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A Need to Understand the Genomic Changes of Breast Cancer Development

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Editorial

Breast cancer is the most common malignancy in women, with over 246,000 cases annually in the United States. Breast cancer develops through the accumulation of genomic abnormalities in breast epithelial cells, and the endogenous hormone estrogen, which is a carcinogen, is a major etiologic factor for breast cancer. Estrogen may be responsible for a range of genomic damage, including point mutations, DNA strand breaks, chromosomal rearrangements, and DNA methylation. We recently reviewed the genomic changes in normal breast tissue at normal risk and at high risk for breast cancer [1]. This demonstrated that genomic changes associated with breast carcinogenesis, including loss of heterozygosity, DNA methylation, and telomere shortening, are already present in normal tissue considered to be at normal risk for breast cancer, such as reduction mammoplasty tissues from women in their 30s. This is particularly important because 50% - 70% of women who develop breast cancer have no identifiable risk factors, and are strongly in need of a method for assessing risk [2,3]. This study also indicated that breast carcinogenesis is clearly underway in many younger women, and emphasized the need to study the onset and development of these genomic changes in normal breast tissue. Our work has focused on characterizing the molecular changes of early breast carcinogenesis in normal breast tissue, from those changes initiating the carcinogenic process in younger women to those associated with a high risk for sporadic breast cancer. An understanding of these changes and their sequence in the carcinogenic pathway will promote development of a much needed molecular signature for risk assessment, promote identification of new targets for breast cancer prevention and improved selection of women for prevention therapy, and potentially clarify etiologic factors and mechanisms of breast cancer initiation and development.

To promote a comprehensive analysis of normal breast tissue at risk for breast cancer we have developed a breast epithelial sampling technique which significantly expands the quantity and quality of epithelial cells acquired and significantly expands the range of molecular studies which can be performed on breast ductal material [4]. In this technique breast epithelium is sampled by breast ductal lavage through a 22G angiocatheter, and multiple individual 1 ml aliquots are obtained with high epithelial cell purity (90% - 100%) and a high cellular yield (median 6 aliquots of >5000 cells per subject). Samples can be collected from women of all ages (age 22-71) and from women at normal risk or at high risk for breast cancer. DNA and RNA are extracted from single aliquots and are suitable for multiple downstream molecular profiling analysis including DNA and RNA amplification, comparative genomic hybridization, gene expression profiling, qRT-PCR, and exosomal and miRNA studies. Cytologic analysis is available for each aliquot. This sampling technique provides an excellent opportunity to study the early changes of breast cancer development and better define the risk for breast cancer in women of all ages.

A racial disparity in the care and management of women with breast cancer is a major cause of poor outcome from breast cancer. The cause of these disparities are multiple and include socioeconomic factors, access to health care, availability of resources, and differences in primary tumor biology. The poor outcome is likely a combination of these factors; however the way in which they interact is poorly understood. We have recently proposed a model describing the important relationship of biological and non-biological factors in health care disparities [5]. This emphasizes the importance of understanding the biological characteristics of tumors in these women to identify causal and potentially unique factors, which may in turn suggest ethnic-related targeted therapy in certain ethnic groups. In addition, the onset of breast cancer occurs at an earlier age in African American (AA) women, and AA women under the age of 40 are considered to be at high risk for breast cancer [6]. The ability to sample and analyze ductal epithelium from younger women (as described above in the newly developed sampling method) in different ethnic groups may provide an important opportunity to understand the molecular profile and the related influential factors

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for the development of breast cancer in these women. Current plans are in progress to study ductal epithelium in different ethnic groups and according to breast cancer risk by molecular profiling including DNA and RNA sequencing to provide important details about the carcinogenic pathway in these women. We are hopeful this will lead to improved methods of risk assessment, prevention and management in these women.

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