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Racism and Cancer Care

Adherence to Endocrine Therapy and Racial Outcome Disparities in Breast Cancer

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Abstract

The disparity in outcomes of breast cancer for Black compared with White women in the U.S. is well known and persistent over time, with the largest disparities appearing among women with hormone receptor-positive (HR+) cancers. The racial gap in breast cancer survival first emerged in the 1980s, a time of significantmen treatment advances in early-stage breast cancer, including the introduction of adjuvant endocrine therapy. Since that time, the gap has continued to widen despite steady advances in treatment and survival of breast cancer overall. Although advanced stage at presentation and unfavorable biology undoubtedly contribute to racial differences in survival of HR+ breast, treatment disparities are increasingly acknowledged to play a key role as well. The recent recognition of racial differences in endocrine therapy use may be a key explanatory factor in the persistent racial gap in mortality of HR+ disease, and may be a key focus of intervention to improve breast cancer outcomes for Black women. ***The Oncologist*** 2021;26:910–915

Implications for Practice: Black women with hormone receptor–positive breast cancer experience the greatest racial disparity in survival among all breast cancer subtypes. This survival gap appears consistently across studies and is not entirely explained by differences in presenting stage, tumor biology as assessed by genomic risk scores, or receipt of chemotherapy. Recent research highlights lower adherence to endocrine therapy (ET) for Black women. Health systems and individual providers should focus on improving communication about the importance of ET use, sharing decisions around ET, providing appropriate support for side effects and other ET-related concerns, and equitably delivering survivorship care, including ET adherence assessment.

Introduction

The disparity in outcomes of breast cancer for Black compared with White women in the U.S. is well known and persistent over time, with recent national statistics suggesting a 40% higher mortality rate among Black women despite similar incidence of the disease [1]. Notably, the racial gap in breast cancer survival first emerged in the 1980s, a time of significant treatment advances in early-stage breast cancer, including the Food and Drug Administration approval of the first adjuvant endocrine therapy, tamoxifen, in 1985 [2]. Since that time, the gap has continued to widen despite steady advances in treatment and survival of breast cancer overall [3]. Although advanced stage at presentation and unfavorable biology undoubtedly contribute to this racial disparity in survival, treatment disparities are widely acknowledged to play a key role in the persistent gap between Black and White outcomes even among women presenting with similar stage and biologic characteristics [4, 5].

Whereas the over-representation of biologically aggressive "triple negative" breast cancer, defined by its absence of estrogen, progesterone, and human epidermal growth factor 2 (HER2) expression, has been a focus of breast cancer research among Black women, the majority of incident breast cancer cases and deaths among Black women express hormone receptors (HR+) and are thus sensitive to endocrine blockade as a

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Table 1. Breast cancer outcomes for Black versus non-Black patients with HR+ breast cancer, 1993–2013

Source[a]	Adjustment Factors	Hazard ratio (95% CI)
Carolina Breast Cancer Study 1993–2006[a] 5 marker (HR/HER2/ HER1/CK 5/6)	Age, diagnosis year, stage	1.9 (1.3–2.9) for BCSS
City of Hope 1994–1998[a] 4 marker (HR+/HER2-/ P53-)	Age, stage	1.9 (0.9–3.9) for BCSS
ECOG 1199 (stage II–II chemotreated)[a] HR+/HER2−	Age, BMI, tumor size, node status, surgery type, hormonal treatment	1.6 (1.2–2.1) for DFS
Carolina Breast Cancer Study 2008–2013 HR+/HER2−	Age, grade, node status, tumor size	Unadjusted: 1.8 for RFS Adjusted: 1.4 (1.1–1.9)

[a]In these studies, outcomes for women with triple negative disease were similar between Black and White patients.
Abbreviations: BCSS, breast cancer specific survival; BMI, body mass index; CI, confidence interval; DFS, disease free survival; HR+, hormone receptor–positive; RFS, recurrence-free survival.

therapeutic strategy [6]. Furthermore, the largest racial disparities in outcomes among patients with breast cancer occur in women with HR+ disease, as shown in Table 1. In the Carolina Breast Cancer Study (CBCS) phase I–II, a large prospective cohort study over-sampling Black women in North Carolina from 1993 to 2006, the risk of breast cancer death in Black women with HR+ and HER2 negative (−) tumors was almost twice that of White women with HR+/HER2− disease (hazard ratio, 1.9; 95% CI, 1.3–2.9), even after adjustment for age and disease stage [7]. More recent analyses of HR+/HER2− cases from CBCS phase III, accrued from 2008 to 2013, also show elevated recurrence risk for Black compared with White women, even after adjustment for expanded biologic features including tumor grade (hazard ratio, 1.4; 95% CI, 1.1–2.9) [8]. Similarly, in a large cohort from the City of Hope between 1994 and 1998, risk of breast cancer death among HR+/HER2− patients was elevated in Black compared with White women (hazard ratio, 1.9; 95% CI, 0.9–3.9) after adjustment for age and stage at diagnosis [9]. These studies are population-based and some of the differences may reflect differences in treatment; however, differences persist even in clinical trials where patients are uniformly treated. A secondary analysis of the ECOG 1199 study, a randomized clinical trial of patients with stage II–III breast cancer, demonstrated that among HR+/HER2− patients, Black women compared with White women had a hazard ratio of 1.6 (95% CI, 1.2–2.1) for disease-free survival after adjustment for age, body mass index, key disease features including tumor size and nodal status, and initial treatment including surgical type and initiation of endocrine therapy [10]. In all of these studies, recurrence risk among women with triple negative breast cancer did not differ by race after adjustment for patient, tumor, and treatment factors, underscoring the importance of focusing on modifiable factors contributing to racial disparities in outcomes of patients with HR+ breast cancer.

Two central hypotheses have emerged over time to explain this racial gap in outcomes of HR+ breast cancer. The first is a *biologic hypothesis*: namely, that HR+ disease among Black patients is more biologically aggressive than that among White patients, in ways that may not be reflected by triple receptor phenotype and other pathologic features such as tumor size and nodal status that are available in large secondary datasets or cancer registries (tumor size, stage, and in some cases histologic grade). There would initially appear to be some support for this hypothesis. In the Carolina Breast Cancer Study phase III (CBCS-III), we previously reported that among patients with clinical HR +/HER2− receptor phenotype, younger Black women were significantly less likely than Whites to have tumors with a good prognosis "Luminal A" intrinsic subtype as measured by PAM50 RNA sequencing [11], with Black women under age 50 with HR+/HER2 clinical phenotype having only a 45% frequency of Luminal A disease versus 56% of young White women and 66% of older White women. Similar patterns of biologic difference by race were found using genomic risk scores, with Black women compared with White with HR+/HER2− disease having higher ROR-PT risk score in the CBCS cohort and Black compared with White women with non–triple negative breast cancer having higher ROR-S score among primary breast cancers in The Cancer Genome Atlas data [12].

Hypothetically, biological differences in HR+ breast cancer by race might be identifiable in clinical practice by consistent use of commercially available gene expression tests to identify higher-risk disease among HR+/HER2 patients. These assays can help predict which patients' recurrence risk could be reduced by inclusion of adjuvant chemotherapy in the treatment plan. However, with regard to commercially available genomic risk profiles, there have been conflicting reports of Black-White differences in test results. In an exploratory analysis of CBCS-III data, distribution of the 21-gene Recurrence Score (RS) did not appear to differ by race among patients with available score information [13]. In contrast, Holowatyj et al. found that in Surveillance Epidemiology and End Results cancer registries, Black women were more likely than Whites to have high risk RS (>30), particularly in women aged 20–49 [14]. Similar results were found in a National Cancer Database (NCDB) cohort in which 10.6% of Black women versus 7.2% of Whites had high RS [15].

An important limitation of all of these studies is potential selection bias introduced by racial differences in access to testing and physician-ordered testing. In fact, the NCDB investigators found that non-Hispanic White compared with Black race/ethnicity was associated with higher frequency of testing after adjustment for clinical characteristics, and our own group similarly found that in a large multipayer insurance database of newly diagnosed patients with breast cancer who met clinical criteria for gene expression tests, Black women were 16% less likely than Whites to receive testing after adjustment for disease and patient characteristics [16]. Racial differences in selection for testing might bias estimates of Black-White risk differences in either direction. If there is a higher clinical "risk threshold" for testing of Black women, meaning that Black patients had to exhibit more clinically concerning disease to receive a test, they might represent

a selected higher-risk group compared with untested Black women or tested White women. Conversely, if gene expression testing is more frequent among women with greater health care access across all races, then tested Black women may have lower-risk disease than Black women with breast cancer in the general population.

Gene expression profiling data from randomized clinical trials can help counter the problem of selection bias in data from observational cohorts. The TAILORx study, which evaluated the benefit of adjuvant chemotherapy added to endocrine therapy for HR+/HER2− and node-negative breast cancer among patients with intermediate genomic RSs, offered an opportunity to examine racial variation in RS. All patients enrolled in TAILORx were tested for genomic recurrence risk, and patients found to have an intermediate RS were randomized to chemotherapy followed by endocrine therapy or to endocrine therapy along [17]. In a key secondary analysis of trial data, Albain et al. found that distribution of RS did not significantly differ between Black and White participants. However, their analysis showed that Black women had higher risk of distant recurrence (hazard ratio, 1.6; 95% CI, 1.1–2.4) both within the intermediate RS cohort (scores of 11–25) and in the entire study population [18]. In spite of unbiased application of chemotherapy in this cohort, this elevated hazard ratio among TAILORx participants is strikingly similar to that found by the earlier analyses from the CBCS, City of Hope, and ECOG 1199 cohorts. In a recent analysis of CBCS phase III data for HR+/HER2− patients, in which we performed uniform genomic recurrence risk testing of all enrolled participants with sufficient tissue using the PAM50 assay, we similarly found that among women with high ROR-PT scores, 5-year standardized (for age and stage) recurrence risk was 18.9% (95% CI, 8.6%–29.1%) for Black women versus 12.5% (95% CI, 2.0%–23.0%) for White women [8]. Taken together, these studies suggest that although tumor biology certainly contributes to Black-White disparities in breast cancer survival, a substantial portion of this survival disparity remains unexplained by racial differences in genomic recurrence risk or in initial chemotherapy treatment.

The second hypothesis to explain racial disparities in outcomes of HR+ disease emphasizes *the structure of and access to health care delivery systems*. Importantly, the racial gap in HR+ breast cancer mortality emerged *with* the development of effective anticancer therapy (adjuvant tamoxifen in the 1980s) and has persisted over time, *despite* overall improvements in treatment and outcomes, because of fundamental barriers to cancer care access that disproportionately affect Black women. This hypothesis is founded on the Fundamental Cause Theory of health disparities, first proposed by Phelan and Link in 1995 [19], which posits that differences in health outcomes between socioeconomically privileged and less privileged groups persist over time, and are more evident as disease becomes more treatable, because privileged social status embodies an array of resources that protect health no matter what specific interventions exist in the system at a given time [20]. Substantial evidence supports this hypothesis in the context of HR+ breast cancer, specifically focusing on a key element of treatment that occurs downstream of diagnosis, surgery, and chemotherapy: receipt of adjuvant endocrine therapy (ET).

Underuse of adjuvant ET, either through lack of initiation, early discontinuation of the drug, or through missed doses, is increasingly recognized as a common challenge among breast cancer survivors, affecting about half of patients by 5 years [21], and has been associated with decrements in survival [22]. There is emerging evidence that Black women are at greater risk of under-treatment with ET. We examined racial variation in initiation of ET in a cohort of commercially insured women under age 65 in North Carolina, finding that Black women with early-stage HR+ breast cancer were 17% less likely to initiate adjuvant ET, and that the disparity was more concentrated among women with prior adjuvant chemotherapy, where Black women were 33% less likely than Whites to initiate [23]. In the same cohort, young Black women were also 29% less likely to be adherent to prescription refills than Whites in the first 12 months following initiation (unpublished data). In the Carolina Breast Cancer Study phase III, we found that Black participants were less likely to report being fully adherent to ET at 2 years after diagnosis (75% adherent vs. 83% for Whites; $p < .001$), reported higher burdens of almost all ET-associated side effects compared with Whites, and were more likely to believe that they had low recurrence risk, and that their risk would not change substantially if ET were discontinued. Shared decision making appeared to protect against nonadherence, whereas beliefs that ET was not effective increased risk of nonadherence [24]. Although not directly addressed in this study, it is likely that well known deficiencies in oncology providers' communication with Black patients [25], as well as disparities in symptom-directed care [26], contributed to these findings. Other studies have similarly found that low decision confidence around taking ET, poor social support and low socioeconomic status are associated with risk of nonadherence among young breast cancer survivors [27]. Although these findings are not race specific, some of these risk factors are likely to be more prevalent among Black cancer survivors who tend to develop breast cancer at younger ages, and multiple studies have reported poor health-related quality of life (HRQOL) among young Black breast cancer survivors [28]. A large patient-reported study, BQUAL, found that attitudes toward ET at baseline and higher baseline HRQOL protected against early discontinuation of ET [29], although sample sizes did not permit subgroup analyses of Black patients.

It is imperative to identify strategies to support ET medication taking that are feasible, scalable, and impactful on ET adherence, as well as salient to Black women. We have found that providers tend to emphasize side effects and side effect management as key components of promoting adherence, but providers also perceived persistent or unsolvable tolerance problems with ET [30]. These observations point to the need for action on several fronts. First, *better systems are needed to uniformly and equitably screen for ET side effects at visits or even between visits*. Because communication quality between physicians and Black patients with breast cancer about symptom experiences is known to be problematic [26, 31], and given the earlier findings that ET side effect burden is higher in these women, we are unlikely to fully appreciate and address the ET-associated symptoms of Black breast cancer survivors without systematic and uniform symptom capture. However, data from survivor survey

and qualitative research highlight that the relationship between side effects and adherence is more complex than providers may appreciate, encompassing the patient's perception of whether a given side effect is tolerable, the relationship with the provider, and the balance between drug benefit and side effects [32]. Similarly, a recent large randomized trial collecting patient-reported outcomes and assessing adherence by urine metabolites, found that emotional, social, and functional well-being and beliefs about medication, in addition to physical symptoms, predicted adherence levels [33]. Patients have also identified social support outside the medical team and emotional support in addition to information, including that provided by other survivors and organizations, as important to adherence [34]. Again, although these are important needs of all breast cancer survivors, it should be noted that Black women have reported less social support from survivor networks while on endocrine therapy [35], and thus, a second need for action is that *interventions should address multifaceted barriers to adherence, including social determinants of health, emotional and supportive care needs and beliefs about medication, in addition to informational needs and reminders*.

Despite adequate evidence of the complexity of adherence barriers for Black and non-Black patients, a review article of published intervention trials focused on ET adherence identified only five, all limited to educational and informational interventions, most focused on older women who are at lower risk of nonadherence, and none focused on Black patients [36]. Twelve ongoing trials were also identified; one, a large cooperative group randomized trial of twice-weekly text reminders among postmenopausal women by Hershman et al., has since reported its results as negative [37]. The remainder of ongoing trials identified in this review continue to focus mainly on informational and reminder interventions, although one includes patient navigation and another, a patient self-management system. A second meta-analysis of eight recent interventional trials of ET supportive interventions found an overall null association of the interventions, again mostly reminder-based, on ET adherence, but indicated that interventions featuring two-way communication between patient and provider showed more effect relative to one-way communication [38]. Again, the demographics of patients enrolled in these trials generally do not overlap well with the patient subgroups known to be at greatest risk of nonadherence including Black women [24], socioeconomically disadvantaged populations such as Medicaid patients [39, 40], and young women [27]. Thus, a third need for action is for *interventions that target interventions to the patients at highest risk of nonadherence*. Hershman et al. recently identified a composite of patient-reported factors that could potentially serve as screeners for at-risk individuals [33]; targeted interventions focused on demographic risk factors such as race, age, or insurance source could be simpler ways to improve the fit between need and intervention. In creating such interventions, our research suggests that barriers among these sociodemographic groups appear less well addressed currently [41], and thus, interventions should be tailored to barriers most salient to these groups and grounded in preliminary evidence of efficacy and acceptability specific to the population of interest.

In the currently active randomized controlled trial, GETSET (Alliance 191901, NCT04379570) [42], we attempt to bring together these principles of ET adherence intervention research. The trial, recruiting participants through 258 sites of the Alliance for Clinical Trials in Oncology network, is designed to over-recruit Black participants and those under age 50, uses materials previously tested with patients in these groups, and addresses multifaceted barriers including social and emotional needs. Participants are randomized in an age- and race-stratified fashion to one of four intervention arms, and all participants are provided with static educational materials and general interactive health coaching for wellness after breast cancer via a study Web site. Half of participants receive daily text message reminders (TMR), and half receive intensive, telephone-based, motivational interviewing (MI) counseling over five sessions in their first year of ET, using a technique adapted from interventions to improve medication adherence in other settings [43, 44]. MI counseling allows for patient-directed identification of, and problem solving for, salient barriers, as well as provides social and emotional support in early–breast cancer survivorship. This approach was rated as highly acceptable and found to improve baseline differences in medication taking self-efficacy among a racial diverse cohort of ET patients in a recent single-arm pilot study of 42 patients (unpublished data). One key to success of the trial's recruitment strategy will be the participation of sites from the National Cancer Institute's National Community Oncology Research Program (NCORP), including Minority/Underserved NCORP sites, which excel at broadening the participant base of cooperative group research [45] and providing feedback on the pragmatic aspects of trial conduct among patients outside large academic medical centers. The trial will compare the effect of enhanced usual care, MI, TMR, and MI + TMR on ET adherence at 12 and 24 months, as measured by electronic pill cap monitoring, with secondary outcomes including cost, cancer recurrence, and a variety of patient-reported outcomes.

Conclusion

The multilevel factors contributing to persistent Black-White disparities in HR+ breast cancer survival are complex and include both biological and access-related determinants, yet data from multiple contexts demonstrate that many of these outcome determinants are modifiable—namely, ensuring equitable access to health care systems and providers that can deliver timely, guideline-concordant, and culturally appropriate care. This care should include clear and compassionate communication about ET risks and benefits at the onset of treatment; ongoing monitoring and responsiveness to patient-reported symptoms during treatment; and identification and implementation of effective and cost-effective targeted interventions to support ET use in the real world, with attention to the social determinants of health, emotional and social needs, and unique barriers experienced by Black women, socioeconomically disadvantaged women, and young women with breast cancer.

In the next generation of breast cancer equity research, we must move the field forward in two central ways. First, research questions must be formed and answered within a theoretical framework that appreciates the existence of complex, bidirectional relationships among the social determinants of health, including the impacts of systemic racism, tumor and host biology, cancer care access, and outcomes.

Second, we must rigorously test interventions, at the policy, health system, community, and individual levels, to create opportunities for the best health outcomes possible for all patients with breast cancer.

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