

Racial differences in genetic factors associated with breast cancer

Foluso O. Ademuyiwa and Olufunmilayo I. Olopade*

Section of Hematology/Oncology, Department of Medicine, University of Chicago, Chicago, IL 60637

Key words: breast cancer, African American, Caucasian, genetic differences

Summary

Breast cancer in African Americans in the US is more aggressive and has a worse outcome than breast cancer in Caucasians. Although the incidence of breast cancer among US whites is higher than among blacks, the mortality rates for blacks are much higher. Breast cancer in blacks is also associated with a more advanced stage at presentation and pathologically aggressive tumors commonly exhibiting estrogen receptor negativity, higher S-phase fractions, and higher numbers of involved lymph nodes. This paper reviews some of the genetic factors that have been shown to be associated with a difference in breast cancer outcome between African Americans and Caucasians in the US such as the *BRCA1* and *BRCA2* genes, *p53* mutations, *UGT1A1* gene polymorphisms, and *HER-2/neu* gene amplifications/overexpression.

I. Introduction

Excluding skin cancers, breast cancer is currently the most common cancer among American women and is second only to lung cancer as the leading cause of cancer-related deaths. An estimated 192,200 invasive breast cancer cases were expected to be diagnosed in 2001. Of this number, almost 41,000 were expected to die from the disease [1]. Between 1973 and 1996, the overall age-adjusted incidence rate of breast cancer increased by 25.3% in the US [2]. During that period there was a disproportionate increase among African American women (36.7%) as compared to Caucasian women (26.2%) [3].

While the current incidence rates of breast cancer among white women are now higher than among blacks, the mortality rates among black women are much higher. Overall mortality rates in African American women are higher at 31.7 per 100,000 as compared to 27.4 per 100,000 in Caucasians [4]. Trends in age-specific mortality rates comparing blacks and whites seem to have been consistent over time, suggesting genetic

rather than environmental differences. It is believed that breast cancers due to genetic mutations tend to occur at a much younger age and have a worse prognosis. Mortality rates, in fact, differ by age group between African Americans and Caucasians. In 1980, black women younger than 45 years had higher mortality rates as compared to whites in the same age group [5]. Between 1993 and 1996, breast cancer mortality rates among those aged 35 years and younger in African Americans were two fold higher than the rates in Caucasians. For those between 40 and 50 years the rates in black women were 1.5 times the rates in whites, while the two races had more or less similar rates for those aged 55 years and older [6].

Racial and ethnic disparities in access to and use of health care services in the US have been a major public health problem. Even among women with similar incomes and access to mammography, African Americans have consistently been reported as having lower rates of usage of such breast cancer screening practices [7]. Factors responsible for this includes black women's health

* Corresponding author.

E-mail: folopade@medicine.bsd.uchicago.edu

beliefs, perceived risks, and physician's tendency to recommend screening [7–10]. Other interactions such as environmental modifiers of risk, different physiologic and hormonal environments, socio-demographic factors, nutritional intake, and cancer treatment may also explain some of the differences observed between breast cancer in African Americans and Caucasians.

Among explanations given for the observed racial disparities in outcomes include the fact that African Americans tend to present at a much later stage of disease than Caucasians [11]. However, even after adjusting for stage of disease, racial differences in mortality have been shown to still exist [2,4,12,13]. Some of these disparities may be accounted for by racial differences in genetic susceptibility factors. Several investigators have demonstrated different associations with breast cancer between races for the following markers: *p53* tumor suppressor gene, *BRCA1* and *BRCA2*, *Her-2/neu* gene amplifications, estrogen and progesterone receptors, and *UGT1A1* gene polymorphisms.

II. Risk factors

Several risk factors for the development of breast cancer have been identified. Among these factors are hormonal and non-hormonal risk factors [14]. A prolonged exposure to estrogens has been repeatedly found to be associated with an increased risk for breast cancer [15]. Conditions such as post-menopausal obesity, the use of oral contraceptives, early menarche, late menopause, nulliparity, hormone replacement therapy, and alcohol consumption all increase endogenous levels of estrogens and have also been associated with an increased risk of breast cancer. Racial disparities which may put an African American woman at a greater risk for breast cancer exist among these factors, however, it is not known whether these factors will predispose to a more aggressive disease outcome. It has been suggested that the higher prevalence of morbid obesity among African American women compared to Caucasians is one factor which may explain the disparity in the advanced disease stage at presentation between these two groups [16]. Oral contraceptive use before the age of 18 years has

also been found to be associated with an increased risk of breast cancer in African American women but not in Caucasian women [17].

III. Pathological characteristics: differences

The pathological characteristics and tumor biology of breast cancer in African American patients is different from Caucasians. African American patients are more likely to have a more advanced disease in terms of primary tumor size and lymph node involvement at presentation. Among the patients studied by Elledge et al. [12] 29.7% of African Americans and 44.5% of Caucasians had tumors less than or equal to 2 cm at presentation. Conversely, tumors greater than 5 cm were found in 27.7% of the African American patients and only 10.9% of the Caucasians (p -value < 0.0001). With regards to regional lymph nodes, 26.6% of blacks had greater than four lymph nodes at presentation while only 21% of the non-Hispanic whites were found to have more than 4 lymph nodes (p -value < 0.0001). Similarly, the results of the 1982 National Survey of Breast Cancer by the American College of Surgeons showed that 15.9% of blacks presented with tumors greater than 5.1 cm as opposed to only 9% of white patients. Black patients also had a higher number of axillary lymph nodes at presentation than the white patients. This study also demonstrated a slightly higher frequency of medullary carcinomas in the black patients [18].

Other biological markers that represent a more aggressive course of disease have been studied in both black and white patients. A positive estrogen and progesterone receptor (ER+, PR+) status is usually associated with improved survival and a disease amenable to hormonal treatments [19,20]. African American women with breast cancer tend to have less ER positive tumors than their counterpart Caucasian women [12,18,20] and therefore a poorer response to hormonal agents. The S-phase fraction, which is a measure of the cell proliferative activity and therefore prognosis, has also been found to be higher in black patients with breast cancer. Elledge et al. [12] determined the median S-phase fraction in blacks to be 8.6% compared to 6.9% in whites. Fifty percent of the blacks in this cohort also had tumors which