per 100,000), female breast cancer	Overall, age-standardized		28.2	20.3
	Age-stratified	35–39 y	10.2	5.8
		40–44 y	22.1	11.5
		45–49 y	30.7	18.3
		50–54 y	47.3	27.3
		55–59 y	57.4	36.6
		60–64 y	71.3	49.2
		65–69 y	80.4	62.2
Stage distribution at diagnosis, female breast cancer		Localized	53%	64%
		Regional	35%	28%
		Distant	8%	5%
		Unknown	4%	3%
5-y cause-specific survival, female breast cancer		All stages	80%	89%
		Localized	93%	96%
		Regional	78%	87%
		Distant	24%	34%
TNBC population-based incidence rates, female breast cancer			27.2	14.4
Population-based incidence rates, male breast cancer			2.04	1.25

Abbreviation: TNBC, triple-negative breast cancer.
Data from Refs.[4,5,72]

rates historically have been lower for AA compared with WA women, and variations in incidence (eg, increasing and declining rates before vs after the 2003 Women's Health Initiative,[2] with findings linking postmenopausal hormone replacement therapy with elevated breast cancer risk) typically occurred in parallel. Most recently, however, breast cancer incidence rates have risen disproportionately among AA women and have now converged with those of WA women.[3] This escalation in the breast cancer burden of the AA community has resulted in a widening of the mortality gap between AA and WA women, which is now a 42% difference.[3] Socioeconomic disadvantages (eg, living below the poverty level, and being underinsured or not insured) that are more prevalent in the AA community undoubtedly contribute to outcome disparities by creating health care access barriers associated with delays in diagnosis and comprehensive treatment. Several lines of evidence, however, indicate that other factors related to tumor biology, the environment, and/or ancestral genetics are likely also contributing to the cause of breast cancer's disparate impact on the AA population. These various characteristics, which cannot be ascribed to socioeconomic resources, include

1. Younger age distribution of breast cancer in AA women. Population-based incidence rates of breast cancer are higher for AA compared with WA women younger than age 40 years.[4]
2. Distribution of breast cancer phenotypes in AA women. Frequency and population-based incidence rates of tumors that are negative for the estrogen receptor (ER), the progesterone receptor (PR), and HER2/*neu* (HER2), commonly called triple-negative breast cancer (TNBC), are approximately 2-fold higher for AA compared with WA women.[5]
   a. Studies from Great Britain[6,7] and Switzerland[8] reveal that prevalence of TNBC is higher among women with African ancestry compared with those with British, European, or Asian heritage.
   b. The association between African ancestry and TNBC appears to be specific for western sub-Saharan African heritage because the highest frequencies of this phenotype have been reported among Ghanaians,[9–11] Nigerians,[12,13] and Malians,[14] with relatively lower frequencies in East African countries, such as Ethiopia,[11] and northern African countries, such as Egypt,[15,16] Morocco,[17,18] and Algeria.[19] These geographically defined correlations are relevant because the forced population migration of the colonial-era trans-Atlantic slave trade brought millions of Africans from western sub-Sharan Africa to North America and, therefore, contemporary AA communities have less shared ancestry with eastern and northern Africans.[1] Furthermore, a SEER-based study looked at breast cancer patients from Africa but residing in the United States and found higher frequencies of ER-negative tumors among the West Africans (most from Nigeria) but lower frequencies of ER-negative tumors among eastern Africans (most from Ethiopia).[20]
3. Meta-analysis of studies reporting breast cancer outcomes in AA compared with WA women after controlling for socioeconomic status reveals a nearly 30% higher mortality rate among AA patients (mortality hazard 1.27; 95% confidence interval, 1.18–1.38).[21]
4. Multiple phase III clinical trials (including the Southwest Oncology Group, the Eastern Cooperative Oncology Group, and the Women's Health Initiative), which would be expected to disentangle socioeconomic status from racial-ethnic identity because of the tightly regulated randomization and management structure, reveal that AA identity remains a statistically significant risk factor for increased mortality.[22–25]
5. Higher population-based incidence rates of male breast cancer in the AA community.

Geographic ancestry is strongly correlated with shared genetic inheritance; therefore, the clear associations of West African geographic ancestry with tumor phenotype and clinical outcomes are a strong indication that genetics plays a major role in these trends.

Advances in genomic technologies that now allow full characterization of germline and somatic DNA sequence, patterns of DNA modifications, and gene expression signatures hold great promise in defining the complex and multifactorial cause of breast cancer disparities, thereby launching opportunities to improve outcomes for all.

GERMLINE GENOMICS

Most of what we know about breast cancer genetics has been defined in the context of European ancestry. Once genomic technologies are applied to West African populations and we are able to establish the breast cancer risk alleles in this ancestral background, our ability to investigate the genetic components of risk in African and AA women will be greatly enhanced. The study of an individual's inherited genome can inform the discussion of breast cancer disparities related to African ancestry in several ways: (1) genetic testing of African ancestry families to evaluate the frequency of mutations in genes known to associated with breast cancer risk, (2) quantification of African ancestry through genotyping to evaluate Ancestry Informative Markers (AIMs), (3) application of genome-wide association studies (GWASs) in African ancestry populations to identify novel loci associated with breast cancer susceptibility, and (4) the study of epigenetics with race-specific or ethnicity-specific modification of the inherited genome.

Hereditary Susceptibility Syndromes in African Ancestry Families

Technology allowing for the sequencing of germline, inherited DNA sequences within genes has revolutionized breast cancer genetics and genetic counseling. These advances have resulted in the identification of a spectrum of genes associated with familial breast cancer. A comprehensive review of breast cancer hereditary susceptibility syndromes is beyond the scope of this article, which summarizes the data available thus far regarding BRCA1 and BRCA2 mutations identified in African ancestry families.

Interesting parallels are observed in the breast cancer burden of AA patients and BRCA1 mutation–associated breast cancer, prompting questions regarding the existence of BRCA founder mutations related to African ancestry. Interpretation of older studies was limited by the relatively sparse genetic testing information available in African ancestry families, resulting in high rates of identification of variants of unknown significance. More recent studies, however, have been successful in reporting prevalence of BRCA disease–associated mutations in families with African ancestry. These reports include the identification of novel founder mutations associated with Bahamian heritage, present in nearly one-quarter of Bahamian breast cancer patients,[26,27] and another founder mutation detected in one-quarter of black South African breast cancer patients.[28] Other founder mutations have also been identified related to West African ancestry.[29,30] The spectrum of BRCA mutations identified in international African ancestry populations is reviewed by Oluwagbemiga and colleagues,[31] as well as by Karami and Mehdipour.[32] Selected results from these studies and reports of BRCA testing in African Americans are summarized in **Table 2**, revealing BRCA mutations in 7% to 56% of high-risk breast cancer patients.

Zhang and colleagues[33] further demonstrated the importance of complete gene sequencing for BRCA1 and BRCA2 among high-risk African ancestry individuals because recurrent mutations identified in an African ancestry population will not

Table 2
Frequency of BRCA mutations in African ancestry populations

Study, y	Study Site	Main Findings (Sample Size, Study Population)
Trottier et al,[27] 2016	Nassau, Bahamas	Bahamian BRCA founder mutations identified in 2.8% high-risk Bahamian women and 0.09% general population of Bahamian women (20/705 unaffected Bahamians with family history of breast or ovarian cancer; 1/1089 unaffected Bahamians unselected for age, family history)
Churpek et al,[98] 2015	Chicago, Illinois	BRCA deleterious mutations identified in 18% (52/289 AA high-risk subjects: personal or family history of breast cancer; TNBC)
Francies et al,[73] 2015	Johannesburg, South Africa	BRCA deleterious mutations identified in 7% (6/85 black South African breast cancer subjects diagnosed younger than 50 y old and/or with TNBC)
Pal et al,[74] 2015	Florida Cancer Registry	BRCA deleterious mutations identified in 12.4% (49/396 AA breast cancer subjects from Florida younger than 50 y old)
Akbari et al, 2014[26]	Bahamas (multiple islands)	BRCA mutations identified in 27% (58/214 Bahamian breast cancer subjects unselected for age or family history; 53/58 were Bahamian BRCA founder mutations)
Sharma et al,[75] 2014	Kansas City, Kansas	BRCA1 large genomic rearrangement mutations identified in 7% (2/30 AA TNBC subjects)
Biunno et al,[76] 2014	Central Sudan	BRCA1 mutations in 56% (33/59 premenopausal Sudanese breast cancer subjects with point mutations, including 1/33 deleterious and 8/33 unknown significance)
Greenup et al,[77] 2013	Duke University, North Carolina, and University of California San Francisco	BRCA deleterious mutations identified in 20% (17/83 AA TNBC subjects including 9/17 BRCA1 and 8/17 BRCA2 mutations)
Pal et al,[78] 2013	Florida Cancer Registry	BRCA mutations identified in 41% as pathogenic; 35% as VUS (3/46 pathogenic variants; 16/46 VUS; all AA breast cancer subjects diagnosed younger than 50 y old)
Judkins et al,[79] 2012	Myriad Genetic Laboratories, Inc (predominantly cases from USA)	BRCA deleterious mutations in 29.4% African ancestry (519/1767 African ancestry women with suspected hereditary susceptibility found to have BRCA1/2 mutations, including 476/519 sequence mutations and 43/519 large genomic rearrangements)
Zhang et al,[33] 2012	University of Ibadan, Nigeria University of Chicago Cancer Risk Clinic, Illinois Barbados National Cancer Study	BRCA1 recurrent mutations in 3.1% Nigerians (11/356 Nigerian breast cancer subjects) BRCA1 mutations in 0.8% AA (2/260 AA breast cancer subjects found to harbor the BRCA1 recurrent mutations identified in the Nigerian cohort) BRCA1 mutations in 0% Barbadians (0/118 Barbadian breast cancer subjects found to harbor the BRCA1 recurrent mutations identified in the Nigerian cohort)

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Table 2
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Study, y	Study Site	Main Findings (Sample Size, Study Population)
Van der Merwe et al,[28] 2012	Western Cape, South Africa	BRCA2 founder mutation identified in 25% (4/16 black western South Africa breast cancer subjects)
Fackenthal et al,[80] 2012	Ibadan, Nigeria	BRCA deleterious mutations identified in 11.1% (48/434 unselected Nigerian breast cancer subjects, including 31/48 BRCA1 and 17/48 BRCA2 mutations)
Donenberg et al, 2011[81]	Bahamas (multiple islands)	BRCA mutations identified in 23% (49/214 Bahamian subjects unselected for age or family history)
Zhang et al,[82] 2010	Ibadan, Nigeria	BRCA1 large genomic rearrangement in 0.3% (1/352 Nigerian breast cancer subjects unselected by age or family history)
Zhang et al,[29] 2009	Ibadan, Nigerian	BRCA1 founder mutation in 1.1% (4/365 unrelated Yoruban Nigerian breast cancer subjects)
John et al,[83] 2007	Northern California Breast Cancer Family Registry	BRCA1 deleterious mutations in 1.3% (8/178 AA breast cancer subjects with high-risk for hereditary susceptibility; 0/163 AA breast cancer subjects with suspected sporadic disease; all diagnosed younger than 65 y old)
Awadelkarim et al,[84] 2007	Wad Medani, Sudan	BRCA deleterious mutations in 14% (5/35 Sudanese breast cancer subjects diagnosed younger than 40 y old, including 2/5 BRCA1 mutations and 3/5 BRCA2 mutations [including 1/3 male])
Malone et al,[85] 2006	Women's CARE Study	BRCA deleterious mutations in 4% cases and 0.9% controls[a] (26/483 cases with BRCA mutation including 10/26 BRCA1 and 16/26 BRCA2; all AA breast cancer subjects diagnosed 35–64 y old) (3/213 AA controls with BRCA2 mutation)
Fackenthal et al,[86] 2005	Ibadan, Nigeria	BRCA deleterious mutations in 3%; VUS in 72% (29/39 BRCA mutations in Nigerian breast cancer subjects diagnosed younger than 40 y old, including 1 BRCA2 deleterious truncating mutation)
Nanda et al,[87] 2005	University of Chicago, Mayo Clinic, and University of California San Francisco	BRCA deleterious mutations identified in 28%; VUS in 44% (7/43 pathogenic BRCA1 and 5/43 BRCA2 mutations; 19/43 VUS; all AA families with high-risk for hereditary susceptibility)
Gao et al,[88] 2000	Ibadan, Nigeria	BRCA deleterious mutations in 4%; VUS in 23% (3/70 pathogenic mutations and 18/70 VUS; all Nigerian premenopausal breast cancer subjects)
Yawitch et al,[89] 2000	South Africa	BRCA1 commonly recurring mutations in 0% (0/206 black South African breast cancer subjects)
Gao et al,[90] 2000	University of Chicago and University of Texas Southwestern (Dallas)	BRCA deleterious mutations identified in 18% (5/28 AA breast cancer subjects with family history of breast and/or ovarian cancer, including 1/5 BRCA1 and 4/5 BRCA2 mutations)

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Table 2 (*continued*)

Study, y	Study Site	Main Findings (Sample Size, Study Population)
Panguluri et al,[91] 1999	Howard University Cancer Center, Washington DC	BRCA1 deleterious mutations in 4%; VUS in 11% (2/45 AA deleterious BRCA1 mutations and 5/45 VUS; all AA breast cancer subjects from families with high-risk for hereditary susceptibility)
Newman et al,[99] 1998	Carolina Breast Cancer Study, North Carolina	BRCA1 deleterious mutations in 0% (0/88 AA breast cancer subjects and 0/79 AA controls)
Gao et al,[92] 1997	University of Chicago Cancer Risk Clinic, Illinois	BRCA1 mutations identified in 56% (5/9 AA breast cancer subjects with suspected hereditary susceptibility)

Abbreviation: VUS, variant of unknown significance.
[a] Reported proportions weighted to account for sample tested as representing entire study cohort.

necessarily be found in other African ancestry populations. These investigators identified recurrent BRCA1 mutations in Nigerian breast cancer patients, but these particular mutations were uncommon among AA and Barbadian breast cancer patients. Genetic counseling and testing is clearly warranted in African ancestry families and expanded results will likely characterize a broader spectrum of deleterious mutations in the BRCA genes.

Ancestry Informative Markers

The AA population represents a heavily admixed community in terms of geographically defined ancestry. Various individuals may self-identify as being AA based on community ties, physical appearance or pigmentation, and familial or personal preferences, but the extent of African versus European or Native American contributions to ancestry can differ substantially between these individuals. Ancestral background can be inferred and quantified by genotyping to evaluate genetic markers associated with substantial differences in allele frequency between geographically defined populations. These genetic patterns, AIMs, can be assessed through the study of uniparental heritage via maternally linked mitochondrial DNA (mtDNA) or Y-linked chromosomal markers. Alternatively, they can be analyzed via autosomal short tandem repeats or single nucleotide polymorphisms (SNPs), with the latter being the most commonly used. Africa is a large, diverse continent and African ancestry can be further stratified by region. The potential value of AIMs to better characterize the genetics of disease associated with racial-ethnic identity has been reviewed extensively.[34–38]

Recent reports have yielded provocative findings with regard to potential novel applications for AIMs in evaluating breast cancer risk. Rao and colleagues[39] studied mtDNA in 92 subjects with TNBC (31 of whom self-identified as AA), and found discordance between self-reported race or ethnicity and genetic ancestry in 13% of cases. Davis and colleagues[40] have reported on African ancestry-specific isoform expression of the atypical chemokine receptor 1 (ACKR1)/Duffy antigen receptor for chemokines (DARC) as being associated with ancestry-specific inflammatory response, with potential implications for several disease processes, including breast cancer.

Genome-Wide Association Studies

GWASs have been used extensively to characterize breast cancer risk associated with various patient populations. In the study of breast cancer burden associated with race or

ethnicity, GWASs have been applied with self-reported identity, as well as in conjunction with AIMs and genetic admixture mapping. In an effort to strengthen sample sizes and power calculations, several large AA cohorts have been assembled for these analyses, such as those of the Black Women's Health Study, the Women's Circle of Health Study, the Carolina Breast Cancer Study (CBCS), the Multiethnic Cohort; and various collaborations of these, as well as additional cohorts (eg, African American Breast Cancer Epidemiology and Risk [AMBER] Consortium; the African Diaspora Study [known as the ROOT Study]; and the African American Breast Cancer Consortium [AABC]). Some of these analyses have identified genetic susceptibility loci for specific breast cancer subtypes in AA women, such as SNP rs8170 associated with TNBC in AA patients,[41] 3 novel regions associated with ER-positive disease in AA patients,[42] a novel gene (FBXL22) associated with ER-negative disease in AA patients,[43] and 3q26.21 as a novel susceptibility locus associated with African ancestry ER-negative breast cancer.[44]

Epigenetics

Epigenetics refers to modification of the primary or inherited genome without alteration of the actual DNA sequence. Most commonly, these epigenetic events occur as DNA methylation or histone modification. Epigenetic changes can influence gene expression and they can be stable, heritable, or reversible. Epigenetics have been implicated in the initiation, promotion, and metastasis of breast cancer, as reviewed by Wu and colleagues.[45] Several investigators have demonstrated that epigenetics may also contribute to breast cancer disparities. Genome-wide methylation patterns have been associated with ER-negative breast cancer in AA patients,[46] have been found to differ in benign breast tissue from WA and AA women,[47] and global DNA methylation has been associated with ancestral admixture variation in breast cancer risk.[48]

Epigenetics may also play a unique role in breast cancer disparities by acting as an intermediary between the genetics of racial-ethnic identity and racial-ethnic identity as a sociopolitical construct.[49] Cumulative stressors over a lifetime, such as poverty and psychosocial adversity, have been theorized to cause biological dysregulation (called allostatic load) that may influence a variety of medical hazards.[49–51] Measures of allostatic load have been found to be elevated among AA individuals,[52] and disparities in allostatic load have been implicated in health disparities between the AA and WA communities.[53] An analysis of the National Health and Nutrition Examination Survey found that allostatic load among AA women was disproportionately associated with breast cancer risk.[54] Epigenetics have been proposed as a method for quantifying stress response and possible allostatic load,[49,55,56] thereby serving as a potential surrogate measure for the effect of socioeconomic disadvantages on breast cancer disparities associated with race or ethnicity.

SOMATIC GENOMICS

In contemporary breast cancer clinical care, immunohistochemistry is routinely used to define breast cancer phenotype based on expression of the protein biomarkers ER, PR, and HER2. Combinations of these results are have prognostic value and predict for response to targeted therapies. The diversity of breast cancer biology is further underscored by gene expression studies that identify an even more complex spectrum of tumor mutations and subtypes, also associated with a range of prognostic risks. Differences in the somatic mutational landscape and tumor subtype represent additional genomic factors that might contribute to breast cancer disparities between AA and WA patients.

Table 3 summarizes data from various studies that have reported on the somatic genomic landscape of tumors from AA and WA breast cancer patients, demonstrating unique and diverse gene signatures in the tumors of AA patients. The Cancer Genome

Table 3
Studies reporting on the landscape of somatic mutations and tumor subtypes in breast cancers of African American and white American subjects

Study	Cases Studied	Selected Findings
Martin et al,[93] 2009	Baltimore, MD 18 AA (72% ER-negative) 17 WA (29% ER-negative)	• Prominent interferon signal in tumors of African American subjects • Phosphoserine phosphatase-like expressed more highly in tumor epithelium and stroma of AA subjects • Thymopoietin expressed more highly in stroma of AA subjects • Chemokine ligands 10 and 11 expressed more strongly in tumor stroma of AA subjects
Field et al,[94] 2012	Clinical Breast Care Project 26 AA (38% TNBC) 26 WA (35% TNBC)	• Crystallin beta B2, lactotransferrin, and L-3-phosphoserine-phosphatase homologue expressed more strongly in AA subjects
Grunda et al,[95] 2012	Birmingham, AL 11 AA (45% ER-negative) 11 WA (9% ER-negative)	• AA subjects more likely to have aberrant G1/S cell-cycle regulatory genes • AA subjects more likely to have decreased expression of cell adhesion genes • AA subjects more likely to have low or no expression of ESR1, PGR, ERBB2 and estrogen pathway genes
Stewart et al,[57] 2013	The Cancer Genome Atlas 53 AA (19% TNBC) 574 WA (12% TNBC)	• Increase in number of differentially expressed genes between AA and WA subjects with each stage of tumor progression • Resistin (a gene that is linked to obesity, insulin resistance, and breast cancer) was expressed more than 4 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,[67] 2013	Yale TNBC Cohort 50 AA 69 WA	• Major transcriptional signature of proliferation found to be upregulated 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

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Table 3 (*continued*)

Study	Cases Studied	Selected Findings
Kroenke et al,[60] 2014	Pathways and Life after Cancer Epidemiology Cohorts 128 AA (30% TNBC) 1176 WA (11% TNBC)	• PAM50 subtyping revealed increased frequency of basal subtype among AA compared with WA cases (41% vs 17%)
Sweeney et al,[61] 2014	Pathways and Life after Cancer Epidemiology Cohorts 115 AA[a] 913 WA[a] 12% of entire cohort with TNBC; frequencies not reported by race or ethnicity	• 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% confidence interval 2.29–8.39)
Keenan et al,[58] 2015	The Cancer Genome Atlas 159 AA (17% TNBC) 711 WA (8% TNBC)	• 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 • Greater intratumoral heterogeneity among AA vs WA cases
Ademuyiwa et al,[59] 2017	The Cancer Genome Atlas 183 AA (33% TNBC) 764 WA (15% TNBC)	• 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,[100] 2017	The Cancer Genome Atlas 154 AA 776 WA	• PAM50 subtyping: increased frequency of basal subtype in AA cases (36% versus 15%; $p<0.0001$) • AA cases with more TP53 and fewer PIK3CA mutations compared to WA (52% versus 31%; $p = 2.5 \times 10-5$ and 24% versus 36%; $p = 0.012$, respectively)

[a] Estimated from percentage distributions provided.

Atlas has been interrogated by several investigators[57–59] and PAM50 has been used extensively for tumor subtyping.[58–61] As noted previously, TNBC is twice as common among AA compared with WA patients; the adverse prognosis of TNBC is related to approximately 80% belonging to the inherently aggressive basal breast cancer subtype defined by gene expression profiling.[62] Not surprisingly, therefore, PAM50 subtyping studies have also confirmed higher rates of basal subtype tumors among AA breast cancer patients. Most recently, Huo et al have utilized Ancestry Informative Markers to distinguish African ancestry from European ancestry breast cancer

Table 4
Findings from selected studies reporting on outcomes in African American compared with White American breast cancer subjects, after accounting for gene expression subtype

Study	Source	Subject Sample (n) AA	Subject Sample (n) WA	Follow-up	Results	AA Outcome Worse?
Kroenke et al,[60] 2014	Kaiser Permanente Northern California and Utah Cancer Registry	128 (38 TNBC, 53 basal-like, 32 luminal A)	1176 (129 TNBC, 205 basal-like, 268 luminal A)	NR	• Hazard ratio recurrence (adjusted for age and stage): *Basal:* 0.81 (0.10–6.49) *Luminal A:* 1.45 (0.59–3.55)	Basal: no Luminal A: yes
Keenan et al,[58] 2015	The Cancer Genome Atlas	159 (27 TNBC, 62 basal-like, 27 luminal A)	711 (58 TNBC, 132 basal-like, 247 luminal A)	AA: 29.9 mo WA: 24.4 mo	• Hazard ratio tumor recurrence (adjusted for age, stage, and *TNBC:* 1.47 (0.68–3.14) *Basal:* 1.48 (0.67–3.27) *All PAM50 Subtypes:* 1.35 (0.62–2.95)	TNBC: no Basal: no
Tao et al,[96] 2015	California Cancer Registry	9738 (1896 TNBC, 4813 HR-positive, HER2-not overexpressed)	93,760 (8589 TNBC, 59,341 HR-positive, HER2-not overexpressed)	3.5 y	• Mortality hazard ratio (adjusted for age, tumor size, nodal status, SES): TNBC: 1.21 (1.06–1.37) *HR-positive, HER2-not overexpressed:* 1.27 (1.12–1.43) *ER/PR-negative, HER2-positive:* 1.09 (0.85–1.39)	TNBC: yes ER-positive: yes HER2-positive: no
Ademuyiwa et al,[59] 2017	The Cancer Genome Atlas	61 (all TNBC)	114 (all TNBC)	6 y	• Disease-free survival worse for AA compared with WA subjects with basal-like tumors ($P<.0001$) but no significant differences for AA compared with WA subjects with TNBC	Basal-like: yes TNBC: no
D'Arcy et al,[97] 2015	Publically available datasets	57 (all luminal A)	108 (all luminal A)	NR	• No survival analyses but AA luminal A cases with higher expression of poor prognosis genes and lower expression of good prognosis genes	NA

(samples sizes estimated based upon reported frequencies if values not provided).
Abbreviations: SES, socioeconomic status; HR, hormone receptor (ER and/or PR); NA, not applicable; NR, not reported.

patients whose tumors have been analyzed through The Cancer Genome Atlas, also demonstrating an association between African ancestry and basal breast tumors. Gene expression studies have not yet completely clarified explanations for breast cancer disparities. As shown in **Table 4**, inconsistent results have been demonstrated in various studies reporting on outcome disparities between AA and WA patients, even after accounting for tumor subtype.

TNBCs themselves have diverse genetic pathways. Lehman and colleagues[63] first characterized these triple-negative subtypes by analyses of gene expression profiles from 21 publically available datasets that included 587 TNBC cases. They identified 6 different subtypes: 2 basal-like, 1 immunomodulatory, 1 mesenchymal, 1 mesenchymal stem-like, and 1 luminal androgen receptor subtype. Similarly, Burstein and colleagues[64] identified 4 TNBC subtypes based on gene expression profiles from 198 cases from Baylor College of Medicine: luminal androgen receptor, mesenchymal, basal-like immune suppressed, and 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[65,66] and may be amenable to endocrine manipulation through anti-androgen therapy. Unfortunately, neither the Lehmann and colleagues[63] nor the Burstein and colleagues[64] studies included meaningful samples of triple-negative tumors from women with African ancestry. Lindner and colleagues[67] evaluated 136 tumors from the Yale TNBC cohort (including 50 AA patients) and found basal-like subtypes to be more common among the AA cases. Using the Cancer Genome Atlas, Keenan and colleagues[58] also found that TNBC tumors from AA were more likely to have the basal-like and mesenchymal triple-negative subtypes. The luminal androgen receptor TNBC subtype appears to be less common in AA patients.

The American Joint Committee's 8th edition of their cancer staging system, will be implemented by tumor registries in 2018 and a major shift is that the new breast cancer staging system will account for results from commercially available gene expression profiles,[68] such as the 21-gene recurrence score, also known as Oncotype DX (Genomic Health, Redwood City, CA, USA). This change represents an opportunity to evaluate disparities related to race or ethnicity in the use of Oncotype testing as a quality of care metric. Thus far, inconsistent results have been reported. The CBCS revealed no disparities in guideline-concordant use of the Oncotype test between AA and WA patients.[69] Two other studies (from the California Cancer Registry[70] and the Virginia Tumor Registry[71]) both found disproportionately lower use of Oncotype testing in AA patients.

SUMMARY

Advances in breast cancer genomics will definitely provide important insights regarding explanations for variations in incidence, as well as disparate outcomes between AA and WA breast cancer patients. Germline genomics are essential in genetic counseling and risk-assessment programs; somatic or tumor-based genomics will be critical in defining prognostic and therapeutic algorithms. It is, therefore, imperative that the oncology community be prepared to apply these technologies equitably to diverse patient populations.

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