

## Breast Cancer Racial Disparities: Unanswered Questions

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### Abstract

Breast cancer is the most common noncutaneous cancer diagnosed in women in the United States and is second only to lung cancer as the leading cause of cancer-related mortality. Although mortality rates have been dropping steadily due to a variety of factors including improved treatment modalities and screening, substantial racial differences in outcome between blacks and whites persist. Although differences in health care utilization and access, tumor biology, and cancer management have been elucidated as possible reasons for disparities seen, it is likely that other interactions exist. The purpose of this review is, therefore, to present a comprehensive overview of the literature on racial disparities in breast cancer outcome and highlight potential causative factors that may contribute to disparities seen among blacks and whites with breast cancer. In addition, we make research recommendations by discussing some of the remaining gaps in knowledge that may lead to further understanding of disparities and consequently improved outcomes for all women with breast cancer. *Cancer Res*; 71(3); 640–4. ©2010 AACR.

### Introduction

Projections indicate that in the United States, approximately 207,000 new cases of breast cancer and 40,000 deaths will be reported in 2010 alone (1). Although mortality rates have been dropping since 1990 due to earlier detection and improved treatment modalities, substantial racial disparities in outcome continue to persist. Although the incidence rates for breast cancer in blacks are lower than whites (113 vs. 123.5 per 100,000), mortality rates are disproportionately higher (33 deaths vs. 23.9 per 100,000 cases; refs. 1, 2). Although reasons for the racial disparities in breast cancer have not been fully elucidated, it has been suggested that factors such as differences in tumor biology, health care access, and disease management may contribute to the poorer outcomes observed. The purpose of this article is to present a comprehensive overview of the literature on racial disparities in breast cancer outcome and highlight potential causative factors that may contribute to disparities seen among blacks and whites with breast cancer. Specifically, we review the role of tumor biology, genetic variants in relation to survival disparities, as well as the impact of factors such as screening

and detection and receipt of optimal care on poorer survival among black women with breast cancer. In addition, we discuss some of the remaining gaps in knowledge that may lead to further understanding of disparities and improved outcomes for all women with breast cancer.

### Methods

A PubMed search was used to retrieve articles published in English between 1980 and 2010. MeSH terms used included "breast cancer," "disparities," "racial," "mortality," "incidence," "treatment," "screening," "genetics," "epidemiology," and "pathology." We also utilized editions of the SEER (Surveillance, Epidemiology and End Results) Cancer Statistics Reviews published by the National Cancer Institute in 2001 and 2007. All articles were peer-reviewed, with the exception of a conference proceeding. Articles that focused primarily on other disadvantaged groups such as Hispanics were excluded.

### Outcome Disparities

A disproportionate number of deaths from breast cancer occur in blacks. Although the overall incidence rates are higher in whites, blacks with breast cancer have a higher breast cancer–specific mortality (33 vs. 23.9 per 100,000). In addition, mortality rates also differ by age group. In 1980, blacks younger than 45 years had higher mortality rates than whites in the same age group (3). Between 1993 and 1996, breast cancer mortality rates among those 35 years and younger in blacks were 2-fold higher than the rates in whites. For those between 40 and 50 years, the rates in blacks were 1.5-fold those of whites; although the two races had more or less similar outcomes for those 55 years and older (4). The 5-year survival rates for all stages also differ by race, with blacks

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**Table 1.** Breast cancer epidemiology by race

Characteristics	Black	White
Incidence per 100,000	113	123.5
Mortality per 100,000	33	23.9
5-y survival, %	78	90
Stage distribution, %		
Localized	51	61
Distant	8	4
Age of presentation <50 y, %	35.1	20.9

NOTE: Modified from references 1 and 5.

being disadvantaged. For example, for locoregional disease, 5-year survival rates for blacks are only 72% versus 85% for whites (1). Table 1 gives a summary of differences in the epidemiology of breast cancer in blacks and whites.

Because of improved diagnostic and treatment modalities, breast cancer mortality has declined over time; but decreases generally have been smaller and less consistent among blacks than among whites (5). In 1975, the age-adjusted death rate from breast cancer for all races was 31.4 per 100,000. By 1990, the rates had increased slightly to 33.1 deaths per 100,000 but subsequently decreased to 22.8 per 100,000 in 2007, reflecting a 27% decline from 1975. Comparing death rates from 1975 to rates from 2007, whites have enjoyed a 30% (31.8 to 22.2 per 100,000) reduction in mortality whereas rates have actually increased by 6.4% (29.5 to 31.4 per 100,000) in blacks in the same period. If the most contemporary period is considered by comparing rates in 2000 and 2007, whites have had a 15.3% reduction in mortality as opposed to 8.7% in blacks.

Factors that contribute to these trends are not fully understood but thought to reflect population differences in tumor biology, genetic underpinnings of aggressive disease, detection, and potential racial differences in management.

### Racial differences in tumor biology

Although socioeconomic factors and access to care are likely to play a role in poorer survival for black women, they are also more likely to be diagnosed at an earlier age than whites and to have tumors with more aggressive characteristics, which may also factor into poorer outcomes. Black women are frequently diagnosed with tumors with high histologic grade and negative estrogen receptor (*ER*), progesterone receptor (*PR*), and *HER-2* receptor status, as well as high nuclear atypia, mitotic index, S-phase fraction, and tumor necrosis (6, 7). They are also more likely to be diagnosed with basal-like breast cancers, which are negative for *ER*, *PR*, and *HER-2*, and overexpress cytokeratins 5/6 and *HER-1/EGFR* (epidermal growth factor receptor), and have high proliferation rates (8). This subtype has a less favorable prognosis than the others, particularly luminal A subtype, which has the highest survival rates (8). In the Carolina Breast Cancer Study (CBCS), the prevalence of basal-like breast cancer was highest (39%) among black premenopausal women compared with other groups of patients (14%–16%; ref. 8). This has been

observed in other studies in the United States (7, 9). It could be suggested that the preponderance of basal-like or hormone receptor-negative tumors among black women could be due to their younger age at diagnosis, but even in older age groups, blacks are more likely than whites to present with triple-negative disease (10).

Until recently, the reasons for these differences in subtypes have been unknown. Historically, the majority of risk factors for breast cancer are related to lifetime exposures to estrogens and, overall, parity has been associated with reduced risk of breast cancer (11). In the CBCS, however, parity was associated only with reduced risk of luminal A subtype and, in fact, increased risk of basal-like breast cancer by almost 2-fold (12). Of importance, the increased risk of basal-like breast cancer with increasing number of live births was totally ameliorated with breast-feeding. These associations have also been observed in subsequent studies in other populations (13, 14). In the Black Women's Health Study, similar associations with parity and breast-feeding were observed in relation to age at onset, with higher parity noted to increase risk of breast cancer before age 45 among black women (12, 15). Because black women are generally more likely to have a greater number of children at a younger age in the United States, and not to breast-feed, these reproductive factors could account, in part, for the higher proportion of basal-like breast cancers in black women. However, because basal-like breast cancers are also more prevalent among women in Africa, a biological or genetic component cannot be ruled out.

It is well established that African Americans have lower circulating levels of serum vitamin D, perhaps due, in part, to higher skin pigmentation, reducing absorption of ultraviolet rays (16). In cell culture and rodent models, vitamin D has shown anticancer properties, but the epidemiologic support for a role in breast cancer risk reduction has been inconsistent. It is possible that the effects of vitamin D may be more important in modulating breast cancer aggressiveness and prognosis than overall cancer susceptibility. Indeed, mice lacking the vitamin D receptor are more likely to develop aggressive *ER/PR*-negative mammary tumors than wild-type mice (17); in human breast cancer cells, vitamin D inhibits the expression of a variety of basal/myoepithelial markers, reverting their transdifferentiation, related to the basal-like subtype (18). Lower serum vitamin D levels have been associated with higher-grade tumors (19) and, in a series of more than 500 women with breast cancer, we observed that serum 25-OHD levels were lowest among women with basal-like breast cancers (Ambrosone and colleagues, unpublished data). Thus, it is plausible that lower vitamin D could contribute to the higher proportion of basal-like tumors among black women. Clearly, genetic, biological, and epidemiologic risk factors for breast cancer subtypes, particularly among black women, need to be further investigated. However, the observation in several studies that increased risk of basal-like breast cancer is associated with higher parity and that breast-feeding reduces this risk, warrants further public health recommendations that breast-feeding be encouraged for all women and, especially for black women, to reduce risk of basal-like breast cancer. In addition, although associations between vitamin D

and breast cancer in black women need to be further investigated, maintenance of adequate vitamin D levels could possibly contribute to lowering the risk of aggressive breast cancer in this population.

#### Racial differences in germline genetic factors

Although certain founder mutations in *BRCA1* or *BRCA2* genes have been seen more commonly in particular groups such as Ashkenazi Jewish individuals, the spectrum of deleterious mutations seems to be different from that observed in black women. Although the frequency for both *BRCA1* and *BRCA2* mutations may be lower than that observed in white or Ashkenazi Jewish individuals with breast cancer (20–23), a higher frequency of sequence variation of undetermined significance is seen in black women (21). It is unclear whether these variants act to modify risk or disease aggressiveness. Breast cancer characteristics seen in blacks are similar to *BRCA1*-associated tumors. As promoter methylation may be a mechanism for inactivating *BRCA1* in sporadic tumors (24), it is unclear what proportion of blacks with breast cancers have methylation of the *BRCA1* gene that may explain similarities between breast cancer in blacks and *BRCA1*-associated cancers.

Admixture mapping is a useful strategy for discovering disease causing genetic variants that differ in frequency across populations and contribute to complex traits such as oncogenesis. A large genome-wide admixture study in blacks with breast cancer from 6 population-based studies did not find an association between breast cancer risk and African or European heritage at any loci, suggesting that genetic ancestry may not contribute significantly to risk (25). This is controversial, however, given the striking similarities between breast cancer in blacks living in Africa and black Americans in the United States (26). We have shown that blacks with breast cancer in Nigeria and the United States have differences in common breast cancer risk factors such as age at menarche, body mass index, number of pregnancies, age at first birth, and lactation duration, despite similar clinicopathologic features (27). It is therefore plausible that genetic factors (and not reproductive and hormonal risk factors) common to the two groups, but different from those observed in whites, may explain the biologically aggressive disease observed in black women irrespective of location. This underscores the need for pooling of epidemiologic studies in black women to have adequate statistical power to investigate complex interactions between genetic and nongenetic factors in the etiology of aggressive breast cancer and evaluation of these and factors related to access and optimal care to disentangle predictors of poorer survival among black women with breast cancer. Although polymorphisms have been extensively studied in relation to risk of overall breast cancer in white women, there are a very few studies in black women, particularly for genetic polymorphisms, that infer susceptibility to early-onset aggressive breast cancer.

#### Racial differences in detection

Although early detection with screening mammography has contributed to declines in breast cancer mortality; not all

women have benefited equally. Even though blacks are less likely to undergo regular mammograms than whites (28), it is unlikely that differences in detection account for the entirety of outcome disparities. It is difficult to estimate the risk attributable to overall outcome due to multiple other factors that influence outcome.

Factors responsible for differences in mammography rates are multifactorial and include a lower likelihood of receiving a recommendation for mammography from a health care provider, lack of insurance, or access to regular health care (29, 30). Although adjusting for socioeconomic and insurance status has often resulted in reports that blacks have greater odds of having a recent mammogram than whites (31), multivariate models suggest that fewer blacks receive regular mammograms than whites, consequently continued effort is needed to reduce access barriers for blacks not regularly screened. Given guidelines that recommend women begin mammography at age 40 or 50, black women may be at increased risk for delayed diagnosis even if they are compliant with current screening guidelines, as greater than 10% of breast cancer cases in blacks are diagnosed in women younger than 40 years compared with 5% of whites (32). Therefore, the optimal age for breast cancer screening in blacks still needs to be defined. This is also particularly important, given the disproportionate mortality in younger black women with breast cancer. If one considers the increased breast density in this group, mammography may not be the best choice. Perhaps, race- and/or age-directed screening with ultrasonography or even more sophisticated techniques with novel biomarkers ought to be developed in the future.

#### Racial differences in management

An important factor that also contributes to the racial gap in mortality is the observed difference in clinical management of the disease. It is plausible that black women have more comorbidities that preclude them from receiving established standards, or perhaps they are not receiving standard therapy due to cultural beliefs/distrust, or alternatively they have more problems tolerating equivalent doses of chemotherapy than their white counterparts. These are some potential reasons why black women with breast cancer frequently receive sub-optimal care; however, more dedicated research to fully elucidate these factors is needed.

For example, a large SEER-Medicare study involving more than 55,000 women showed that blacks were less likely than whites to be treated at high-quality hospitals (defined as hospitals with the top quartile rates of radiation following breast-conserving surgery) and consequently less likely to receive definitive primary therapy, a finding partially explained by having surgery at a high-quality hospital (33). When blacks do undergo breast-conserving surgery, they are less likely to receive radiation than whites. In this study, the odds of radiation omission were more pronounced in blacks who lived in high-poverty areas or in areas farther from cancer centers (34). Interestingly, these factors did not affect radiation use among whites.

The favorable impact of adjuvant chemotherapy on outcomes is minimized when full doses of therapy are not given as

planned. Griggs and colleagues revealed that despite controlling for clinical and sociodemographic characteristics, blacks with breast cancer had systematic differences in chemotherapy administration as opposed to whites (35). They had a higher tendency to receive less relative dose intensity and more first-cycle dose reductions. Underlying reasons for these discrepancies remain unclear, as biological reasons such as lower neutrophil counts or chemotherapy tolerance were not associated with these disparities. In addition to receiving less than full doses of chemotherapy, significant delays in initiating chemotherapy are associated with lower survival (36, 37). Although, Hershman and colleagues did not find significant racial differences in chemotherapy, initiation delays in women who were 65 years or older with early-stage breast cancer (36), a larger study involving almost 108,000 women found a higher risk of delays in blacks and Hispanics than in whites (38).

Blacks on chemotherapy protocols seem to benefit from chemotherapy with racial differences in stage-specific outcome versus whites. An analysis of patients on Southwest Oncology Group Protocols between 1974 and 2001 showed that blacks with breast cancer had increased mortality than whites despite being on the same chemotherapy protocols (39). This finding does not support the assumption that standardized treatments result in consistent outcome but supports the argument that black race has an independent detrimental effect on outcome.

Underuse of endocrine therapy in early-stage hormone receptor-positive disease is also associated with inferior outcomes. A study between 1999 and 2000 found that blacks were less likely to receive adjuvant hormonal therapy than whites (71% vs. 80%) even after controlling for stage, comorbidity, age, insurance, and medical oncology referral (40).

Given the worse health outcome for blacks compared with whites, ensuring access to clinical trials to improve therapies for this group has been a focus of the NIH. Unfortunately, the proportion of nonwhite clinical trial participants declined significantly between 1996 and 2002, particularly for breast, lung, and colorectal cancers (41). Lack of trust in the health care system, not being offered participation by physicians, and lack of access to health care in general and thus clinical trials are possible explanations for these differences (42, 43). In addition, ethnic-related variability in stage of diagnosis and trial exclusion criteria may also contribute to disparities in clinical trial participation.

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In summary, although the literature has provided important insights into the magnitude of disparities in clinical management, a major unanswered question is at which point in the process of care disparities arise, particularly for women, within similar socioeconomic classes. Several programs to evaluate the quality of breast cancer care have been developed by professional organizations. These processes are potentially modifiable and are therefore useful tools in addressing racial disparities. In fact, studies have shown that vulnerable groups such as older blacks with early-stage breast cancer are less likely to receive adequate care than whites even after adjusting for tumor characteristics and comorbidities (44). Data specific to younger women with breast cancer are not readily available, yet they are fundamental to fully understanding differences in outcome in this population of patients. Omission of requisite care may be related to failed referral, and this may be more common in minorities (40). Programs to address these disparities must, therefore, include systems to track or "navigate" vulnerable patients in the medical system.

## Conclusion

Although several intervention programs to reduce breast cancer disparities have been instituted recently, the persistent magnitude suggests that current strategies may be inadequate. We have shown that although a substantial amount of information is known about racial differences in outcome and associated factors, several gaps in knowledge exist. Addressing racial disparities in breast cancer, therefore, requires a multidisciplinary approach with innovative research to answer questions that are generally considered "outside the box" of traditional health care research. Disparities in access and quality of care may be eliminated by understanding and addressing cultural and economic barriers. Biological differences in tumors in all racial groups need careful study to allow personalization of care and optimization of outcomes. Closing these gaps in knowledge will in the future hopefully translate to interventions that lead to improved outcomes for all women with breast cancer.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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