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Despite a lower incidence of breast cancers in African Americans than in Caucasians, mortality rates from breast cancer are higher in African Americans. This review summarizes disparities in characteristics of breast cancer diagnosed in African Americans as compared with Caucasians, such as more advanced stage at diagnosis and less estrogen-receptor positivity of disease, in an effort to explain differences in their survival outcomes. Multifactorial explanations are offered, including differences in access to care, disparity utilization of mammography screening and often differences in treatment course—as well as biologic factors, such as higher incidence of aggressive breast cancer phenotypes, higher grade of tumor and higher growth index of tumors in African Americans as compared with Caucasians. Multiple population-based studies have been reviewed and screening and treatment interventions proposed in order to heighten awareness of these differences and to improve disease outcomes among this high-risk population.

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INTRODUCTION

In the United States, breast carcinoma is the most common cancer diagnosed in women of all racial groups, but is the leading cause of cancer-related mortality in African-American women. While the incidence for breast carcinoma is lower in African-American women as compared with Caucasian women, a greater proportion of African-American women with breast cancer are found in younger age groups than Caucasian women, and age-adjusted breast cancer mortality rates are worse in African-American women, with the risk of death from breast cancer up to 67% higher than for Caucasian women. Breast carcinomas diagnosed in African-American patients are more aggressive than those in Caucasian patients by virtue of several characteristics. The National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER) database shows that African-American women are more likely to be diagnosed at later more-advanced stages (IIIB and above) of the disease and to present with higher-grade tumors. African-American women are more likely to have more aggressive breast cancer pathology such as inflammatory, medullary or papillary carcinomas, and less likely to have lobular or tubular carcinomas than Caucasian women. Furthermore, African-American women are less likely to have positive estrogen and progesterone receptors than Caucasian women. Race is therefore a significant independent risk factor for breast cancer mortality. We wish to summarize here the findings of several population-based studies which seek to explain differences in breast cancer characteristics between African Americans and Caucasians in an effort to provide specific interventions and treatments that can potentially impact disease outcome.

THE MULTIFACTORIAL NATURE OF RACIAL DISPARITIES IN BREAST CANCER

Racial differences in breast carcinoma mortality rates are felt to likely be multifactorial in nature since they span external reasons as well as intrinsic genetic reasons, which are the catalyst for studies on the biology of these tumors. Multiple variables affecting the stage at diagnosis include lower utilization of mammography among African-American women (thereby delaying the diagnosis), access to care and other socioeconomic factors. Diet, increased body mass index and obesity, increased parity, an earlier age at first full-term pregnancy and lower incidence of breastfeeding—all of which may affect duration of circulating estrogen levels—are other variables which have been associated with poorer prognosis and higher-stage tumors among African-American women. Specifically, a study by Zhu et al. found that methyl-deficient diets and lower use of antioxidant vitamins may be associated with breast cancer risk by influence on African-American-specific CYP1A1 polymorphisms.
Another external variable which may also have an effect on outcome in African Americans with breast cancer is treatment course. Minority women (and men), including African Americans, may be less likely to receive necessary adjuvant treatments (radiation, chemotherapy and/or hormonal therapy) due to differences in comorbidities and lack of insurance despite equivalent rates of oncologic consultation when compared with Caucasian patients.25-29 Psychosocial barriers leading to frequent modifications of adjuvant chemotherapy administration may be more frequent in African-American patients.30 African-American patients have been reported to be more likely to receive fewer cycles of treatment than expected,31 and have been reported to be more likely to terminate chemotherapy prematurely, this being associated with poorer survival.32 Of those patients who terminated treatment early, survival was poorer. However, an important distinction is that of those whose treatment was delayed (due to low white blood cell counts) but completed, survival was not reduced.31 More delays in the initiation of radiation treatment in African-American women may also be associated with poorer survival.33 A study stemming from survival data, however, from clinical trials of adjuvant chemotherapy, found that African-American women were more likely to have higher rate of relapse due to other prognostic features such tumor size and receptor status,34-36 and analyses of clinical studies in metastatic breast cancer have shown that African-American patients still have higher survival despite similar response from chemotherapy.37 These highlight the importance of studying the pathologic characteristics of breast cancers in African Americans in addition to demographic differences, with the hopes of further identifying better more specific treatment interventions.

**BIOLICAL DIFFERENCES IN BREAST CANCERS IN AFRICAN AMERICANS**

Studies in African Americans with breast cancers have identified some interesting unique signatures of these tumors. Biologically, numerous BRCA mutations have been reported among African-American breast cancer patients38-40 and point to the existence of founder mutations among both African-American and native-African women.34-41 However, knowledge and awareness about breast cancer genetic testing is lower among African Americans,42,43 and African Americans have been reported to participate in genetic testing less than Caucasians.44 Other differences in specific gene expressions seen more frequently in African Americans have been reported from case control studies (Table 1) and include higher expression of cell-cycle regulators such as cyclin E, p16, p5345,46 and specifically identified polymorphisms in cytochrome p450 oxidoreductase related to metabolism of endogenous hormones,47 and in nucleotide excision repair genes related to exposure and duration of cigarette smoking.48-50

Pathologically, it has been found that in African-American women these carcinomas are more likely to be negative for expression of the estrogen receptor than in Caucasians.34,50-54 Genomic analyses of breast cancer phenotypes which have subclassified breast cancers into ≥4 categories, with increasingly aggressive behavior and worsened prognosis [luminal A (ER+ and/or PR+, HER2-); luminal B (ER+ and/or PR+, HER2+), HER2-positive (ER-, PR-) and basal-like (ER-, PR-, HER2-, CK5/6+ and/or HER1+) phenotypes],51,52,56 have also identified that African-American women, particularly premenopausal, have a higher likelihood of developing the basal (“triple-negative”) phenotype of breast cancer than Caucasian women.52 These molecular subtypes of breast cancer respond differently to chemotherapy,57 with the basal-like or erbB2/HER2+ phenotype being more sensitive to regimens in the preoperative setting which contain standard agents paclitaxel, doxorubicin57 and cyclophosphamide.58 Breast cancers of the basal phenotype have more p53 mutations, higher mitotic index, nuclear pleomorphism and tumor grade.59 In vitro, basal-like breast cancer cell lines show expression of epidermal growth factor receptor (EGFR) and, importantly, have shown sensitivity to carboplatin and EGFR inhibitors such as cetuximab.56,59 Morris et al. have shown that of 2,230 patients in the Thomas Jefferson University Hospital’s Kimmel Cancer Center Tumor Registry, a higher rate of triple-negative breast cancers occurred in African Amer-

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<tr>
<th>Table 1. Disparate gene expressions reported in breast cancers in African Americans associated with worsened prognosis</th>
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<tr>
<td><strong>Gene</strong></td>
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<tr>
<td>Overexpression of cell-cycle regulators25,45</td>
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<tr>
<td>Cyclin E</td>
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<tr>
<td>p16</td>
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<td>p5345,46,72,73</td>
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<td>Lower expression of cyclin D145</td>
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<tr>
<td>Alterations in c-met (stem-cell factor/hepatocyte-growth factor receptor)46</td>
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<tr>
<td>Polymorphisms in cytochrome-P450-1A147</td>
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<tr>
<td>Polymorphisms in nucleotide excision repair genes45,46</td>
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<td>NR: not reported</td>
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ican, consistent with data from NCI SEER’s database; they were also noted to have higher p53 expression and ki-67 proliferation index, all of which were associated with worsened survival among African-American breast cancer patients as compared with Caucasians.60 In addition, Bauer et al. have corroborated the triple-negative phenotype as more prevalent in African Americans than in Caucasians in California.61

FUTURE INTERVENTIONS: IMPROVEMENT OF SYSTEMIC TREATMENTS

As highlighted, registry studies have thus given valuable information regarding the multifactorial differences in breast cancer outcomes among African Americans as compared with Caucasians, from which distinct biologic differences are emerging. More specific large studies are needed in order to fully explain these differences in a targetable fashion.62 Additional microarray analyses between samples from African-American patients matched to breast cancer phenotypes but compared with Caucasian subjects are proposed in order to identify biologic differences at the mRNA level.53,64

Since African Americans have higher likelihood for developing aggressive phenotypes of breast cancers which are likely to recur after standard chemotherapy, the onus is to improve treatments as well as to improve early detection for this population of women, in particular. Clinical trials for basal-like breast cancers are underway to evaluate response to platinum-containing regimens in the setting of recurrence65 as well as incorporation of therapy targeted to angiogenesis. With the knowledge that basal-type and erbB2+ subtypes of breast cancer may respond better to certain chemotherapy regimens (as observed in the preoperative setting), the higher propensity for the former subtype in African-American women with breast cancer should heighten prompt initiation of aggressive and specific chemotherapy regimens once diagnosed.97 Because the ki-67 proliferation index is elevated in African-American breast cancers, differences in cell-cycle proteins may warrant the incorporation of cell-cycle inhibitors and/or cyclin-dependent kinase inhibitors into treatment regimens.

FUTURE INTERVENTIONS: IMPROVEMENT IN DETECTION AND MANAGEMENT OF RISK FACTORS

Early detection of lower-stage tumors will also potentially reduce breast cancer mortality in African Americans. As previously mentioned, several studies have noted possible underutilization of breast screening techniques among African-American women of lower socioeconomic status,2,15-21,24 and these data should heighten the need to employ these techniques to increase detection rates in this high-risk population.65 One example is the African-American Breast Cancer Screening Outreach project, a Texas community-based participation intervention designed to increased the numbers of African-American women screened for breast cancer, which serves as a model strongly needed across the country.66 In addition, the South Carolina Cancer Disparities Community Network has identified disparities in breast cancers as well as proposed community-based research areas which will potentially hold promise for reducing these disparities.67 A population-based study in Chicago has urged the development of interventional programs for accessibility to mammography in order to reduce the disparities found in breast cancer mortality.68 Breast cancer preventive measures such as reduction of body mass index, moderation of diet and alcohol consumption, and the utilization of breastfeeding69 should also be contemplated and recommended for this high-risk group of women.4,23 A study by Millikan et al. estimated that up to 68% of basal-like phenotype of breast cancer can be prevented by breastfeeding and reducing abdominal adiposity,69 as long duration of breastfeeding is associated with lower relative risk of both estrogen receptor-positive and -negative tumors.70

Early intervention once detected will be a key component to improvements in breast cancer-related survival in this high-risk population. This summary should serve to heighten awareness for early screening and for the institution of aggressive and specific treatment regimens for different breast cancer phenotypes.71 More future studies identifying differences in gene expressions will help to target and enhance treatment more specifically.72,73

REFERENCES


Aggressive Breast Cancer Characteristics


