

# Breast Carcinoma in African-American and White Women

## *Application of Molecular Biology to Understand Outcome Disparities*

Lisa A. Newman, M.D., M.P.H.

Breast Care Center, University of Michigan, Ann Arbor, Michigan

The excellent study reported by Jones et al. in this issue of *Cancer*<sup>1</sup> provides an example of how advances in medical technology are allowing the oncology community to explore population-based variations in breast carcinoma epidemiology on a more scientific level. Differences in breast carcinoma incidence and mortality related to ethnic background are observed on a worldwide, international basis. The incidence is reported to be > 80 per 100,000, and mortality is > 20 per 100,000 in North American countries such as the U.S. and Canada, as well as in Northern European/Norwegian countries such as the Netherlands, Switzerland, and Denmark. In contrast, incidence and mortality rates are reported to be < 20 per 100,000 and < 10 per 100,000, respectively, in Asian countries such as China and Korea, and in many parts of Africa.<sup>2</sup> Intermediate between these two extremes are the rates noted in some European countries such as Spain and Greece, and certain South American countries such as Argentina. Numerous parallels to these differences in breast carcinoma burden related to ethnic background have been reported within the diverse population of the U.S. Confounding the study of possible ethnicity-related variation in primary tumor biology, however, are the many coexisting differences in socioeconomic status, lifestyle, culture, and dietary habits.

The largest magnitude differences in breast carcinoma outcomes within the U.S. have been observed between African-American women and white women. Breast carcinoma incidence is lower for African American women compared with white women, yet mortality rates, paradoxically, are higher.<sup>3</sup> Other poorly understood features that characterize the impact of breast carcinoma on African-American women include a more advanced stage distribution and an increased prevalence of high-grade, hormone receptor-negative tumors.<sup>3,4</sup> The age-incidence curves for breast carcinoma in African-American women and white women also differ; for women age < 45 years, the incidence of breast carcinoma is higher in African-American women compared with white women.

The increased poverty and noninsured rates among African Americans may explain many of the breast carcinoma disadvantages that have been documented, but they do not account readily for the entire picture. A recent meta-analysis of breast carcinoma survival

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Address for reprints: Lisa A. Newman, M.D., M.P.H., Department of Surgery, Breast Care Center, University of Michigan, 1500 East Medical Center Drive, Ann Arbor, MI 48109; Fax: (734) 647-9647; E-mail: lanewman@umich.edu

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**TABLE 1**  
**Selected Studies of Breast Morphology and Primary Tumor Features in African-American Women Based on Advanced Molecular Biology and/or Breast Tissue Studies**

Study	Sample size	Technology/analysis	Findings
Elledge et al., 1994 <sup>15</sup>	4885 W breast ca patients, 1016 AA breast ca patients, and 777 Hispanic-American breast ca patients	Immunohistochemistry for ER/PR, HER-2/ <i>neu</i> , p53; flow cytometry for S-phase fraction and DNA ploidy status	Tumors in AA women more likely to be hormone receptor negative with higher S-phase fraction
Shiao et al., 1995 <sup>16</sup>	47 W breast ca patients and 45 AA breast ca patients	PCR single-strand conformational polymorphism analysis and DNA sequencing	Similar rates of somatic p53 mutations, but specific alterations varied between AA and W patients
Guillemette et al., 2000 <sup>17</sup>	200 AA breast ca patients and 200 AA controls	RT-PCR analysis	AA-specific polymorphisms in UG1A1 (a steroid-metabolizing gene)
Poola et al., 2002 <sup>18</sup>	24 AA breast ca patients	RT-PCR to analyze ER isoforms	Decreased expression of ER- $\beta$ and increased expression of ER- $\alpha$ exon 5 $\Delta$ isoforms
Mehrotra et al., 2004 <sup>19</sup>	44 W breast ca patients and 67 AA breast ca patients	Methylation-specific PCR to analyze HIN-2; twist; cyclin-D-2; RASSF1A; in situ hybridization PCR to analyze HIN-1 mRNA	Increased frequency of multiple gene methylation in young AA women with ER-negative and PR-negative tumors
Chen et al., 2004 <sup>20</sup>	149 AA women, 67 Asian-American women, and 266 W women	Computer-assisted measurements of mammographic density in Asian-American, AA, and W women	Ethnic differences in breast density correlated with ethnic variation in risk require adjustment for age, BMI, and reproductive factors; measurements of absolute density were more meaningful than the proportion of dense tissue
Jones et al., 2004 <sup>1</sup>	177 W breast ca patients and 145 AA breast ca patients	Immunohistochemistry for <i>c-met</i> and p53	Increased prevalence of p53 alterations among AA women as well as higher histologic grade, nuclear grade, and more likely to be high risk on multiple factors (e.g., negative status on both ER and PR)

Ca: carcinoma, W: white; AA: African American; ER: estrogen receptor; PR: progesterone receptor; PCR: polymerase chain reaction; RT: reverse transcriptase; BMI: body mass index.

studies that have reported on outcomes after adjusting for socioeconomic status revealed a persistent, 22% higher mortality hazard for African-American women, independent of income bracket, age, and disease stage at the time of diagnosis.<sup>5</sup> Other factors that have been implicated in the etiology of these outcome disparities include higher obesity rates among African Americans, with > 50% of African Americans age > 40 years reported to be obese<sup>6</sup>; higher dietary fat intake/poorer overall nutritional status<sup>7</sup>; and menstrual/reproductive factors.

The younger age distribution for African-American patients with breast carcinoma has been a particularly disturbing feature because of the general impression that early-onset breast carcinoma represents an inherently more aggressive disease. However, even within the category of very young patients, breast carcinoma tends to imply a worse prognosis among African-American women.<sup>8,9</sup> This pattern of early-onset disease, coupled with breast carcinoma characterized by higher rates of aneuploidy and hormone receptor negativity, also is observed for breast carcinoma de-

tected in western African nations such as Nigeria and Ghana.<sup>10-14</sup> This region of continental Africa shares a common ancestry with many African Americans, because it was a principal component of the colonial-era slave trade.

The parallels in breast carcinoma occurrence between African-American women and western continental African women suggest the influence of some as yet unidentified founder mutations in breast carcinoma susceptibility genes or in genes related to hormone metabolism. It also is possible that environmental exposures or lifestyle factors of disproportionate prevalence in the African-American community have an effect on primary breast tumor biology that currently remains undefined. Progress in the study of these theories will require the application of advanced molecular biologic techniques, including microarray analyses of tumor genetic content.

Elledge et al. conducted a landmark immunohistochemistry analysis of nearly 5000 breast tumors in a mixed-ethnicity tumor bank in 1994<sup>15</sup>. They found higher rates of estrogen receptor negativity and in-

creased S-phase fractions for the African-American subset. In the 10 years after the study by Elledge et al., several other investigators, such as Jones et al. (in this issue of *Cancer*)<sup>1</sup> have come to appreciate the need to go beyond observations of crude disease incidence and mortality rates if we are to ever develop meaningful insights regarding ethnicity-related variations in breast carcinoma burden. Jones et al. and the Yale University team of epidemiologists and pathologists studied the primary invasive breast tumors of 145 African-American patients with breast carcinoma and 177 white patients with breast carcinoma.<sup>1</sup> They utilized immunohistochemical staining to analyze the expression of p53, HER-2, and *c-met* in addition to the more routinely reported estrogen receptor/progesterone receptor status and tumor grade. This study represents important new information regarding the increased prevalence of p53 alterations in African-American patients with breast carcinoma. The well established patterns of advanced stage distribution, higher nuclear grade tumors, and negative hormone receptor status also were observed.

Table 1 summarizes the results of Jones et al. as well as a few selected studies that also have applied innovative tumor analyses to the study of breast carcinoma in African-American women.<sup>1,15-20</sup> Determining whether any of these observations are reproducible or are in fact random findings will require the repetition of these analyses in other patient populations. The critical message, however, is that the door to the improved understanding of ethnicity-related variation in breast carcinoma risk and outcome has now been wedged open by the powerful tools of molecular biology. It is our responsibility as clinicians and investigators to accept the challenge of conducting the studies, collecting and interpreting the data, and validating the results. Hopefully, the return from our success in meeting this challenge will be the ability to lower risk and improve the treatment efficacy for our collective, diverse patient populations.

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