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Disparities in Cancer Care

Disparities in Breast Cancer Treatment and Outcomes: Biological, Social, and Health System Determinants and Opportunities for Research

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ABSTRACT

Racial disparities in breast cancer mortality have been widely documented for several decades and persist despite advances in receipt of mammography across racial groups. This persistence leads to questions about the roles of biological, social, and health system determinants of poor outcomes. Cancer outcomes are a function not only of innate biological factors but also of modifiable characteristics of individual behavior and decision making as well as characteristics of patient-health system interaction and the health system itself. Attempts to explain persistent racial disparities have mostly been limited to discussion of differences in insurance coverage, socioeconomic status, tumor stage at diagnosis, comorbidity, and molecular subtype of the tumor. This article summarizes existing literature exploring reasons for racial disparities in breast cancer mortality, with an emphasis on treatment disparities and opportunities for future research. Because breast cancer care requires a high degree of multidisciplinary team collaboration, ensuring that guideline recommended treatment (such as endocrine therapy for hormone receptor positive patients) is received by all racial/ethnic groups is critical and requires coordination across multiple providers and health care settings. Recognition that variation in cancer care quality may be correlated with race (and socioeconomic and health system factors) may assist policy makers in identifying strategies to more equally distribute clinical expertise and health infrastructure across multiple user populations. ***The Oncologist*** 2013;18:986–993

Implications for Practice: Disparities in breast cancer outcomes result not only from racially specific tumor differences, but also modifiable social and health system determinants, such as poor access to care and health education, lack of financial resources, problematic patient-provider interactions, and structural barriers within the health system itself. Breast cancer care requires a high degree of multidisciplinary team collaboration; therefore, ensuring that care is delivered in a coordinated, continuous, culturally and socioeconomically sensitive fashion is critical to ensuring equitable receipt of guideline recommended treatments, which in turn, will help improve outcomes across racial groups. Understanding how biological, social, and health system factors act in concert to influence outcomes may help clinicians, researchers, and policy makers to identify more innovative strategies to address breast cancer disparities going forward.

INTRODUCTION

Overview of Breast Cancer Treatment Disparities

Health disparities in breast cancer treatment and outcomes have been widely documented for several decades. In spite of marked advances in breast cancer survival, disparities persist with respect to timeliness of diagnosis, receipt of treatment, and long-term health outcomes. These differences have been particularly stark between white and black patients [1–14]. Although breast cancer is diagnosed more often in white women, breast cancer mortality is higher among black women [15]. Racial trends in breast cancer incidence and mortality also vary depending on age (Fig. 1) [16]. Specifically, younger black women (<50 years old) have a higher incidence of breast cancer than younger white women, but around the time of menopause, this trend reverses, and older white women have higher breast cancer incidence [17, 18]. Epidemiology studies suggest that disparities in outcomes by race and ethnicity have not improved over time, despite the fact that

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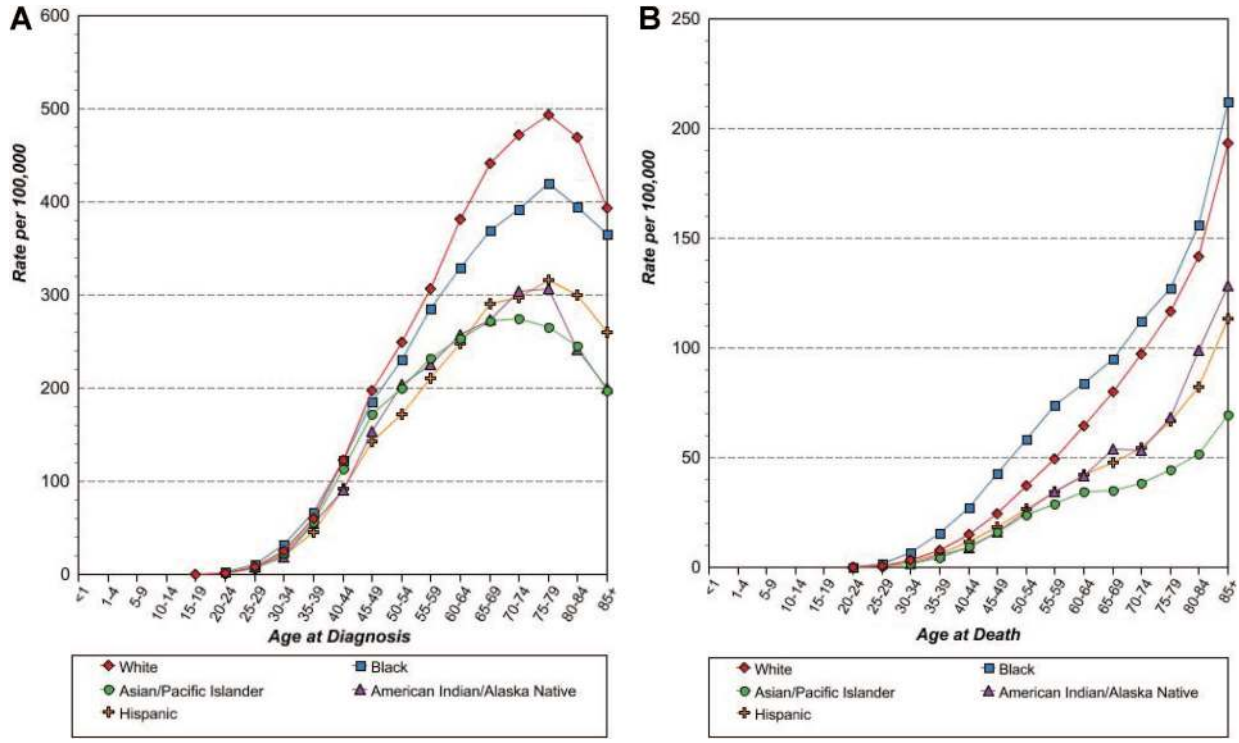


Figure 1. Breast cancer incidence and mortality by age at diagnosis and race/ethnicity. **(A):** Age-specific SEER female breast cancer incidence rates by race/ethnicity, all ages, 1992–2010. **(B):** Age-specific US female breast cancer mortality rates by race/ethnicity, all ages, 1992–2010 [16].

the use of screening mammography is now nearly equivalent nationally among black and white women of all ages [19, 20]. Consequently, in the *Healthy People 2010* report, the United States Department of Health and Human Services made it clear that elimination of health disparities was a national priority [21].

Although developing interventions to ensure high-quality cancer treatment and optimal outcomes in the general population is of critical importance, we should be especially concerned about persistent disparities in treatment and outcomes within vulnerable subpopulations. In many cases, vulnerable subpopulations have not benefited equally from novel interventions to improve cancer outcomes [22, 23]. Over time, if the quality of cancer care improves, on average, in the general population but poor-quality care persists among minority groups, inequities in treatment that lead to disparate health outcomes may have been essentially ignored, resulting in widening gaps in outcomes between groups. Understanding the reasons for persistent disparities in care for vulnerable populations may indicate opportunities to improve outcomes by targeting modifiable factors that disproportionately affect vulnerable patients. In addition, basic tenets of medical ethics compel health care providers to pay attention to such inequities.

Factors Contributing to Breast Cancer Disparities

The picture of health disparities in breast cancer is multifaceted and complex. Although black women, for example, are diagnosed at a more advanced disease stage [24], survival differences persist between blacks and whites diagnosed at similar stages of illness, suggesting that breast cancer in black women is fundamentally different from that in white women. Other support for biological disparity comes from studies finding that although differences in patient stage largely disappear when mammography receipt is controlled, black women still have significantly more high-grade breast cancers [25]. Moreover, black women are at substantially higher risk of developing "triple-negative" (hormone receptor- and HER2-negative) breast cancer [26]. After controlling for patient and biologic tumor characteristics at diagnosis, such as comorbidities and hormone receptor and HER2 status, a clear stage-specific survival gap remains [27]. This gap has been essentially stable over the past two decades, despite significant gains in overall breast cancer outcomes. This gap suggests that nonbiologic factors and factors independent of stage of disease at presentation, such as treatment differences, may also explain a significant portion of observed outcome disparities.

Organizational, structural, socioeconomic, and sociopolitical dynamics of the American health system likely contribute to racial and ethnic health disparities and may not be amenable to rapid change. In epidemiological terms, racial and ethnic differences in breast cancer-related morbidity and mortality can be thought of as being produced by multiple complementary causes [9, 14], none of which is sufficiently explanatory alone. Possible explanations for enduring racial and ethnic disparities include biological differences in tumor behavior and morphology [6, 26, 28–30], differences in therapeutic response [31], patient-level psychosocial or behavioral factors [32], socioeconomic status and access to care [9, 33, 34], and treatment differences [8, 11, 35]. Determining which of these multifaceted factors can be adjusted to improve outcomes is vital and requires deeper understanding of the complex relationships between biological, behavioral, and social determi-

nants of health. Genetic susceptibility to more aggressive cancers, for example, cannot be changed by public health efforts; however, understanding racial differences in tumor biology may point to environment-gene interactions that could benefit from targeted intervention. In addition, sociodemographic factors that tend to vary by race, such as access to insurance coverage, income, and educational attainment, may be slow to change over time; however, if access to care and socioeconomic status are held constant, there is no good reason why a black woman should be offered lower quality treatment than a white woman with the same clinical disease.

Biological Factors

As previously noted, black women diagnosed with breast cancer tend to have more aggressive tumors and worse prognosis than white women [17, 24, 26, 27, 36–39]. Younger black women are also more likely to have triple-negative breast cancers and less likely to have estrogen receptor (ER)-positive cancers [26, 29, 37, 40]. Understanding the characterization and clinical behavior of cancers with different biological features has become increasingly important in recent years [24, 26]. Indeed, many clinicians and researchers would argue that the various biological subtypes of breast cancer are so strikingly different from one another that they represent entirely different diseases and must be treated as such [26, 36, 37, 41, 42]. Given the diversity in tumor biology in breast cancer and the importance of differential signatures by race, understanding the biological uniqueness of tumors presenting in black women is essential [37, 43, 44].

Histological features of breast cancers also vary by race and ethnicity [6, 28, 30, 45]. Chen and colleagues adjusted for age, stage, socioeconomic status, body mass index, reproductive history, insurance status, and location and found that black breast cancer patients had greater nuclear atypia and more necrosis compared with white women [40]. Although it had long been recognized that black women were more likely to have hormone receptor-negative breast cancer, recent studies have shed additional light on this phenomenon. A series of immunohistochemical studies on tumors obtained within the population-based Carolina Breast Cancer Study (CBCS) found that a significantly lower proportion of black women had the good-prognosis, hormone receptor-positive, HER2-negative breast cancer; conversely, a higher proportion of black women, particularly younger black women, had the poor-prognosis, triple-negative breast cancer. Triple-negative disease is so called because it lacks all three of the known targetable breast cancer proteins, the ERs and progesterone receptors, and the signaling pathway member HER2.

Some protective factors, like early age of menarche, obesity, and breastfeeding, were far stronger for basal-like breast cancer than for luminal hormone receptor-positive, HER2-negative breast cancer. Other factors actually appeared to have opposite effects: Multiparity and young age at first full-term pregnancy, long acknowledged to be protective factors, appear to be protective only for luminal breast cancer and rather to be risk factors for basal-like breast cancer.

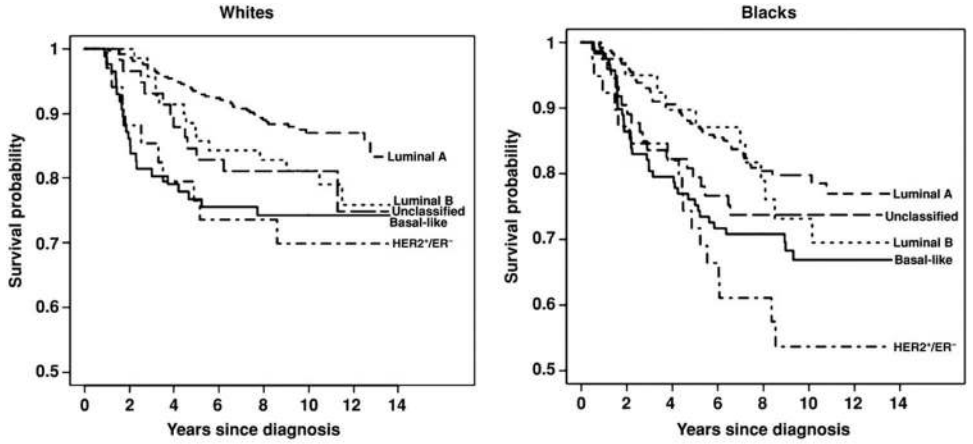
Higher incidence of triple-negative breast cancer has also been observed among West African breast cancer patients [46]. Intriguingly, the CBCS analysis and others have suggested that traditional risk factors varied by subtype [36, 47]. Some protective factors, like early age of menarche, obesity, and breastfeeding, were far stronger for basal-like breast cancer than for luminal hormone receptor-positive, HER2-negative breast cancer. Other factors actually appeared to have opposite effects: Multiparity and young age at first full-term pregnancy, long acknowledged to be protective factors, appear to be protective only for luminal breast cancer and rather to be risk factors for basal-like breast cancer [36]. These studies imply that lifestyle exposures may be responsible for variations in outcomes by race in certain breast cancer subtypes; meanwhile, recent genome-wide association studies implicate novel breast cancer risk variants in women of African ancestry [48].

In a review of the literature on tumor aggressiveness in black women, Morris and Mitchell report that in addition to these known differences in pathologically defined subtypes and BRCA mutations, black women also have more overexpression of cell-cycle regulators, such as cyclin E, p16, and p53, and polymorphisms in nucleotide excision repair genes [45]. This large body of evidence lends considerable support to the hypothesis that breast cancer in black women is biologically different. It is clear, however, that biological factors cannot explain all of the racial disparity in morbidity and mortality [5, 36, 27, 49].

Social Factors and Screening Behaviors

Although biologic differences contribute to breast cancer disparities, it is also widely agreed that social and behavioral factors play a large role in the racial differences observed in breast cancer mortality. In the CBCS, after controlling for biologic differences in tumor subtype, racial disparities in outcomes not only persisted but were particularly prominent among the good-prognosis, hormone receptor positive, HER2-negative tumors, suggesting that social and behavioral factors that vary by race may have been driving outcome differences (Fig. 2) [27]. Persistent racial disparity has been linked to underuse of screening mammography and lack of diagnostic follow-up after an abnormal mammogram result [6, 49]. Use of screening mammography, however, has been nearly equivalent among racial and ethnic groups for a decade [49, 50], and even when controlling for stage at diagnosis and insurance status, differences in mortality persist; although secular trends in disease-specific mortality have shown improvements in the past 30 years, the relative difference between mortality rates for black women and non-Hispanic women has not changed (Fig. 3) [16]. Rather, the gap appears to be widening.

Social factors, including poverty and financial insecurity, lack of transportation, poor access to care, poor health literacy, low educational attainment, and lack of health insurance contribute substantially to differences in breast cancer outcomes [5, 9, 12, 51–56]. Lower income and uninsured cancer patients are especially sensitive to the high costs of cancer care and may be more likely to be from minority groups [57]. Regardless of insurance status, the hidden costs of cancer



HRs for the effect of race on breast cancer–specific mortality

	HR for race (black vs. white) adjusted for age at diagnosis and date of diagnosis (95% CI)	HR for race (black vs. white) adjusted for age at diagnosis, date of diagnosis, and stage at diagnosis (95% CI)
Luminal A	1.9 (1.3–2.8)	1.9 (1.3–2.9)
Luminal B	1.4 (0.6–3.1)	1.3 (0.6–3.0)
Basal-like	1.2 (0.7–2.1)	1.3 (0.8–2.3)
HER2+/ER-	1.7 (0.8–3.8)	2.2 (1.0–5.1)
Unclassified	1.4 (0.7–2.9)	1.2 (0.6–2.6)

Figure 2. Race-stratified Kaplan-Meier plots and race effect estimates for breast cancer-specific mortality by immunohistochemical subtype in the Carolina Breast Cancer Study, 1993–2006 [27]. Abbreviations: CI, confidence interval; ER, estrogen receptor; HR, hazard ratio.

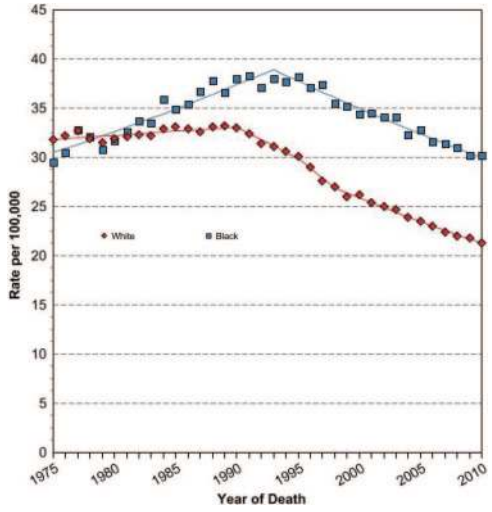


Figure 3. Age-adjusted U.S. female breast cancer-specific mortality rates by race, 1975–2005 [16].

care, including transportation and the inability to work, may be especially burdensome to the minority cancer patient [58]. The addition of novel biologic therapies such as trastuzumab to standard treatment for breast cancer has increased costs to such a point that even insured patients may face staggering copayments and other shared costs [59, 60]. In one national survey of cancer patients and families conducted by the Kaiser Family Foundation, *USA Today*, and the Harvard School of Public Health (2006), nearly one in four privately insured patients had exhausted all or most of their personal savings to pay for cancer-related care, and 13% of cancer patients reported being contacted by a collection agency demanding payment for cancer treatment [61]. As treatment options become more sophisticated and prognosis continues to improve, costs associated with treatment, survivorship, and surveillance will become increasingly important issues to consider in understanding racial variation in outcomes.

Several other patient-level social and behavioral factors may help explain why different patients receive different treatments and experience worse health outcomes. These include health literacy and personal preferences [62], cognitive and social network correlates [32], trust in the health care system, and health care-seeking behavior [35, 63].

Finally, competing comorbidities, which differ by race, also affect breast cancer screening, diagnosis, and outcomes [14]. Higher comorbidity burden among blacks could affect both overall survival and disease-specific survival, if care for comorbidities competes with cancer care priorities. In addition, if functional status or mental health status is compromised by comorbid conditions, these may also inhibit—rather than promote— health-seeking behaviors for cancer diagnoses [14].

Health System Factors

Although much research has been published in the areas of biological tumor variation and social and behavioral factors as they relate to race and ethnicity-related breast cancer disparities, relatively little has been published about how characteristics of the health system itself, including provider- and facility-level factors, affect racial variation in treatment and outcomes. Structural and organizational differences in health services available to women can explain some of the racial and ethnic disparity in breast cancer treatment and outcomes [64–66].

Some of the principal structural and organizational factors known to affect the quality of cancer care are summarized in Table 1. These physician- and facility-level factors have varying degrees of influence on quality of cancer care received. Several may be more or less problematic for particular patient subpopulations. For example, distance to care may pose a

Table 1. Health system organizational and structural factors affecting cancer care quality

Environmental	Distance to care
	Geographic location
Organizational	Volume (cancer, surgical, or overall)
	Caseload severity
	Radiotherapy on site
	Specialist consultation
	Notification and reminder systems
	Stated commitment to quality improvement
	Incentive-based systems in place
	Facility type, practice setting, profit status, and size
Institutional affiliations	Cancer care organizations
	Research alliances
	Academic and teaching status
Provider	Physician training and education
	Specialist-generalist collaboration
	Physician gender, age, and race

greater barrier to care for older women, given the transportation and mobility difficulties many elderly women face [67]. In addition, health-seeking behavior and use of health services with certain structural and organizational characteristics likely vary by subgroups. For example, some ethnic groups may prefer to access health care facilities that recognize and address language barriers by hiring translators; those health facilities that can afford to offer such patient services are likely different in terms of organization and size from those facilities that do not offer bilingual services. In addition, membership in racial and ethnic groups may correlate with community residence, and type and location of health facilities may be related to sociodemographic makeup of the local user population. Consequently, innovative care processes may be distributed unequally. If distribution and diffusion of evidence-based innovations are disproportionately benefiting certain women compared with others, differential quality of care may be observed across sociodemographic groups.

Finally, patient sociodemographics could be associated with the types and the quality of providers and health facilities that are available to the local user population. Black cancer patients may have worse access to well-trained providers and more often be treated by physicians who lack measurable skills, board certification, and technical resources [68]. In one study, physicians of black cancer patients more often reported that they were unable to provide the best care to their patients, although the reasons are somewhat unclear [68].

Health services characteristics are rarely considered in empirical analyses to confound or modify the effect of race on breast cancer treatment and outcomes. Analyses that have included health system variables as covariates in addition to race and ethnicity, such as one study using data from the National Cancer Database [69], have generally highlighted the importance of a few structural and organizational variables as potential confounders only. In this study, after controlling for hospital teaching status, regional supply of radiation oncologists, surgical volume, and ratio of specialists to generalists in predicting receipt of breast-conserving surgery over time, race was statistically nonsignificant. In addition, black women who failed to receive timely screening mammography reported that they lacked physician referral or recommendation for the test [70].

The interactive effects of structural and organizational variables and race and ethnicity have been explored to a greater degree in the literature of other cancers. In prostate cancer, black men have poorer access to health care and less continuity of care for screening and, once diagnosed, are more likely to be treated by lower volume surgeons [63, 71]. In rectal cancer, black patients are more likely to be treated by low-volume physicians and less likely to receive adjuvant therapy [72]. In a study of advanced lung cancer patients, black patients, particularly of lower socioeconomic status, were less likely to see an oncology specialist and subsequently less likely to receive clinically recommended chemotherapy, after controlling for age, sex, year of diagnosis, region, hospital teaching status, and comorbidities [73].

To date, the breast cancer literature has rarely considered the role of multiple health service organization measures explicitly on racial and ethnic disparities in treatment and outcomes. The exceptions are two Surveillance Epidemiology and End Results (SEER)-Medicare studies that showed that health system factors, including distance to care, may modify the relationship between race and ethnicity and receipt of guideline-recommended breast cancer treatment, including radiation therapy and chemotherapy [65, 66]. Research suggests that pinpointing system-level factors that may contribute to persistent disparities can help policy makers focus efforts to equalize health care access and quality across diverse user populations.

Treatment Differences

Differences in treatment, working in parallel with race-based biological differences, are believed to account for a large portion of the variation in breast cancer outcomes, in particular, the persistent state-specific survival gap observed between white and black women [5]. If certain subpopulations receive less-than-standard treatment (i.e., treatment appropriate for the features of the cancer), differences in outcomes are likely to result. Black women, more often than other women with the same stage disease, fail to receive timely diagnosis and recommended treatment for breast cancer [13, 74].

Multiple studies have documented racial disparities in almost every aspect of breast cancer treatment. Black and Hispanic women fail to receive definitive local therapy for curable breast cancers more often than whites, after adjustment for age and tumor characteristics [8]. Similar patterns are seen for adjuvant chemotherapy and radiotherapy, with black and Hispanic women failing to receive appropriate adjuvant therapy more often than whites, even after controlling for access to a medical oncologist [3]. Black women are four to five times more likely to experience treatment delays longer than 60 days and significantly less likely to receive cancer-directed surgery, radiation therapy after lumpectomy, and hormonal therapy for hormone receptor-positive tumors, after controlling for tumor characteristics [11]. Such findings of treatment disparities appear to be consistent across geographical areas, having been documented in studies in Detroit, Michigan [1];

Atlanta, Georgia [11]; and in national SEER samples [8, 66]. In a SEER-Medicare study using a composite measure of adequate breast cancer that included appropriate radiation therapy following breast-conserving surgery, documentation of ER status, and surveillance mammography, black and Hispanic women were significantly less likely to receive adequate care, and the disparity actually increased over time [10]. Even in the controlled setting of a large randomized clinical trial, black women were significantly more likely to have early treatment discontinuation or delay than the white participants [75].

Studies examining treatment disparities have several limitations that complicate attempts to determine the root causes of differences in treatment. These include limited follow-up periods in national datasets such as SEER, underreporting of adjuvant therapies, and limited information regarding patient socioeconomic status and other social factors. Black women with breast cancer also have more comorbidities than their white counterparts [1], a factor that may influence treatment decision making, and not all studies have been able to control for this difference.

Because the racial gap in breast cancer survival is known to be largest among estrogen-sensitive subtypes in whom prolonged treatment over years is key to improving outcomes, and because nonadherence has been demonstrated to affect survival outcomes, differences in utilization of antiestrogen therapies may well explain some portion of the disparity in outcomes for these patients.

Racial disparities also exist in access to cutting-edge breast cancer treatments, both in the clinical trial setting and as innovations move into standard clinical practice. Black women are more reluctant to enroll in clinical trials and thus may have poorer access to trial-based innovations in cancer care [22, 23, 76–78]. In addition, few breast cancer randomized trials analyze outcomes based on race and ethnicity because of insufficient sample size, indicating a failure to report data that may inform disparities-focused interventions [79]. Consequently, certain groups may be denied research-related innovations, and this trend may continue as novel treatments move into clinical treatment settings. Black women, for example, less often receive sentinel lymph node biopsy (SLNB), a morbidity-sparing approach to axillary lymph node staging [7, 80]. Despite overall higher levels of uptake of SLNB between 1998 and 2005, racial and ethnic gaps in receipt of SLNB remained largely the same over time [7]. Black women are also less likely to receive any type of lymph node surgery for axillary staging [81].

Additional review articles overwhelmingly echo the findings of the specific empirical studies highlighted above [13, 14]. Shavers and Brown reported on several other treatment disparities between racial and ethnic groups, including differences in receipt of biomarker testing, follow-up after diagnosis and initial treatment, and surveillance mammography [13]. In addition, black and Hispanic women suffer more often from inadequate pain management and serious side effects of treatment [5, 14, 82]. Other authors concluded that disparities in treatment were the result of patient- or tumor-related, provider-related, and health system-related differences but that these factors were rarely considered explicitly in empirical studies as acting together [14, 35].

Significant gaps remain in our understanding of treatment disparities in breast cancer. Among the most prominent is the use of endocrine therapy in hormone receptor-positive patients, who compose the majority of breast cancer survivors. Although the problem of early discontinuation and nonadherence to endocrine therapy has been documented in a variety of patient populations [83–93], little is known about differences in endocrine therapy adherence among women of different races. Studies have shown conflicting relationships between race and endocrine therapy utilization among hormone receptor-positive subtypes [85, 87, 88, 94]. Because the racial gap in breast cancer survival is known to be largest among estrogen-sensitive subtypes in whom prolonged treatment over years is key to improving outcomes [27], and because nonadherence has been demonstrated to affect survival outcomes [95], differences in utilization of antiestrogen therapies may well explain some portion of the disparity in outcomes for these patients.

Opportunities and Recommendations for Future Research

Improving health-seeking behavior and trust in the health care system are difficult targets for research interventions, given the complex historical experiences of American minority groups [9, 96]. Similarly, advances in understanding of molecular differences in breast cancer by race that will enable individualized therapy are still on the horizon. As a starting point, ensuring equal access to provider- and facility-level health care resources should be a priority.

Although biologic and behavioral differences may influence outcomes to some extent, evidence suggests that when women across racial and ethnic groups receive equal treatment, equal outcomes follow [97, 98]. Black patients are at no greater risk for chemotherapy-related hematologic toxicity than white patients [99], and clinical trial results suggest that patterns of response to local and systemic therapy are similar for black and white women with clinically equivalent disease [75, 100–102]. In light of this evidence, it is critically important that the health system itself is designed in such a way that all women have access to life-prolonging cancer treatments, regardless of race, age, or socioeconomic status.

Conclusion

Cancer outcomes are a function not only of innate biological factors but also of modifiable characteristics of individual behavior and decision making as well as characteristics of the patient-health system interaction and the health system itself. Attempts to explain persistent racial and ethnic disparities have mostly been limited to discussion of differences in insurance coverage, socioeconomic status, stage at diagnosis, comorbidity, and molecular subtype of the tumor. Because breast cancer care requires a high degree of multidisciplinary team collaboration, ensuring that critical guideline-recommended treatment is received (e.g., endocrine therapy for ER-positive and progesterone receptor-positive patients) is critical and requires coordination across multiple providers and health care settings. Recognizing that variation in quality of cancer care received may be correlated with sociodemographic and health system characteristics may

assist policy makers in identifying strategies to more equally distribute clinical expertise and health infrastructure across multiple user populations.

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