A Perfect Storm: How Tumor Biology, Genomics, and Health Care Delivery Patterns Collide to Create a Racial Survival Disparity in Breast Cancer and Proposed Interventions for Change

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It is well known that there is a significant racial divide in breast cancer incidence and mortality rates. African American women are less likely to be diagnosed with breast cancer than white women but are more likely to die from it. This review explores the factors that may contribute to the racial survival disparity. Consideration is paid to what is known about the role of differences in tumor biology, genomics, cancer screening, and quality of cancer care. It is argued that it is the collision of 2 forces, tumor biology and genomics, with patterns of care that leads to the breast cancer mortality gap. The delays, misuse, and underuse of treatment for African American patients are of increased significance when these patients are presenting with more aggressive forms of breast cancer. In the current climate of health care reform ushered in by the Affordable Care Act, this article also evaluates interventions to close the disparity gap. Prior interventions have been too narrowly focused on the patient rather than addressing the system and improving care across the continuum of breast cancer evaluation and treatment. Lastly, areas of future investigation and policy initiatives aimed at reducing the racial survival disparity in breast cancer are discussed. **CA Cancer J Clin 2015;65:221-238. © 2015 American Cancer Society.**

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Introduction

According to the American Cancer Society, an estimated 231,840 new cases of female breast cancer will be diagnosed in 2015. These diagnoses represent 29% of all new cancer cases among women. Regrettably, there will also be an estimated 40,290 deaths from breast cancer, which represent 15% of all cancer deaths among women.[1] It is well known that there is a significant racial divide in breast cancer incidence and mortality rates. White women are more likely to be diagnosed with breast cancer, but African American women are more likely to die from it. According to National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, the 2007-2011 age-adjusted incidence rate for breast cancer for non-Hispanic white women in the United States was 128 per 100,000 women per year compared with 123 for non-Hispanic African American women. However, the mortality rate for non-Hispanic white women was 21.7 per 100,000 per year compared with 30.6 for non-Hispanic African American women.[2]

The overall mortality trend reveals that breast cancer death rates in women have decreased nationally in the United States since 1990; however, the decreases in death rates began earlier and have been larger in proportionate terms for whites versus African Americans (Fig. 1).[3,4] SEER data from 1975 to 2011 indicate that white women had a 23% increase in breast cancer incidence and a 34% decrease in mortality, whereas African American women experienced a 35% increase in incidence and a 2% increase in mortality.[5] Hunt et al[6] examined race-specific breast cancer mortality rates and the corresponding black/white rate ratios (a rate ratio of 1.00 indicates no disparity between black and white mortality rates) for the largest US cities. Data were analyzed from 41 cities, and 35 saw an increase in the black/white rate ratio between 1990-1994 and 2005-2009. The researchers found that the disparity occurred because "white rates improved substantially over the 20-year study period, while black rates did not."[6]

In addition to Hunt et al,[6] further studies have explored these regional variations in breast cancer mortality by race (Fig. 2).[7] DeSantis et al[3] analyzed mortality data from the National Center for Health Statistics from 1975 to 2004.

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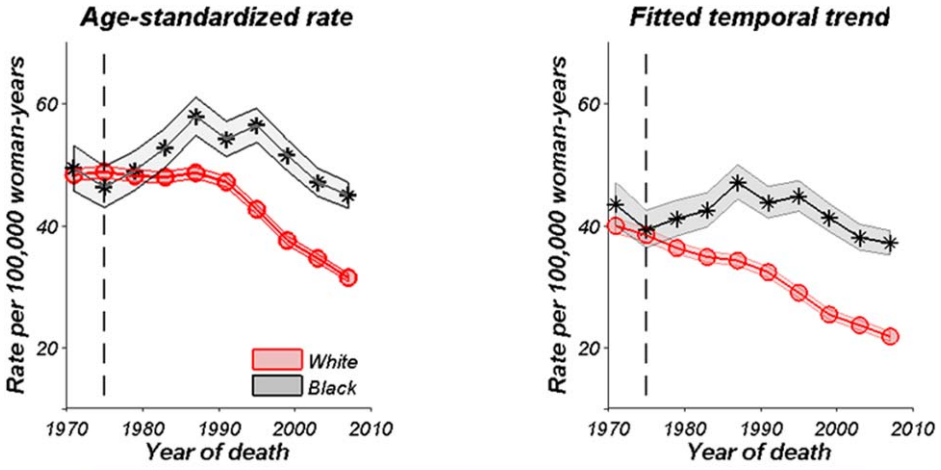

Timeline	Event
1980+	Widespread screening
1980+	CMF and Adriamycin chemotherapy
1983	NATO-Tamoxifen

FIGURE 1. Mortality Trends by Race (SEER9, 1968-2008). CMF indicates cyclophosphamide, methotrexate, and fluorouracil; NATO, Nolvadex Adjuvant Trial Organization. Courtesy of William F. Anderson, MD, MPH, Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute.

The authors found that trends in breast cancer death rates varied widely by region. While breast cancer death rates in white women were decreasing in all 50 states, among African American women, breast cancer death rates increased in 2 states, were level in 24 states, and decreased in only 11 states. Many of the states in which African American breast cancer death rates were level or rising were in the South and Midwest. This article will review differences in the natural history, biology, genomics, and patterns of care of breast cancer in African Americans that may contribute to this disparity in mortality and will review innovative interventions to close the disparity gap.

Age and Stage

Past reviews of this topic have dwelled on differences in age and stage at diagnosis between African American and white women. Indeed, although the overall incidence of breast cancer is higher in whites, the incidence profile changes when the data are stratified by age. Among African American women with breast cancer, 33% are diagnosed at an age less than 50 years, whereas 21.9% of white women are.[8] In women younger than 35 years, the incidence of breast cancer in African American women is 1.4 to 2.0 times that in whites.[9] In addition, African American women do present at more advanced stages of disease. Using data from the California Cancer Registry, Kurian et al[10] found that compared with African American patients, white patients had a higher proportion of tumors that were diagnosed at a local stage (64.5% vs 54.5%) and that were diagnosed at a size of 2 cm or less (61.7% vs 48.6%). More recently, Iqbal et al[11] conducted an observational study of 373,563 women with invasive breast cancer from 2004 to 2011 who were identified in the SEER 18 registries database. In that study, African American women were less likely to be diagnosed with stage I breast cancer than non-Hispanic white women across all age groups (non-Hispanic white women, 50.8%; African American women, 37.0%). Taking the analysis further, Iqbal et al evaluated these small breast tumors and looked at the percentages of nodal metastases and distant metastases and the hormone receptor status by race/ethnicity for women presenting with tumors ≤ 2 cm in size. The authors found that an African American woman with a small-sized breast tumor was more likely to present with lymph node metastases (24.1% vs 18.4%), distant metastases (1.5% vs 1.0%), and a triple-negative tumor (17.2% vs 8.0%) than a non-Hispanic white woman. African American women were also more likely to die of breast cancer with small-sized tumors (9.0%) than non-Hispanic white women (4.6%). Thus, we argue that age and stage by themselves are not significant but rather gain importance by how they highlight differences in tumor biology, genomics, and patterns of care (Fig. 3).

Tumor Biology: The First Element in the Perfect Storm (Fig. 4)

Hormone Receptor Status and Human Epidermal Growth Factor Receptor 2 (HER2)/*neu*

As stated previously, a factor likely contributing to the noted differences in age and stage at diagnosis for African

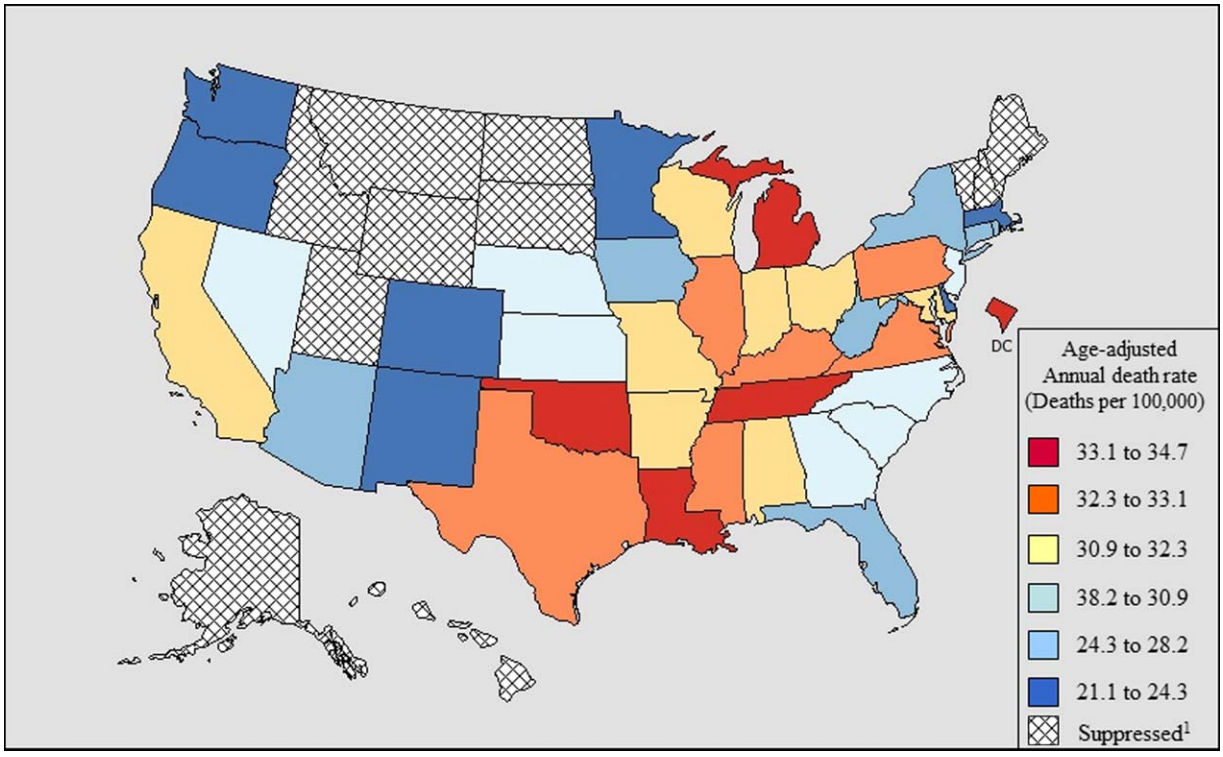

FIGURE 2. Age-Adjusted African American Breast Cancer Mortality for the United States, 2007-2011. [1]Counts are suppressed if fewer than 16 cases were reported in a specific area-sex-race category. Source: State Cancer Profiles. statecancerprofiles.cancer.gov/map/map.withimage.php?00&001&055&02&2&02&0&1&6&0#results. Accessed November 21, 2014.[7]

American women is differences in tumor biology. Breast cancer is not a single entity, and breast cancer subtype classifications are used in the clinical setting to determine prognosis and guide management. The distinct subtypes readily identified in the clinical setting are based on tumor markers: estrogen receptor (ER), progesterone receptor (PR), and HER2/*neu* amplification. HER2 is a member of the human epidermal growth factor receptor family and is encoded on the long arm of chromosome 17; it promotes cell growth. These heterogeneously diverse tumors have different disease-specific survival rates. Hormone receptor-positive tumors benefit from targeted therapies such as selective ER modulators and aromatase inhibitors. Thus, these tumors have a more favorable disease-specific survival than hormone receptor-negative tumors.[14]

African American women are more likely to present with hormone receptor-negative tumors. In an analysis of the California Cancer Registry, which has collected information on ER and PR status since 1990, whites had a higher proportion of tumors that were luminal in comparison with African Americans (71.6% vs 53%), with luminal tumors defined as ER-positive, PR-positive, or both and HER2-negative.[10] Even with stratification by tumor stage, African Americans continue to have a significantly higher proportion of hormone receptor-negative tumors than whites for localized and advanced disease.[15] Evaluating changes in breast cancer incidence with the reduction of hormone replacement therapy, Pfeiffer et al[16] employed data from the SEER database and demonstrated this trend in hormone receptor status: they found that for non-Hispanic white women aged 50 to 69 years, the incidence of ER-negative tumors declined 4.7% from 2000-2001 to 2003-2004, whereas for African American women of the same age during the same time period, ER-negative tumors increased 4.0%.

Although hormone receptor status varies significantly by race, HER2 status does not show the same divergence. HER2 amplification or overexpression is present in approximately 20% of primary invasive breast cancers. HER2-positive, hormone receptor-negative tumors demonstrate more aggressive features and worse breast cancer-specific survival than hormone receptor-positive and HER2-negative tumors,[14] although survival has vastly improved with new targeted therapies such as trastuzumab, lapatinib, and pertuzumab. Unlike the hormone receptor status, the Carolina Breast Cancer Study did not find an association between the percentage of HER2-positive/ER-negative tumors and race.[14] In addition, Elledge et al[17] did not find a difference in HER2 expression between African Americans and whites in a pathological analysis of more than 6000 tumors. Nonetheless, access to appropriate diagnosis and effective HER2 targeted therapies may be limited in resource-poor settings, leading to worse outcomes for African American women with HER2-positive breast cancer.

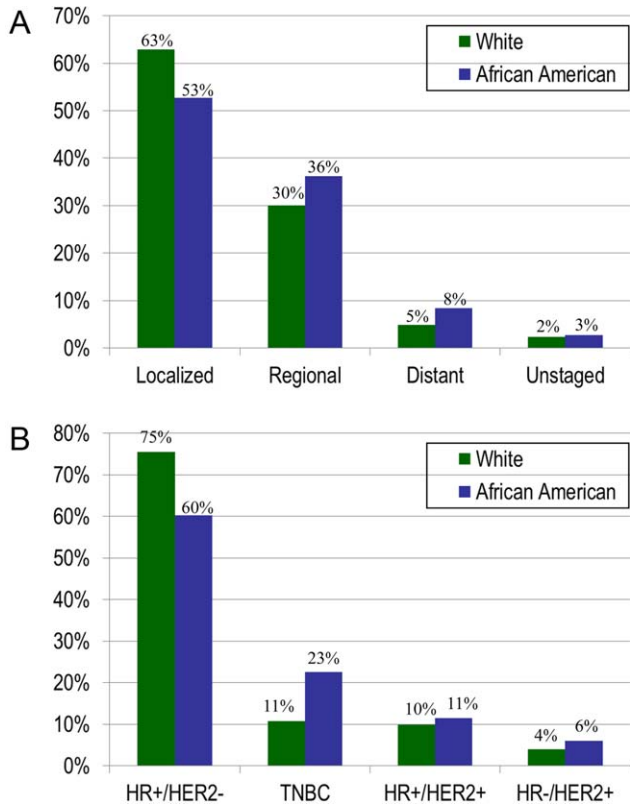

FIGURE 3. (A) Breast Cancer Stage Distribution by Race: 2002-2011. Source: Surveillance, Epidemiology, and End Results Program. Fast stats: breast; 2014. seer.cancer.gov/faststats/selections.php?#Output. Accessed August 6, 2014.[12] (B) Breast Cancer Distribution by Receptor Status and Race: 2010. HER2 indicates human epidermal growth factor receptor 2; HR, hormone receptor; TNBC, triple-negative breast cancer. Source: Demographic and clinical characteristics of breast cancer subtypes in women with invasive breast cancer, SEER-18, excluding Alaska, 2010.[13] Source: Howlander N, Altekruse SF, Li CI, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *J Natl Cancer Inst.* 2014;106:dju055.[14]

Triple-Negative Breast Cancer

The triple-negative breast cancer subtype lacks the markers of ER, PR, and HER2 overexpression. The term *triple-negative* is often used interchangeably with *basal-like breast cancer* because basal-like breast cancers are negative for ER, PR, and HER2 and overexpress cytokeratins 5 and 6 and Her1/epidermal growth factor receptor.[14,18] As discussed previously, although other subtypes have benefited from drug development regarding hormonal therapies and HER2-targeted treatments, triple-negative breast cancer has not experienced the same pharmacologic breakthroughs. As such, even after analyses control for the stage at diagnosis, women with this subtype have poorer survival than those with other breast cancers.[19] African American women have a higher incidence of triple-negative breast cancer than white women.[20] The Carolina Breast Cancer Study found that 26% of African American women had triple-negative breast cancer, whereas 16% of non-African American women did.[14] This subtype was most common among premenopausal African American women (39% of diagnosed cancer subtypes). In Iqbal et al's study[11] of 373,563 women from the SEER 18 registries database, 17.2% of African American women had triple-negative breast tumors ≤ 2 cm in size, whereas 8.0% of non-Hispanic white women did. Kurian et al[10] calculated the lifetime risk of triple-negative breast cancer to be highest in African American women at 1.98% (1.80%-2.17%) versus 1.25% (1.20%-1.30%) for non-Hispanic whites and 1.04% (0.96%-1.13%) for Hispanics. Interestingly, in the Carolina Breast Cancer Study and the recent analysis of the SEER database by Iqbal et al., when triple-negative breast cancer patients were excluded from the analysis, breast cancer-specific survival remained significantly worse among premenopausal African American women.[14] Accordingly, this argues that although the increased incidence of triple-negative breast cancer in part explains the poor outcomes, factors associated with the effective treatment of different subtypes of breast cancer could also in part explain the disparity seen in mortality for African American and white women.

Histologic Grade

Histologic grade is another characteristic of tumor biology used to identify more aggressive breast tumors. Schwartz et al[21] showed that for each combination of tumor size and lymph nodes, a categorical increase in histologic grade was associated with a progressive decrease in 10-year survival. Using data from the SEER program, Henson et al[22] investigated histologic grade as it relates to the stage of disease, tumor size, and survival between African American and white women. The researchers found that regardless of age, African American women had "proportionately more Grade III tumors and fewer Grade I and Grade II tumors for all stages combined and for each individual stage group."[22] In addition, for every tumor size, except for tumors smaller than 1.0 cm, African American women had significantly more grade 3 tumors than white women. Relatedly, other studies have demonstrated that African American women more frequently have tumors that present with necrosis, which also portends a worse prognosis.[23] Thus, the research has demonstrated that tumor biology is different in many African American and white patients, and it must be assessed as a potentially significant contributing factor to the survival disparity.

Genomics

Germline Mutations: *BRCA1* and *BRCA2* Mutations

In addition to tumor biology, cancer genomics have become increasingly important in guiding cancer prognosis and treatment. Approximately 5% to 10% of breast cancer cases present in individuals with inherited mutations in autosomal dominant, highly penetrant breast cancer susceptibility genes.[24] Accounting for 80% to 90% of families containing

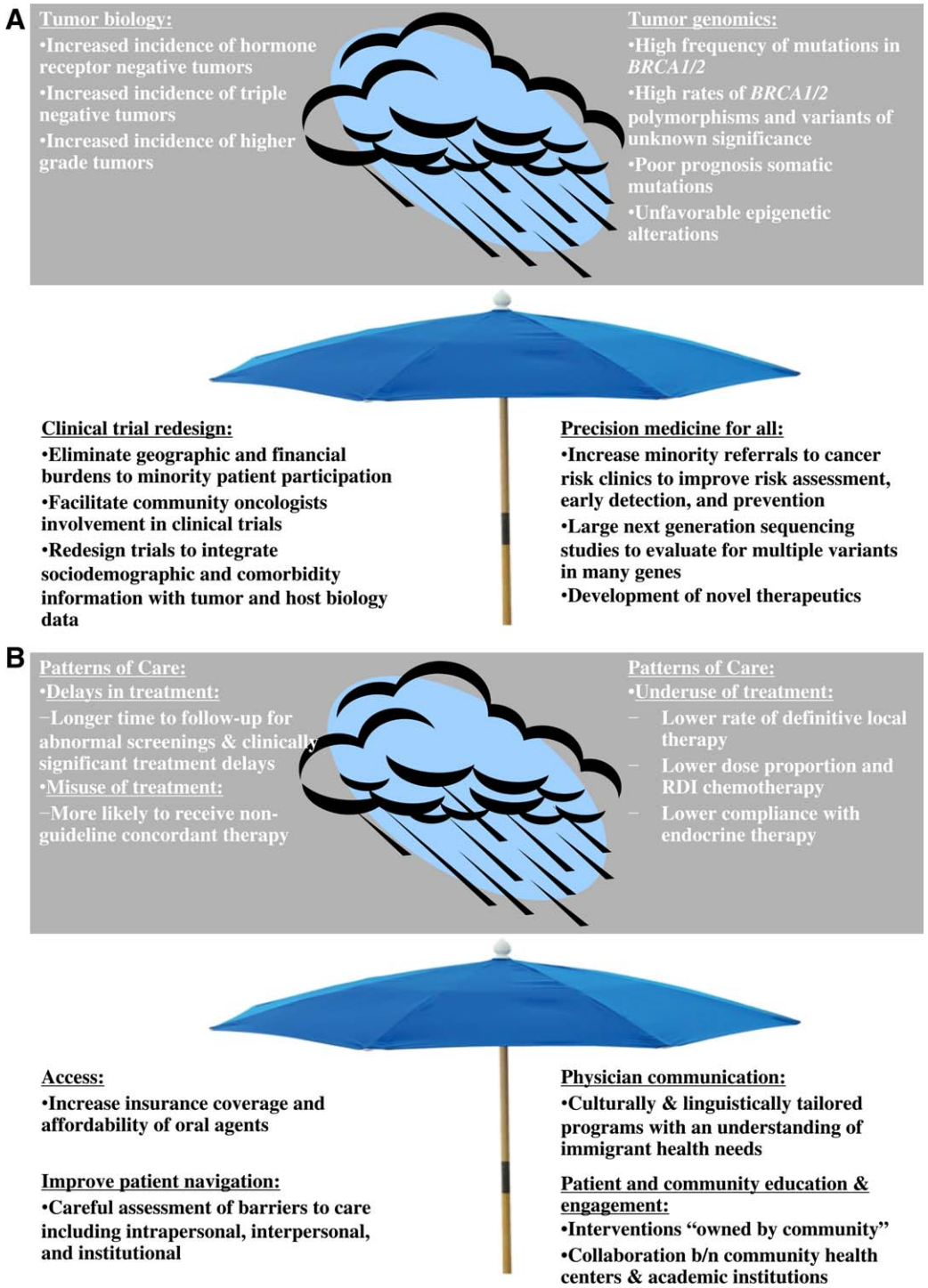

FIGURE 4. The Perfect Storm: The Racial Survival Disparity in Breast Cancer and Interventions for Change. (A) The first element in the storm: tumor biology and genomics. (B) The second element in the storm: patterns of care. RDI indicates relative dose intensity.

multiple cases of breast and ovarian cancer, *BRCA1* and *BRCA2* germline mutations are the most common of the breast cancer susceptibility genes.[25] The profile of these patients is often the younger patient with a higher grade tumor that is hormone receptor-negative, which, as discussed previously, also often matches the profile of the African American breast cancer patient.[26]

Despite similarities between *BRCA1*-associated breast cancers and breast cancer in African Americans, genetic abnormalities in African American breast cancer patients remain underresearched. In one study, Nanda et al[27] performed a comparative analysis of genetic testing in an ethnically diverse cohort of high-risk women. The researchers found that *BRCA1* and *BRCA2* mutations occur with appreciable

frequency in high-risk families of African ancestry, with 28% testing positive for a deleterious mutation in one of these genes. This frequency, however, was at a lower rate than that found in non-Hispanic, non-Jewish whites, who had a rate of 46%, because African Americans had a higher rate of polymorphisms and variants of unknown significance (44% vs 12% for non-Hispanic, non-Jewish whites). As genomics testing for multiple genes becomes widely adopted, determining the significance of unclassified variants in minority populations in breast cancer etiology remains an area for further research.[27] African Americans are not a monolithic group, and the results of any one study can never be extrapolated to the general population of African Americans or blacks of African or Caribbean ancestry in the United States. Nonetheless, high frequencies of mutations in *BRCA1* and *BRCA2* have been reported in unselected breast cancer patients of African ancestry from Nigeria and the Bahamas, and this could inform population-specific approaches to screening.[28,29] In a population-based study from the Northern California site of the Breast Cancer Family Registry, the *BRCA1* mutation prevalence was 16.7% in African American cases diagnosed under the age of 35 years versus 7.2% in non-Hispanic, non-Ashkenazi Jewish whites in the same age category.[30] In a recent report on a large cohort of self-reported African American patients from a single urban institution that integrated mutation results from next-generation sequencing, clinical characteristics of the patients, and tumor phenotype, Churpek et al[31] showed that inherited mutations in the *BRCA1* and *BRCA2* genes were the strongest predictors of breast and/or ovarian cancer risk. In that study, 68 damaging germline mutations were identified in 65 of 289 African American patients tested (22%; 95% confidence interval [CI], 18%-28%). They found that 10.0% (29 of 289) of cases carried pathogenic *BRCA1* mutations, and 8.0% (23 of 289) of cases were *BRCA2* mutation-positive. A much smaller fraction carried mutations in *PALB2*, *CHEK2*, *BARD1*, *ATM*, *PTEN*, or *TP53*. More than 2 decades after the *BRCA1* and *BRCA2* genes were identified, larger studies using next-generation sequencing in diverse populations are still needed to derive true estimates of the burden of mutations in both genes in underserved and understudied populations.

Somatic Mutations: *TP53* Mutations

In addition to germline *BRCA* mutations, somatic mutations are also known to contribute to breast cancer outcomes. Germline mutations in *TP53* account for less than 1% of female breast cancers, but somatic mutations are found in approximately 50% of breast cancers and are associated with a worse prognosis.[32] In fact, Dookeran et al[33] demonstrated that *TP53* is an independent predictor of survival after adjustments for the effects of age, stage, grade, and subtype. Although *TP53* mutations have been found to occur with equal frequency in whites and African Americans,[17] several studies have found differences in the specific gene alterations.[34,35] These genetic variants have been demonstrated to have potentially different impacts on survival. Shiao et al[34] found a significant increase in mortality in African American patients with p53 mutations that was not observed in white patients. Accordingly, the specific gene alterations found in African American and white patients could have a differential effect on breast cancer behavior, but this has not been explored with sufficient rigor. The Cancer Genome Atlas and the International Cancer Genome Atlas are large collaborative projects that should specifically recruit biospecimens and oversample breast tumors from women of African ancestry to address differences in the spectrum of clinically relevant germline and somatic gene mutations.[36,37]

Epigenetics and Metabolomics: *RASSF1A*, *BRCA1*, and *MYC* Activation Signature

Epigenetics is another focus of genomics and metabolomics research that could potentially be significant in explaining the survival disparity. In a meta-analysis, promoter hypermethylation of the tumor suppressor gene RAS-association domain family 1 isoform A (*RASSF1A*) conferred a higher risk of relapse and worse survival in patients with breast cancer.[38] A study that compared molecular alterations at the epigenetic level found that African American women, less than 50 years of age, with hormone receptor-negative tumors have a significantly higher frequency of hypermethylation of *RASSF1A* than white women.[39] *BRCA1* methylation has also been shown to play a role in a significant proportion of triple-negative breast cancers and is a plausible biological mechanism for breast cancer disparities.[40] At its promoter, *BRCA1* transcription is controlled by several mediators of metabolic transduction, including histone acetyltransferases, p300, and P300/CBP-associated factor, which play distinct roles in upregulating *BRCA1* transcription through histone acetylation.[41] This activity is opposed by the action of nicotinamide adenine dinucleotide (NADH) through the NADH-activated C-terminal–binding protein (CtBP) complexes.[42] Gardner and his colleagues have shown that CtBP serves as a direct molecular link between *BRCA1* expression and the metabolic status of the cells, where metabolic manipulation of NADH levels, through alterations of glycolysis or hypoxia, could directly influence the transcription of the *BRCA1* gene. This thus provides molecular evidence of a link between conditions of metabolic imbalance such as obesity and diabetes, which is highly prevalent among African Americans and breast cancer.[42] Terunuma et al[43] also recently showed that African American breast cancer patients develop a breast tumor with an *MYC* activation signature more commonly than

European-American patients, and this signature occurs mostly in ER-negative tumors. The occurence of this signature can be partly explained by single nucleotide variants (SNPs) at the 8q24 genomic locus, which has been linked to a higher risk of prostate cancer in African American men.[44] Patients with the 8q24 variant, which encodes a transcription factor 4 binding site, are more likely to have an *MYC* activation signature in their tumors. Thus, in part, the heightened occurrence of the *MYC* signature in African American patients compared to white patients seems to be linked to ancestry, which affects metabolism and breast cancer biology. Interestingly, the tumor metabolome of ER-negative breast tumors with the *MYC* activation signature is very different from that of ER-negative tumors without this signature. This again underscores the heterogeneity between the biology of African American and white breast cancer tumors.

Cancer Risk Clinics: Patterns of Referral

These genetic variations in African Americans, with their associated aggressive breast cancer characteristics, highlight the need for further study of breast cancer genomics in minority populations. However, Armstrong et al[45] illuminated the existence of racial/ethnic disparities in patterns of referral to cancer risk clinics. In their study, African American women with a family history of breast or ovarian cancer were significantly less likely to undergo genetic counseling for *BRCA1/2* testing than white women with this family history (odds ratio [OR], 0.22; 95% CI, 0.12-0.40). The results of this study were significant for the magnitude of the disparity, with white women having an almost 5 times greater odds of undergoing this clinically important evaluation.[45] It has also been demonstrated that there is a lack of education in the African American community by physicians about the role and importance of cancer genomics and genetic counseling.[46] In focus group sessions, Matthews et al[47] found that among a sample of African American participants with a strong family history of cancer, nearly one-half (48%) reported rarely discussing cancer-related issues with family members, and none had knowledge of breast cancer genomics, genetic counseling, or the BRCA genes. Wideroff et al[48] have reported that the factor most strongly associated with physician use of genetic services, more so than availability of services, is patient inquiry about whether she or he can or should get tested (OR, 5.52; 95% CI, 3.97-7.67).[48] These differences in patterns of referral contribute to the paucity of data on African American genetic variants in *BRCA1* and *BRCA2* susceptibility genes and the potential misclassification of deleterious mutations as unclassified variants.

Although these differences in tumor biology and genomics tell part of the mortality disparity story, they are not the only voices, and there is more of the story to be told. In a study of African American and white patients in South Carolina, Adams et al[49] determined survival rates by ethnicity adjusted for disease stage and other prognostic characteristics. After they controlled for age, stage, ER, and HER2 as well as insurance status, African American women still had a 2-fold excess risk of death from breast cancer (hazard ratio [HR], 2.41; 95% CI, 1.21-4.79). Henson et al[22] demonstrated that for each combination of grade and stage, the 6-year disease-specific survival rate was consistently lower for African American women versus white women, and Menashe et al[50] showed that the hazard of breast cancer death was statistically significantly higher in African American women versus white women, regardless of ER expression, and it persisted after adjustments for multiple tumor and demographic characteristics. Finally, in another study that examined survival after controlling for stage and hormone receptor status, the authors found that African American women younger than 50 years had significantly lower stage-specific survival rates for ER-positive and ER-negative tumors.[51] Thus, in addition to differences in the innate characteristics of the breast tumors, racial differences in patterns of care for women with breast cancer must be considered in unraveling the observed disparity in mortality.

Patterns of Care: The Second Element of the Perfect Storm

Screening and Treatment

Mammography

Despite advances in breast cancer imaging technology, the mainstay of breast cancer screening has remained mammography. Chu et al[51] found that African American females have less early-stage disease in every age group for each hormone receptor status, and this raises the concern that mammography screening might be inadequate in this population. Although historically African American women used mammography less than white women, this difference has fortunately almost disappeared with time.[4] According to results from the 2010 National Health Interview Survey, among women who were 40 years or older, 50.6% of non-Hispanic African Americans and 51.5% of non-Hispanic whites reported having a mammogram within the past year.[52] A study by van Ravesteyn et al[53] designed to further investigate how much of the mortality disparity could be attributed to racial differences in factors such as uptake in mammography demonstrated that the effect of reduced screening use on breast cancer mortality rates was relatively small (7%-8%).

However, although mammography uptake may be similar, there remain differences in the quality and follow-up of abnormal imaging results. A study of mammography

capacity and quality in a large urban setting found that the facilities that served predominantly minority women were less likely to be academic (27% vs 71%) or private institutions (29% vs 43%), less likely to have digital mammography (18% vs 71%), and less likely to have dedicated breast imaging specialists reading the films (23% vs 87%). The authors concluded that the mammography process was broken, with quality differences in the manner in which the centers provided care and reported back results.[54] Highlighting the importance of place on breast cancer care, Gehlert at al.[55] asserted that ensuring that inner-city health facilities have up-to-date, well-maintained equipment and that mammographers have access to continuing training and opportunities for consultation should help reduce African American breast cancer mortality.

With respect to follow-up of abnormal imaging results, a large retrospective cohort study of 6722 women with an abnormal mammogram from January 2002 through December 2002 at a New York academic medical center found longer times to diagnostic follow-up for African American versus white women. The median number of days to diagnostic follow-up after an abnormal mammogram was 20 days for African American patients and 21 days for Hispanic patients versus 14 days for white patients, and racial disparities remained significant after the researchers controlled for age, Breast Imaging Reporting and Data System (BIRADS) category, insurance status, provider practice location, and median household income. More importantly, in the population of women with a BIRADS classification of 4 or 5 who did not have same-day additional imaging, the median number of days to follow-up was 26 for African American women and 23 days for Hispanic women versus 14 days for white women ($P < .05$).[56]

Delays in Treatment

A cascade of delays has been documented in breast cancer care for African American women in addition to the delays just discussed regarding abnormal mammogram follow-up. Silber et al[57] recently investigated factors associated with differences in African American and white breast cancer outcomes in a large population-based study using SEER-Medicare data. The mean time from diagnosis to treatment was 29.2 days for African Americans versus 22.5 days for whites ($P < .001$). The authors also found that African Americans were more likely to have very long treatment delays. Six percent of African Americans did not initiate treatment within the first 3 months of the diagnosis, whereas only 3% of whites did not ($P < .001$). Gwyn et al[58] also found potentially clinically significant treatment delays more often for African American women versus white women. The time from medical consultation to the initiation of treatment was greater than 3 months for 22.4% of African American women versus 14.3% of white women. Three months was chosen as clinically significant because Richards et al[59] demonstrated that a delay greater than or equal to 3 months may affect survival. The impact of treatment delays on survival was also explored by McLaughlin et al[60] in a study of North Carolina Medicaid enrollees diagnosed with breast cancer. A large proportion of this population (44.3%) were racial minorities. The authors found that 1 in 10 women waited $\geq$60 days to initiate treatment after a diagnosis of breast cancer, and a delay of this length among patients with late-stage breast cancer was associated with 66% and 88% increased risks of overall and breast cancer-related death, respectively. Thus, delays in the diagnosis and treatment of African American women are eroding factors that worsen the survival gap.

Misuse of Treatment

Once treatment is initiated, studies have demonstrated that African Americans are often receiving inappropriate therapy. Li et al[61] examined SEER data from 1992 to 1998 to evaluate the relationship between race and ethnicity and breast cancer treatment. African American women with stage I or II disease were 40% more likely to receive inappropriate treatment ($P < .05$), which was defined as not meeting 2000 National Comprehensive Cancer Network practice guidelines. In another study, a prospective analysis of 957 patients in 101 oncology practices, Griggs et al[62] found more frequent use of non–guideline-concordant adjuvant chemotherapy regimens in African American women. In a univariate analysis, African American patients were more likely to receive a nonstandard regimen than whites (19% vs 11%, $P = .047$). Although we will discuss further in this review whether guidelines based on clinical trials are appropriate for African American patients, the studies demonstrate that these women are not uniformly receiving standard-of-care treatment.

Underuse of Treatment

Aside from the misuse of treatment, studies have also examined undertreatment of African American patients with breast cancer. Freedman et al[63] examined racial disparities in local therapy for early-stage breast cancer. For women with stage I and II breast cancers, guidelines recommend breast-conserving surgery with whole breast radiation or modified radical mastectomy for definitive local therapy. The authors found lower rates of definitive local therapy for African American patients versus white patients (86.0% vs 82.8%, $P < .0001$).

Beyond local treatment, another study examined chemotherapy administration among African American patients with stage I to III breast cancer at 10 different treatment sites. African American patients received a lower dose proportion (actual vs expected dose) and relative dose intensity

than white patients (0.80 vs 0.85 [$P = .03$] and 0.76 vs 0.80 [$P = .01$]). The authors found that differences in biological and medical characteristics, such as tolerance of therapy, comorbidity, and leukocyte counts, did not explain the difference. In fact, despite the association between lower leukocyte counts and African American ethnicity, there was no evidence that the white blood cell level accounted for the difference in dose proportion or relative dose intensity. Most significantly, the authors discovered that more African Americans had chemotherapy dose reductions for the first cycle of treatment (OR for nonoverweight African Americans, 3.7; $P < .05$), and this perhaps indicates physician assumptions regarding African American patients' ability to tolerate chemotherapy.[64]

Smith et al[65] also examined ethnic differences in the administration of adjuvant chemotherapy for breast cancer. The authors found that modification of chemotherapy administration was more common among African American patients (65.2% vs 41.8%, relative risk, 1.56; $P = .04$), and African American patients were also 2.49 times more likely than white patients to receive reduced cumulative doses of chemotherapy ($P = .03$). In contrast to their hypothesis and similarly to the aforementioned study, they also did not find excess hematologic toxicity among African American patients as the source of these chemotherapy modifications.

Silber et al[57] also examined differences in the administration of chemotherapy between white and African American breast cancer patients. The authors found that 3.7% of African Americans received both an anthracycline and a taxane, whereas 5.0% of whites matched to African Americans at presentation did. Bickell et al[66] explored further racial disparity in the underuse of adjuvant breast cancer treatment. The researchers examined the medical records of 677 women treated surgically for stage I or II breast cancer in 1999 to 2000. The study defined underuse as omissions of radiotherapy after breast-conserving surgery, adjuvant chemotherapy after the resection of hormone receptor-negative tumors ≥ 1 cm, or of hormonal therapy for receptor-positive tumors ≥ 1 cm. Underuse of appropriate adjuvant treatment was found in 34% of African American patients versus 16% of white patients ($P < .001$). There were racial disparities present in all 3 adjuvant therapies assessed.

Oral hormonal therapy has been demonstrated in clinical trials to be effective in preventing breast cancer recurrence and death in women with early-stage breast cancer.[67] Bickell et al's study[66] documented underuse of this treatment in African American patients. Partridge et al[68] conducted the largest study of the use of oral antineoplastics outside a clinical trial setting. Their study consisted of 2378 primary breast cancer patients enrolled in New Jersey's Medicaid or pharmaceutical assistance program, with the main outcome being the number of days covered by filled prescriptions for tamoxifen in the first year of therapy. The study found that nonwhite patients had significantly lower adherence rates than white patients (OR, 1.62; 95% CI 1.26-2.09). Although further investigation is needed to determine the drivers of this nonadherence to oral antineoplastics in African American patients, the cost of these medications has been proposed as a significant factor leading to their underuse. Streeter et al[69] analyzed a nationally representative pharmacy claims database for oral antineoplastics and calculated the abandonment rate for the initial claim. Not surprisingly, high cost sharing and low income were associated with a higher abandonment rate ($P < .05$). Despite being an important component of health equity research, treatment adherence has been recently identified by the Association of American Medical Colleges as a critically underrepresented area in disparities-focused health services research; it represents only 4% of health outcomes assessed in disparities-focused research projects.[70] More attention to this area is needed to understand the underuse of hormonal therapies in African American breast cancer patients.

The treatment strategies that have been shown to be delayed, underused, or misused in African American patients in the aforementioned studies have been demonstrated to improve disease-free and overall survival in large randomized trials. Furthermore, diminished total dose and dose intensity of adjuvant chemotherapy for breast cancer have been associated with lower survival rates.[71,72] Thus, these quality-of-care failures in breast cancer treatment for minority patients are thought to partially explain the racial survival disparity because it has been proposed that African American and white patients derive a similar benefit from systemic therapy when it is administered in accordance with their clinical and pathologic presentation.[73] This assumption, though, becomes more nuanced when the clinical trial experience is reviewed.

Clinical Trial Experience

Dignam[73] examined survival by race in several National Surgical Adjuvant Breast and Bowel Project trials. He found that the benefit from systemic adjuvant therapy for recurrence and mortality reduction was comparable between African American and white patients. His survey of trials consistently indicated equivalent disease-free survival. However, a mortality deficit for African Americans was also consistently found. There was a 21% excess risk of mortality among lymph node-negative African American patients and a 17% excess risk of mortality among lymph node-positive African American patients. This excess mortality risk was thought to be attributable to greater mortality from noncancer causes among African American patients rather than

a failure of African American patients to respond to breast cancer treatment.

In contrast to Dignam's findings,[73] Hershman et al[74] assessed the association between race and treatment discontinuation/delay, white blood cell counts, and survival in women enrolled in Southwest Oncology Group adjuvant breast cancer trials. The study found that African American women were significantly more likely to experience treatment discontinuation/delay than white women (87% vs 81%, respectively, $P = .04$). These delays were not accounted for by toxicities because these were experienced in similar proportions by race. African American women were also more likely to miss appointments than white women (19% vs 9%, $P = .0002$); perhaps, as Hassett and Griggs[75] speculated, this speaks to economic barriers, including the inability to arrange alternate child care, miss work, or afford transportation to the clinic. However, despite these barriers to care for African American patients, they still received the same mean relative dose intensity as white patients (87% for African Americans vs 86% for whites).

In their survival analysis, Hershman et al[74] controlled for treatment-related factors such as dose reductions and delays, body surface area, baseline white blood counts, and other predictors of survival and still found that African American women had worse disease-free (HR, 1.56; 95% CI, 1.15-2.11) and overall survival (HR, 1.95; 95% CI, 1.36-2.78) than white women. The authors concluded that the study was "unable to demonstrate that any factor related to treatment quality or delivery contributed to racial differences in survival between the groups."[74] The study thus established 2 important findings related to the disparity gap. First, even in the controlled setting of a clinical trial, African American patients faced barriers to optimal treatment,[75] and, second, despite attempts to control for treatment quality and delivery, African American women still had worse outcomes.

Role of Comorbidity and Obesity

Beyond tumor, diagnostic, and treatment factors, researchers have argued that other clinical factors, including obesity and associated comorbidities, are the significant contributing factors to the racial mortality disparity. Using a historical cohort from the Henry Ford Health System, Tammemagi et al[76] evaluated the role of comorbidity in racial disparity among breast cancer survivors. The researchers found that at least one adverse comorbidity was observed in 86% of African Americans versus 65.7% of whites (OR, 3.20; 95% CI, 2.17-4.72), and comorbidity explained nearly half of the overall survival disparity. Diabetes and hypertension were particularly significant in explaining the disparity.

Tammemagi et al[76] also found a preponderance of obesity among African American patients. A body mass index of 25 kg/m^2 or higher (classified as overweight) was observed in 72% of African Americans versus 49.7% of whites ($P < .001$). Ogden et al[77] also demonstrated that the prevalence of obesity dropped 13.2% among non-Hispanic white women 60 years old or older from 1999-2000 to 2003-2004 but increased 7.6% among African American women in the same age group during the same time period. Obesity has been proposed to affect breast cancer survival through a variety of mechanisms, including mammography use, screening performance, mammography follow-up, and treatment efficacy.[78–80]

Despite these findings, studies controlling for comorbidities and obesity have still found a racial survival difference. Griggs et al[62] found that comorbidity was not associated with receiving nonstandard treatment. In addition, as discussed previously, the survival difference remains in clinical trials, which would presumably control for significant clinical comorbidities,[20] and a survival disparity was found despite researchers' controlling for body surface area in Hershman et al's study[74] examining data from Southwest Oncology Group trials. Finally, Curtis et al[81] examined SEER-Medicare data to evaluate racial differences in breast cancer survival after adjustments for several factors, including comorbidity. Comorbidity contributed relatively little to the racial differences noted (approximately 2% in their model).

Thus, the search for the source of the breast cancer racial survival disparity has identified multiple contributing agents. We have reviewed the fact that tumor biology and genomics are significantly different between African American and white patients. We have also discussed that there are differences in screening, follow-up, and treatment by race, with African American patients receiving inferior quality of care. However, the consensus from the research is that neither of these features alone is sufficient to explain the breast cancer survival gap. The conclusion to be drawn is that in closing this gap, policymakers must consider both the biological differences and the patterns-of-care differences concurrently to form effective interventions.

Interventions

Insurance

Eliminating racial disparities in cancer mortality through effective interventions has become an increasingly important imperative in federal, state, and community health care programs. It is one of the American Cancer Society's 2015 challenge goals and of the American Society of Clinical Oncology.[4,82] It has been posited that interventions aimed at providing insurance coverage to minority patients will be able to reduce racial health care disparities.[83] Studies have indicated that women without insurance present with more advanced-stage disease,[84,85] are more likely to not undergo breast-conserving surgery for nonmetastatic T1/T2 tumors,[85] and are more likely to receive nonstandard treatment.[86] However, outside of cancer care, a large study of Medicaid expansion in Oregon demonstrated that

Medicaid coverage alone generated no significant improvements in measured physical health outcomes in the first 2 years.[87] Thus, coverage alone does not ensure that patients will be able to navigate the health care system and that quality care will be provided.

In breast cancer, Hoffman et al[88] evaluated the effect of race and health insurance on the diagnostic time, which was defined as the number of days from a suspicious finding to diagnostic resolution (either no evidence of malignancy on diagnostic mammogram or definitive diagnosis by biopsy), in a large urban setting. The authors' hypothesis was that every insured patient would receive the same timely diagnosis as any other patient with equivalent insurance, regardless of race or ethnicity. The study found that non-Hispanic whites with government insurance had significantly shorter diagnostic times than non-Hispanic African Americans with government insurance ($P = .0003$): the average diagnostic times were 12 and 39 days, respectively. In addition, privately insured non-Hispanic whites also had significantly shorter diagnostic times than privately insured non-Hispanic African Americans (16 versus 27 days). The odds of non-Hispanic African Americans having diagnostic delays greater than 60 days (ie, past the guideline recommended by the Centers for Disease Control and Prevention) were 1.6 times greater than the odds for non-Hispanic whites. The authors concluded that the lack of health insurance is not the only barrier to quality care for African American patients.

This study supports the findings discussed earlier by Press et al,[56] who examined median days to follow-up after an abnormal mammogram. Their study found that differences remained significant in their multivariate model after they controlled for insurance. In addition, Short et al[89] demonstrated that when the health plan status was held constant in a retrospective study of 476 white patients and 99 African American patients with newly diagnosed breast cancer, African Americans had a higher mortality rate (8.1% vs 3.6%, $P = .06$) and were diagnosed at a later stage (OR, 1.71; $P = .02$). Accordingly, interventions must go beyond just providing health insurance to minorities in order to have a significant impact on the mortality gap.

Patient Education and Physician Communication

An underlying cause frequently cited for the delayed diagnosis and treatment of African American patients with breast cancer is a lack of patient education and physician communication. These elements are essential components of quality care. In a qualitative study of low-income, ethnically diverse women older than 40 years, Allen et al[90] identified salient themes differentiating women who received timely follow-up from those who did not. For the women who delayed follow-up, prominent themes were dissatisfaction with the communication of results, disrespect on the part of providers and clinic staff, logistical barriers to accessing services, anxiety and fear about a possible cancer diagnosis, and a lack of information about breast cancer screening and symptoms. In another study, Masi and Gehlert[91] employed focus group interviews of African American adults to characterize perceptions of breast cancer treatment. Their analysis revealed a core set of themes, including mistrust of the medical establishment and concern about the effect of racism on treatment quality; they concluded that "in the eyes of many study participants, the issues of trust, race, and quality of care were closely intertwined."[91] With interventions aimed at improving patient education and physician communication, these barriers identified by Allen et al and Masi and Gehlert can likely be overcome, and this will allow more timely diagnosis and treatment.

Janz et al[92] examined racial differences in the adequacy of information and support for women with breast cancer. The researchers used survey data from a population of 1766 women diagnosed with nonmetastatic breast cancer and reported to the Los Angeles County SEER registry. The study found that across treatment- and survivorship-related issues, African American women desired more information than white women ($P < .001$). One of the explanations for the unmet information needs posited by the authors is a failure to provide culturally appropriate information related to health issues. This breakdown in patient education and communication was demonstrated by Hawley et al[93] to hold across providers and locations.

Hawley et al[93] evaluated the association between minority patients' knowledge of breast cancer treatment risks and benefits and provider characteristics and treatment locations. The provider characteristics included surgeon-level independent variables, such as breast cancer procedure volume and demographics (years in practice and sex). The treatment location variable was categorized into 1 of 3 groups: National Cancer Institute-designated cancer center, American College of Surgeons cancer program, or no specific cancer program. Provider characteristics and treatment location are factors previously identified to be associated with high-quality care. The study employed a multivariate regression to identify associations between patient, surgeon, and treatment setting factors and accurate knowledge of the survival benefit and recurrence risk related to mastectomy and breast-conserving surgery with radiation. The authors found that minority women were significantly less likely to have adequate survival knowledge and more likely to be uncertain about recurrence risk than white patients ($P < .001$). In the multivariate logistic regression model, neither provider characteristics nor treatment setting attenuated observed racial disparities in knowledge. Quality health care depends on the ability to make an informed treatment decision. Although patient education also plays a

role, it has been demonstrated that breast cancer death rates are substantially higher for African American women than white women with the same education level.[94] As the authors concluded, this study underscores the need for providers to communicate information effectively to all patients, and effective communication relies on the cultural competency of providers.[95] Without effective, culturally competent communication, there are treatment delays and omissions that result in poor quality care. Currently, the research has established that these communication deficits are found across provider and treatment center types.

African-born immigrants, one of the fastest growing immigrant groups in the United States, are a population in which the lack of culturally competent patient communication has been especially evident. In a systematic literature review of cancer care among African immigrants, Hurtado-de-Mendoza et al[96] found that African immigrants have limited knowledge about cancer care, associate breast cancer with certain death, and sometimes attribute breast cancer to a punishment from God. These perceptions create barriers to screening and treatment because these patients have limited knowledge and awareness about screening practices, have emotions at odds with screening (shame, modesty, and fear of screening procedures), and have cultural values perceived to be at odds with medical practices.[96] Interventions that have been shown to be successful with immigrant breast cancer health are those that employ linguistically and culturally tailored programs.[97] This was demonstrated by Percac-Lima et al[98] in a study in which immigrant patients were educated on breast health and breast cancer detection with a linguistically and culturally tailored breast cancer screening program. During the 4-year study period, the adjusted mammography rates for refugee women in the program climbed from 64.1% (vs an English-speaking rate of 76.5% and a Spanish-speaking rate of 85.2%) to 81.2% at the end of the program.

Patient Navigation

Patient navigation has been championed as a method of improving care in breast cancer by enhancing patient communication and education and removing barriers to timely care. Patient navigation empowers patients to become knowledgeable about their own health and supports patients through the course of care.[99] Patient navigation programs have been developed to address the patient communication breakdowns and the underuse and misuse of treatment among vulnerable populations that have already been detailed in this review and are thought to be contributing to the racial mortality gap.[100]

A benefit of patient navigation has been suggested in studies evaluating the time to diagnosis and follow-up from an abnormal screening. Markossian et al[101] evaluated the efficacy of a Chicago-based cancer patient navigation program developed to reduce the time from abnormal screening to definitive diagnostic testing. The majority of patients in this study were Hispanic (66%) and African American (32%). Compared with controls without navigation, the breast navigation group had a shorter time to diagnostic resolution (adjusted HR, 1.65; 95% CI, 1.20-2.28; $P = .002$). Hoffman et al[102] evaluated patient navigation in the District of Columbia to determine its ability to reduce the breast cancer diagnostic time (the number of days from abnormal screening to a definitive diagnosis). African American women composed 48% of the study population. They found that navigated women reached their diagnostic resolution significantly faster than nonnavigated women, and there was a nearly 4-fold reduction in the time to diagnostic resolution for navigated women versus nonnavigated women who resolved with cancer. Finally, another study of urban minority women examined delays in follow-up after an abnormal mammogram by randomly assigning patients to usual care or usual care plus patient navigation.[103] Women in the intervention group had shorter times to diagnostic resolution (mean, 25 versus 42.7 days; $P = .001$) and also had lower mean anxiety scores and higher mean satisfaction scores.

In a national multicenter study, Ko et al[99] were the first to evaluate whether patient navigation can improve the quality of breast cancer care. The authors hypothesized that breast cancer patients assigned a navigator would be more likely to receive recommended standard treatment than patients without a navigator. Three separate quality measures of breast cancer care, including initiation of anti-estrogen therapy, radiation therapy, and chemotherapy, were evaluated. The participants in the study were racially and ethnically diverse, with a plurality being African American (37.5%). The study produced mixed results: navigated patients had a statistically significant higher likelihood of receiving anti-estrogen therapy than nonnavigated controls (OR, 1.73; $P = .004$), but navigated patients eligible for radiation therapy were no more likely to receive radiation (OR, 1.42; $P = .22$) than controls. The initiation of chemotherapy could not be accurately assessed because of a limited sample size. The study concluded that navigation alone does not remove all of the barriers to quality care for breast cancer patients, and barriers are diverse and potentially specific to the treatment modality.

A study by Tejeda et al[104] used a systematic framework to characterize the barriers faced by minority patients with breast and cervical cancer. They categorized barriers as intrapersonal (defined as characteristics of the individual; eg, knowledge, belief, attitudes, and transportation and financial barriers), interpersonal (processes that involve other people; eg, social support system, child care, and employment issues), and institutional (characteristics and policies of organizations). The authors found that although navigators were able to easily resolve intrapersonal-level

barriers, ongoing navigation was needed to address institutional-level barriers. Thus, patient navigation in a vacuum does not work, and it is only in examining the entire health care system that changes can be implemented to eliminate barriers to quality care and close the racial mortality chasm.

System Change

To this effect, Clarke et al[105] performed a systematic review of the disparities intervention literature to understand which interventions are being evaluated to improve minority health. The authors found that the majority of disparities interventions are focused on changing the patient rather than the system that serves her, with the most common strategy to improve minority health being education and training (37% of strategies studied). Interventions aimed at health care system improvements were surprisingly few, with the responsibility for change resting with the patient rather than the care delivery system. Interventions incorporating community involvement were also severely lacking and reflected only 6.5% of the reviewed intervention tactics. The role of place or the community where care is delivered is hard to underestimate because it affects access to and quality of care; therefore, interventions need to be owned by the community to be sustained through time.[55] The majority of interventions failed to involve major stakeholders, including providers, health care institutions, community organizers, and policy makers, and accordingly were unlikely to succeed in creating meaningful change.

In breast cancer, there have been examples of successful system-based approaches to reducing the racial mortality disparity. At New York area hospitals, Bickell et al[106] implemented a tracking and feedback registry to close the referral loop between surgeons and oncologists to decrease the underuse of valuable adjuvant treatments. The intervention targeted important quality issues in both communication (the breakdown in dialogue among providers of different specialties and between providers and patients) and the underuse of adjuvant treatment in minorities. The intervention was designed to address failures in the health care system through the involvement of leadership from pathology, surgery, and oncology. The intervention also incorporated technology, with the tracking software prompting contact with patients who had failed to follow up. Among African American and Hispanic women, there were statistically significant decreases in the underuse of radiotherapy (23% before the intervention vs 10% after the intervention, $P = .02$), chemotherapy (26% before the intervention vs 6% after the intervention, $P = .01$), and hormonal therapy (27% before the intervention vs 11% after the intervention, $P = .01$). After the intervention, minority race was no longer a risk factor for low rates of oncology consultation (adjusted relative risk, 1.0; 95% CI, 0.7-1.3) or for underuse of adjuvant therapy (adjusted relative risk, 1.0; 95% CI, 0.8-1.3).[106] Interestingly, 4 of the 6 hospitals involved in this study had a patient navigation system in place; however, as discussed, just the navigation system alone was not enough to address the system failures leading to the disparities in care.

Ansell et al[54] also described a system-based approach to reducing the breast cancer mortality disparity in Chicago. The Metropolitan Chicago Breast Cancer Taskforce was composed of 102 individuals and 74 Chicago area organizations to address the growing African American/white breast cancer mortality disparity. The taskforce identified a number of themes underlying the disparity gap, including a need for breast cancer education and outreach programs for African American women, a broken mammography process leading to quality differences between African American and white patients, and a number of barriers to diagnosis and treatment, including fear, a lack of primary care, the burden of insurance copays/deductibles, and the noncompletion of treatment for social and economic reasons. After identifying these underlying causes, the taskforce proposed that addressing one aspect of the health care system would not correct the problem, but rather quality improvement initiatives would have to occur across the continuum of care for breast cancer.

In Delaware, such a broad system-based intervention was implemented to eliminate health disparities in colorectal cancer.[107] Delaware created a comprehensive statewide colorectal cancer screening and treatment program combining many of the interventions discussed previously, including insurance coverage, patient education and communication, and patient navigation, to address the entire health care system and its treatment of African American patients with colorectal cancer. The state also partnered with underserved community organizations to tailor programs locally and create targeted marketing campaigns.

The results of this system-based approach were impressive, with screening rates among African Americans increasing from 48% to 74% and equaling the rate among whites. In addition, the percentage of patients diagnosed at advanced and regional stages among African Americans declined from 79% to 40%, and the percentage diagnosed at a local stage increased from 16% to 50%. Most importantly, the mortality rate declined by 42% for African Americans, and this resulted in a rate almost equal to that among whites ($P < .001$ for African Americans, $P = .002$ for whites).[107] Significantly, this program was also found to be economically viable because cost savings from reduced cancer incidence and the stage shift to cancers requiring less aggressive treatment offset the cost of the program. As the authors concluded, this model of a comprehensive, system-wide approach to the racial mortality difference would lend itself

to other cancers, and more research is needed to assess and build such an approach to breast cancer.

Delivery System Reform

As demonstrated in the aforementioned studies, multifaceted interventions that address all stakeholders are needed to close the racial disparity gap in breast cancer. The Patient Protection and Affordable Care Act (PPACA) emphasizes delivery system reform with a focus on the triple aim of better health, better health care, and lower costs.[108] One component of this reform will be accountable care organizations (ACOs). ACOs could potentially assist in closing the racial mortality gap because groups of providers will take responsibility for improving the health of a defined population and will be held accountable for the quality of care delivered.

In the ACO model, an integrated network of providers, led by primary care practitioners, will evaluate the necessity, quality, value, and accountable delivery of specialty diagnostic and therapeutic procedures, including cancer care.[109] ACOs will also collect extensive patient data through the meaningful use of medical records.[109] These detailed data can then be used to shape locoregional protocols for clinical decision making in oncology and can be used to evaluate physician performance. Intermountain Healthcare is an example of an organization that has had success with instituting these clinical protocols to highlight best practices and improve the quality of care.[110] In breast cancer, oncologists will need to be prepared to develop and follow protocols tailored for their communities, which will lead to standardized, improved care for minority populations.

The oncology medical home is one example of an ACO delivery system reform that has the potential to reduce the racial mortality gap. The oncology medical home replaces episodic care with long-term coordinated care and replaces the fee-for-service model with a performance and outcomes–based system. A key trait of the oncology medical home is care that is continuously improved by measurement against quality standards.[111] The model oncology home accomplishes this by incorporating software to extract clinical data as well as provider compliance with locoregional guidelines to provide oncologists with feedback regarding the quality of care that they are providing for their patients.[112] Through this system reform, oncologists will be held accountable for the care that they deliver, and it is hoped that this will eliminate the delays, misuse, and underuse of treatment. Trial oncology medical homes in North Carolina and Michigan have yielded promising results regarding improved care (fewer emergency department visits and inpatient admissions) and high adherence to national and practice-selected guidelines.[113,114]

PPACA also increases funding for community health centers and provides grants to support community health workers; this highlights again the importance of place in racial health care disparities.[115] Encouraging collaboration between community health centers and academic institutions, this funding could build bridges between minority communities and high-quality health care institutions while also improving patient communication and education.[115] As this review has discussed, a failure to provide culturally appropriate clinical information can lead to issues with follow-up and adjuvant treatment compliance and further widen the breast cancer racial mortality gap.

Conclusion

Delivery system reform has the potential to help close the disparity gap by improving the quality of care delivered to minority breast cancer patients. As Chin et al[116] describe in their analysis of effective strategies for reducing health disparities, successful interventions are "culturally tailored to meet patients' needs, employ multidisciplinary teams of care providers, and target multiple leverage points along a patient's pathway of care." ACOs have the financial incentive to meet these features of a successful intervention and improve quality across the continuum of breast cancer care. Equity of care is a fundamental component of quality of care, and efforts to reduce disparities will need to be integrated into ACO quality improvement efforts. In the face of this new era of organizational structures focused on coordinated, population-based care, oncology providers put themselves at financial risk if they do not position themselves for policy and reimbursement changes that reduce disparities.[116] However, ongoing research will be needed to ensure that as these changes are implemented, the racial mortality gap in breast cancer tightens and that no vulnerable patient populations are left out.

Precision Medicine for All

In addition, as discussed earlier in this review, there are differences in the tumor biology and genomics of breast cancer in African American patients. Beyond quality interventions, initiatives to reduce the mortality gap should focus on precision medicine for all and making research strides to better understand these biologic and genomic differences and tailor breast cancer treatments to respond to these differences. PPACA has taken steps in this direction as well by being the first federal law to require group health plans and state-licensed health insurance companies to cover standard-of-care costs associated with participation in clinical trials.[117] The clinical trial regulations also expressly require plans to show that administrative burdens are not used to create barriers to cancer care for anyone who might benefit from participation in a clinical trial.[115] The overarching goal of this push to eliminate financial and administrative barriers is to increase the enrollment of minority patients and

especially those patients who do not live close to academic medical centers. Community medical oncologists will be called upon to facilitate and encourage clinical trial participation by their minority patients and should be supported in this endeavor by academic medical centers. However, with greater minority patient involvement, there should also be further research on trial designs that lead to clinically significant findings for minority patients. As Polite et al[118] argue, at a bare minimum, basic sociodemographic and detailed comorbidity information should be prospectively collected and integrated with tumor and host biology data to better examine racial differences in cancer outcomes.

Initiatives are also needed to address the gap in referrals to cancer risk clinics so that more data are available on African American genetic variants and to create more robust risk assessment models. Risk assessment relies on predictive statistical models to estimate an individual's risk of developing cancer, and without accurate estimates of mutation prevalence in minority subgroups, these models' reliability is compromised.[119] As shown in a recent study at the University of Chicago cancer risk clinic using targeted genomic capture and next-generation sequencing, nearly 1 in 4 African American breast cancer patients referred to the clinic had inherited at least one damaging mutation that increased their risk for the most aggressive type of breast cancer.[120] To identify damaging mutations after a diagnosis of incurable breast cancer is failure of prevention. As has been documented in Ashkenazi Jewish populations, there is evidence of high rates of inherited mutations in genes that increase the risk for aggressive breast cancers in populations of African ancestry. This is a fertile area for further research to better understand how these mutations affect the clinical course of breast cancer, what targeted interventions will increase the proportion of breast cancer diagnosed at stage 1, and what molecularly targeted treatments will produce a response in these tumors. Churpek et al[120] also demonstrated the need for continued technological innovation to reduce the disparity gap because next-generation sequencing is a faster and more cost-efficient way to evaluate for multiple variants in many genes, and this is particularly valuable for African Americans, who tend to have greater genetic diversity.[121] The current administration is also heralding this approach to cancer care. In his 2015 State of the Union address, President Obama announced a precision medicine initiative including a request for $70,000,000 for the National Cancer Institute to investigate genes that may contribute to the risk of developing cancer.[122] African American women should no longer be left behind in the push for personalized medicine that caters to a patient's tumor biology and genetic profile.

In conclusion, there is an opportunity in the current climate of health care reform ushered in by the Affordable Care Act to address many of the discussed elements leading to the persistent racial mortality gap in breast cancer. We have argued that 2 substantial factors lead to this eroding gap. One is differences in tumor biology and genomics, and the second is a quality difference in patterns of care. In describing the perfect storm, Sebastian Junger[123] wrote of the collision of 2 forces—a hurricane's warm-air, low-pressure system and an anticyclone's cool-air, high-pressure system—that combined to create a more powerful and devastating meteorological force. Similarly, we argue that it is the collision of these 2 factors, tumor biology and genomics, with patterns of care that leads to the breast cancer mortality gap because the delays, misuse, and underuse of treatment that we have underscored are of increased significance when patients are presenting with more aggressive forms of breast cancer. Interventions to close this gap will take leaders at the patient, provider, payer, and community levels to drive system change. Interventions can no longer focus on the patient as the agent of change but must, as in Delaware, involve the entire continuum of care. ■

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