

Breast Cancer in African-American Women: Differences in Tumor Biology from European-American Women

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Abstract

Disparities exist between African-American and European-American women in the incidence and nature of breast cancer. African-American women are more often diagnosed with breast cancer at an earlier age and with more aggressive disease, characterized by higher grade and negative estrogen and progesterone receptor status. Recent findings reveal specific gene expression patterns associated with the more aggressive breast cancers observed in African-American women. An overview of the current literature about racial differences in breast cancer prompts questions for future research to elucidate causes for the apparent disparities in tumor biology. (Cancer Res 2006; 66(17): 8327-30)

Epidemiology

Breast cancer is the most common cancer diagnosed among women in the United States, with >130,000 cases diagnosed yearly. The Surveillance, Epidemiology, and End Results (SEER) database, a large population-based database, has shown that breast cancer incidence and mortality rates have differed between African-American and European-American women over the past 2 decades (1). Between 1998 and 2002, European-American women had higher age-adjusted breast cancer incidence rates compared with African-American women (143 per 100,000 versus 119 per 100,000; ref. 1). Among women ages ≥ 50 years, European Americans were at a greater risk for developing the disease compared with African-American women (397 per 100,000 versus 323 per 100,000), but the pattern was reversed among women ages <35 years. For each age group <35 years, incidence rates were higher among African-American women. Furthermore, compared with European-American women, African-American women have the highest age-adjusted mortality rates from the disease. Between 1995 and 2001, the 5-year survival rate from breast cancer was 75.9% for African-American women and 89.5% for European-American women, with age-specific breast cancer mortality rates among younger African-American women approximately twice that of younger European-American women (1).

It has been suggested that higher mortality and lower survival rates among African-American women are due to factors associated with lower socioeconomic status and later stage at diagnosis (2–5). However, in several studies, racial differences in survival remained after adjustment for stage at diagnosis, access to health care, treatment, comorbid illness, marital status, and other pathologic and sociodemographic variables (4, 6–9). These data

point to possible differences in the nature of the disease itself, supported by the observation that breast cancer in African-American women is more aggressive at presentation, characterized by an increased prevalence of high-grade, hormone receptor-negative tumors as shown in Table 1. In this article, we review the current literature about breast cancer in African-American women, with a focus on tumor biology, particularly in comparison with breast cancer in European-American women.

Tumor Biology

Tumor grade. African-American women are more likely to be diagnosed with high-grade disease compared with European-American women. Histologic grade is typically scored as a three-level variable (1, 2, and 3) based on the Scarff-Bloom-Richardson system, where patients with grade 3 tumors have poorer overall survival compared with those who have grade 1 or 2 tumors ($P < 0.0001$; ref. 10). In a study of >106,000 female breast cancer patients from 11 population-based SEER registries, 57% of African-American women were diagnosed with high-grade disease compared with 41% of European-American women (6). A study conducted in Atlanta, Georgia to evaluate racial differences in breast tumor characteristics found that the odds of a breast carcinoma diagnosis at a younger age and at later stage were higher for African-American women than for European-American women, and African-American women were more likely to have high-grade tumors after adjustment for age and disease stage [odds ratio (OR), 4.0; 95% confidence interval (95% CI), 1.7–9.2; ref. 11]. Similarly, the National Cancer Institute population-based Black/White Cancer Survival Study found that, after adjustment for age, stage, and metropolitan area, African Americans were significantly more likely to have grade 3 tumors compared with European-American breast cancer patients (OR, 1.58; 95% CI, 1.02–2.45; ref. 4).

Estrogen and progesterone receptors. Women with estrogen receptor (ER)-positive and progesterone receptor (PR)-positive tumors have a better prognosis compared with women with receptor-negative disease. Using SEER data from nine geographic regions, Joslyn et al. (12) evaluated hormone receptor status in more than 12,000 African-American and 141,000 European-American women. In that study, 39% of female African-American breast cancer patients had ER-negative tumors compared with 23% of European-American patients, whereas 46% of African-American women had PR-negative tumors compared with 32% of European-American females. Women with ER-negative, PR-negative tumors had the worst survival. Similar proportions of ER negativity were found in a large multicultural study of breast tumor specimens collected from 31 hospitals throughout the United States from 1,016 African-American and 4,885 European-American women (38% and 22%, respectively; ref. 13). Fifty-nine percent of African-American women were PR negative compared with 44% of European-American women. The authors also reported that

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Table 1. Breast cancer epidemiology and tumor characteristics among African-American and European-American women

Characteristic	African Americans	European Americans
Incidence rate	119/100,000 (1)	143/100,000 (1)
Mortality rate	34/100,000 (1)	25/100,000 (1)
Age at diagnosis	Incidence higher among women <35 years (1)	Incidence higher among women >35 years (1)
Tumor grade	Increased prevalence of high-grade tumors (4, 6, 11)	Increased prevalence of low-grade tumors (4, 6, 11)
ER status	Increased prevalence of ER ⁻ tumors (6, 12-16)	Increased prevalence of ER ⁺ tumors (6, 12-16)
PR status	Increased prevalence of PR ⁻ tumors (6, 12-16)	Increased prevalence of PR ⁺ tumors (6, 12-16)
HER-2 expression	No significant differences in expression compared with European Americans (11, 13)	
Other molecular characteristics	Tumors associated with higher mitotic index, overexpression of cyclin E and p53, lower expression of cyclin D1, and higher S-phase fraction compared with tumors from European-American women (4, 11, 13)	
Basal-like phenotype	Increased prevalence of basal-like subtype among African-American women compared with European-American women (27)	

African-American women had lower overall survival at 5 years (65%) compared with either European-American (75%) or Hispanic women (70%). The Women's Health Initiative study, a longitudinal study of postmenopausal women's health, also reported a higher incidence of ER-negative [hazard ratio (HR), 1.54; 95% CI, 1.11-2.14] and PR-negative (HR, 1.29; 95% CI, 1.00-1.67) tumors among African-American women compared with European-American women, and African-American women had higher mortality after breast cancer compared with European-American women (HR, 1.79; 95% CI, 1.05-3.05; ref. 8). The Carolina Breast Cancer Study (CBCS), a population-based case-control study of breast cancer in African-American and European-American women, evaluated tumor characteristics in ~800 breast cancer patients with invasive disease and reported that African-American women had more aggressive disease features, including a greater odds of having both ER-negative and PR-negative tumors (OR, 2.2; 95% CI, 1.5-3.2; ref. 14). One might conclude that higher proportions of high-grade, ER-negative breast cancer among African-American women are the result of the earlier age at onset of the disease. However, in a study of >13,000 women with breast cancer by Gapstur et al. (15), African-American women were more likely than European Americans to have ER-negative breast cancer within each 15-year stratum of age at diagnosis from age 20 to 79.

HER-2. The *HER-2* gene (*c-erbB-2*) is a proto-oncogene located on chromosome 17q that encodes a tyrosine kinase receptor protein, a member of the epidermal growth factor receptor (EGFR) or HER family. HER-2 is overexpressed in ~30% of breast cancers (16) and associated with greater disease recurrence and metastasis and shorter survival (17). Unlike the racial differences observed in the distribution of ER/PR in African-American and European-American women, significant differences in the expression of HER-2 by race have not been observed. In a multiethnic study conducted by Elledge et al. (13), HER-2 expression did not differ between African-American and European-American women ($P = 0.55$). Similar findings were reported by Porter et al. (11), who found that, after adjustment for age and tumor stage, there were no racial differences in expression of HER-2 (OR, 0.9; 95% CI, 0.4-1.7).

Other molecular characteristics. Many cell cycle components are deregulated in oncogenesis, which may contribute to a more

aggressive tumor phenotype and poorer prognosis among African-American breast cancer patients. In the Porter study (11), after adjustment for age and tumor stage, African-American women were more likely to have a higher mitotic index (OR, 2.2; 95% CI, 1.3-3.9), overexpression of cyclin E (OR, 4.3; 95% CI, 2.0-9.2), overexpression of p16 (OR, 2.5; 95% CI, 1.5-4.2), overexpression of p53 (OR, 1.7; 95% CI, 1.0-2.9), and lower expression of cyclin D1 (OR, 0.5; 95% CI, 0.3-0.8) compared with European-American breast cancer patients. Significant differences in mitotic activity were also reported in the Black/White Cancer Survival Study (OR, 2.05; 95% CI, 1.34-3.14; ref. 4). Breast cancer patients with low S-phase fraction (a measure of proliferative action) had significantly longer disease-free survival compared with patients with high S-phase fractions ($P = 0.0008$; ref. 18). Differences in the distribution of S-phase fraction by race were reported by Elledge et al. (13). In that study, African-American women had higher levels of S-phase fraction compared with European-American women ($P = 0.001$).

Basal-Like Phenotype and Breast Cancer

Clinicians caring for breast cancer patients have for some time appreciated the fact that "breast cancer" is a disease that shows significant biological diversity with a broad spectrum of clinical behaviors and outcomes. Molecular profiling of patient samples has provided new insights for these clinical observations by suggesting that this biological heterogeneity can, in part, be explained by differences in the molecular genetic composition of the primary tumor.

Gene expression studies have used microarray technology to assess the molecular heterogeneity of breast cancer phenotypes. Evaluating gene expression patterns using hierarchical clustering, Sorlie et al. (19) identified five tumor subtypes with different prognoses: normal breast-like, HER-2 overexpressing, luminal A and B (predominantly ER⁺), and basal-like subtypes. The difference in gene expression patterns among these subtypes is likely to represent distinct tumor phenotypes influencing overall survival and response to treatment. Indeed, breast cancers with the basal-like phenotype exhibit aggressive disease characteristics and are associated with shorter disease-free survival times (20-22). The basal-like subtype is associated with a high frequency of *TP53*

mutations, grade 3 disease, elevated mitotic count, ER negativity, HER-2 negativity, younger age, and overexpression of cytokeratins 5, 6, and 17, which are markers of the basal cell layer of the normal mammary gland (23, 24). Breast cancer patients with germ-line *BRCAl* mutations are more likely to exhibit the basal-like phenotype compared with noncarriers (25). The CBCS evaluated the basal-like phenotype in 260 African-American and 397 non-African-American women (26). The authors reported that 26% of all breast cancers were basal-like, although a greater proportion of tumors from African-American women exhibited the basal-like phenotype (33.9% versus 21.2%; $P = 0.0003$). The basal-like phenotype was more common in premenopausal African-American women compared with postmenopausal African-American women (44.3% versus 24.6%; $P = 0.0008$).

Given the triple-negative receptor status of this aggressive phenotype, patients with basal-like breast cancer are not candidates for endocrine therapy or trastuzumab, leaving only standard cytotoxic chemotherapy as a treatment option. Interestingly, Nielsen et al. (27) reported on a series of basal-like tumors previously characterized by gene expression profiling, which by immunohistochemistry were negative for ER and HER-2 and positive for basal cytokeratins and, in addition, showed EGFR expression in a significant number of cases. In this series, EGFR expression was seen in 54% of the tumors and associated with a more aggressive clinical course and poor survival independent of nodal status and tumor size. There has been increasing interest in EGFR as a therapeutic target, and several drugs, including therapeutic antibodies and small-molecule tyrosine kinase inhibitors, have been developed and are in clinical trials for several solid tumor types (28, 29). Although clinical efficacy for EGFR inhibitors in breast cancer remains to be evaluated fully, targeted therapies along with cytotoxic agents may be appropriate for carefully selected subsets of patients, such as African-American patients with basal-like breast cancer.

Breast Cancer in Africa

In a recent review of the literature on breast cancer in Africa, breast cancer epidemiology, risk factors, tumor biology, and genetics were compared between sub-Saharan African women and African-American women (30). Striking similarities in disease epidemiology and biology were observed between the two populations. Although breast cancer incidence rates among sub-Saharan African women are quite low (10-40 per 100,000), these women experience higher mortality rates (5-20 per 100,000) and they are more often diagnosed at a younger age with peak incidence rates between ages 35 and 45 years. Although data on ER, PR, and HER-2 expression are limited among sub-Saharan African breast cancer patients and were not discussed in the review,

studies have indicated that sub-Saharan African women are more likely to have aggressive tumor characteristics, including high-grade disease, higher mitotic indices, more extensive necrosis, and more nuclear atypia similar to histologic characteristics in African-American breast cancer patients. It is possible that the observed similarities in disease presentation among African-American and sub-Saharan African women are influenced by a genetic component, such as an unidentified founder mutation in breast cancer susceptibility genes or in genes related to hormone metabolism, or there is a lack of variation in the distribution of environmental or lifestyle factors that influence breast cancer risk (31).

Future Directions

African-American women have a distinct tumor phenotype characterized by aggressive molecular characteristics. To date, there are few clues to identification of genetic or nongenetic factors that may predict this early onset, aggressive breast cancer in African-American women. Targeted efforts to determine risk factors for aggressive breast cancer in African-American women will likely lead to identification of women who are susceptible, particularly at a younger age, and enhance efforts for targeted screening and preventative interventions. Furthermore, evaluation of risk factors while accounting for factors related to socioeconomic status may also elucidate the proportion of higher mortality that may be accounted for by tumor characteristics.

The lessons learned from gene expression studies in breast cancer are leading us in the direction of more clinically relevant, molecular classifications of this disease and provide us with new tools and a different perspective with which to address the disparities and ethnic differences that have been described for breast cancer patients. Given the biological diversity and spectrum of clinical behaviors and outcomes that can be seen in a single population, it seems likely that racial differences will ultimately be explained by differences in the molecular and genetic alterations that caused tumors in these populations and drive the clinical course of the disease. Finally, a better understanding of the key molecular determinants and genetic alterations that underlie clinical behavior in these different populations will almost certainly lead to more rational and objective criteria to guide the selection of appropriate and effective therapies for breast cancer patients.

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