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OVERVIEW

Genetic Surrogate Endpoint Biomarkers in Early Breast Neoplasia

"Biomarkers in Early Breast Neoplasia," presented by D. Craig Allred. The biological mechanisms of breast cancer evolution are poorly understood. Furthermore, this problem has been difficult to study because potential precursor lesions of fully developed invasive breast cancer have not been unequivocally identified, and candidate precursors have been difficult to evaluate due to their microscopic dimensions. The involvement of known cancer-associated genes in these lesions can still be comprehensively studied by established methods, such as immunohistochemistry and *in situ* hybridization. Important novel genes may be identified using newer technologies, such as loss-of-heterozygosity analysis and differential display. These complimentary approaches have the potential to identify biomarkers that can be used as surrogate endpoints in future chemoprevention trials.

"c-*erb*B-2 Amplification in Mammary Carcinoma," presented by Diana Barnes. The c-*erb*B-2 oncogene has been extensively studied in breast cancer, including both abnormal gene amplification and protein overexpression. Many studies have shown that these abnormalities are more common in non-invasive than invasive breast cancer, that they are associated with poor prognosis only in certain subsets of invasive breast cancer, and that they may be associated with an inability to respond to various types of adjuvant chemotherapy. Further study is necessary to more fully understand the biological role of c-*erb*B-2 in breast cancer.

"Cytogenetic Profiling Using Fluorescence *In Situ* Hybridization and Comparative Genomic Hybridization," presented by Curtis Thompson. Fluorescence *in situ* hybridization (FISH) and comparative genomic hybridization (CGH) are novel techniques allowing cytogenetic analysis of tissues without cell culture. CGH detects and maps allelic imbalances by simultaneous *in situ* hybridization of differentially labeled tumor and normal DNA in metaphase cells. FISH displays gene copy number irregardless of the cell cycle. Both techniques can provide cytogenetic information within a retained histological context using archival tissue, making them particularly appropriate to study genetic differences in lesions involved in breast cancer evolution.

"Molecular Aspects of Breast Cancer Progression," presented by Helene Smith. Breast cancers are biologically and clinically heterogeneous. Evidence suggests that the fully developed, malignant, invasive phenotype may result from many overlapping permutations of genetic abnormalities. In this sense, abnormalities imparting the abilities to escape growth control, invade, and metastasize may be acquired randomly during tumor progression, and with differing levels of aggressiveness. The implication of such a "stochastic" model of breast cancer evolution is that it may involve a very large number of biological pathways, all of which are now poorly understood. Such complexity may make it very difficult to identify stable (or at least predictable) biomarkers for use as surrogate endpoints in chemoprevention trials.

"Biomarker and Cytologic Abnormalities in Women at High and Low Risk for Breast Cancer," presented by Carol Fabian. Pilot studies have been initiated to evaluate whether or not morphological and biological abnormalities can be identified in fine-needle aspiration (FNA) biopsies of breasts from women at risk for developing breast cancer. Preliminary results suggest that cytological hyperplasia, cytological dysplasia, aneuploidy, overexpression of epidermal growth factor receptor, and overexpression of p53 are associated with high risk. Such studies hold the promise that biological risk assessment for the development of breast cancer may be possible by relatively non-invasive procedures.

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