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Gene Expression Profiling of Breast Cancer in Ethnic Populations: An Aid to Gene Discovery for the Benefit of All

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While a cure for breast cancer is likely if the cancer is detected early and remains localized, many patients will succumb to the disease if the cancer recurs and/or disseminates to secondary organs. Although significant progress has been made in detecting and treating the primary tumor, the ability to predict the behavior of a patient's tumor and eradicate or control disseminated malignancy remain major clinical challenges in breast oncology. Greater knowledge of the molecular mechanisms involved in breast tumor progression is required to facilitate advances in prognostic evaluation for individual patients and in the design of therapeutic interventions to inhibit the process. Understanding the genetic factors responsible for the differences observed between races with respect to breast tumor behavior is an area of research that may provide valuable insights in this context.

Multiple studies have established the value of certain breast tumor characteristics, such as tumor stage, tumor size, lymph node involvement, and hormone receptor status, as prognostic indicators (1). However, the origins of differences in breast cancer incidence and survival with respect to ethnic populations are much less clearly understood. For example, African American women have a lower incidence of breast cancer than their Caucasian counterparts, but when they are diagnosed with breast cancer they have significantly reduced overall survival and disease-free survival rates. A major factor in this difference may be low socioeconomic status, with the consequent likelihood of reduced screening visits, delayed diagnosis, and presentation with more advanced disease. However, breast cancer in African American women also occurs at a younger age, is more often estrogen receptor negative, and more frequently exhibits aggressive biologic behavior as judged by histopathologic grade and high tumor cell proliferation rate (2,3).

These findings have prompted investigators to evaluate race as an independent prognostic factor. While no absolute consensus has been achieved (4,5), reports from the National Surveillance, Epidemiology, and End Results (SEER) program have supported race as a reliable predictor of clinical outcome. In an analysis of 135,424 women diagnosed with primary breast carcinoma between 1988 and 1995, African American women had a significantly increased risk of death from breast carcinoma compared with Caucasian women, independent of the effects of other predictor variables, including tumor stage (6). In a study reported in this issue of *The Breast Journal*, Crowe et al. (7) investigated the association of race with overall and disease-free survival of women diagnosed with infiltrating breast cancer. Within a cohort of 2325 women from the northeastern Ohio region, it was found that African American women were more likely than Caucasian women to have hormone receptor-negative primary tumors, positive axillary nodes, and positive nodes associated with smaller tumors. Furthermore, independent of socioeconomic status,

African American patients were more likely to have poorer overall survival and disease-free survival for breast cancer relative to Caucasian patients. It is possible that postoperative care differentials such as access to adjuvant therapy, clinical follow-up, and compliance with long-term treatment might affect clinical outcome in this group, but in the Ohio study, the African American patients already displayed established independent poor prognostic factors at the time of diagnosis. It is also noteworthy that this situation is closely mimicked in African American men with prostate cancer (8,9). The epidemiologic features and the tumor biology of breast cancer in African American women serve to stress the particular importance of developing effective, specifically tailored strategies for early diagnosis in this ethnic group, but a greater understanding of the genetic basis of racial differences in breast cancer progression may benefit all women with this potentially fatal disease.

Despite the mounting evidence that breast tumors in African American women are more aggressive compared with breast tumors in other women, little is known about associated genetic alterations that may be of prognostic or biologic importance. Studies to date have concentrated on the evaluation in African American cohorts of a number of molecular “usual suspects,” such as p53, *BRCA-1*, and angiotensin-converting enzyme (ACE) (10–12), but a more global, unbiased profiling approach would seem particularly suited to this problem.

On the basis of the knowledge provided by the Human Genome Project, powerful new high-performance screening techniques have revolutionized the ways in which researchers can study the pathogenesis of disease. The advent of DNA microarrays allows the simultaneous analysis of the expression of tens of thousands of genes in a tissue in a single experiment. In microarray technology, fluorescent probes derived from RNA prepared from tumor tissue are hybridized to gene-specific target sequences on glass or silicon arrays. For each gene, the relative intensity of the fluorescent signal reflects its RNA expression level (13). Powerful statistical methods have been developed to either systematically search for single genes that may be related to clinical parameters or to classify tumors on the basis of similarity of expression profiles (14). We can use these patterns to classify histologically similar tumors into specific subtypes, a process that provides clinically relevant information. In recent studies of breast tumor tissues, DNA-microarray data predicted prognosis better than classic prognostic indicators such as grade, stage, and nodal status in a multivariate analysis. Through statistical reduction of data from 25,000 genes per sample, the set of genes that distinguished the good- and poor-prognosis groups consisted of only 70 genes (15). Subsequent testing of the reduced gene set in a further 295 patients confirmed its utility as a predictor of the appearance of distant metastases during the first 5 years after treatment (16). In addition, microarray analysis has been used to identify breast tumors with distinct patterns of gene expression, indicating “basal type” and “luminal type” (17), and to distinguish cancers associated with *BRCA-1* or *BRCA-2* mutations, estrogen receptor status, and lymph node status (17–21). The chief implication of these studies is that the gene expression profile is a better predictor of clinical outcome than any of the currently used criteria.

Based on these findings, it is reasonable to expect that comprehensive gene expression profiling studies comparing matched tumors with respect to physical and clinical characteristics, but from distinct ethnic backgrounds, will provide panels of genes which may act coordinately to drive a more aggressive tumor phenotype. This is a case where “racial profiling,” that is, gene expression profiling, would be an effective approach. While array-based analyses continue to evolve and improve (22,23), one major requirement for comprehensive gene expression profiling is the need for fresh tumor tissue for the analysis. Institutions with well-documented frozen tumor tissue banks will play a pivotal role here, however, microarray data alone do not provide a definitive answer. Due to the multiple steps involved in the manipulation of RNA for array analyses, data can contain considerable bias

and variation, and so validation of specific candidate genes is required in independent samples. In the case of prognostic marker gene discovery, this will be best performed in archival formalin-fixed tissues with long-term clinical follow-up data, a resource available in most diagnostic laboratories. It is clear that collaborative efforts between multiple institutions will be required for these studies. It is hoped that such studies will enable the “tailoring” of medical treatment to the individual and to underserved populations, but also will identify biologically relevant genes and pathways involved in breast cancer progression. The identification of novel therapeutic targets will likely benefit all breast cancer patients and perhaps even patients with other tumor types.

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