Evaluation of Cytophotometric DNA Content Abnormalities in Premalignant and Preinvasive Breast Lesions

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Abstract Progression of breast neoplasia is characterized by a variety of causal and nonspecific molecular, karyotypic, and cellular level genetic alterations. These include allelic losses, chromosomal rearrangements, and aneusomies, as well as widely divergent clonal DNA content aberrations. Establishment of the sequence and the pathologic significance of individual changes has been challenging owing to disease heterogeneity, protracted natural history, and difficulties in sampling and localizing precursor lesions. These limitations have driven attempts at cytophotometric evaluation of premalignant/preinvasive proliferations using histologic (*i.e., in situ*) microdissection of intact paraffin-embedded tissue sections. Using image cytophotometric measurements in preserved sections, clonal DNA content abnormalities are identified in up to three-fourths of preinvasive breast carcinomas. The incidence of DNA aneuploidy is grade-dependent and similar in degree to invasive lesions. Comparison of ploidy determinations between preinvasive and corresponding invading populations, however, suggests host tissue permeation is accompanied by measurable DNA content shifts in many cases. Image cytophotometric DNA content abnormalities are also detectable in florid/atypical proliferative lesions, albeit less frequently (~25% of cases) and to a lesser extent (*i.e.*, near diploid) than cytologically malignant lesions. Although the sensitivity of cytophotometric ploidy assessments in tissue sections is limited by nuclear sectioning, the presence of genomic instability in premalignant lesions is supported by evidence of individual chromosome aneuploidy, demonstrated by interphase cytogenetics with fluorescent centromere-specific probes. These data suggest cytophotometrically detectable DNA content anomalies may precede unequivocal morphologic transformation in breast neoplasia. Further, clonal DNA content heterogeneity in breast carcinoma may accompany biologically critical steps in neoplastic progression of breast tumors.

Subjects and Recruitment Strategies for a Short-Term Phase II Chemoprevention Trial of Breast Cancer Using Surrogate Endpoint Biomarkers

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Abstract No validated serum markers of breast cancer risk have been identified. Therefore, the identification of women for a clinical trial of surrogate endpoint biomarkers (SEBs) is complicated by the need for repeated sampling of breast parenchyma to determine the biologic effect of the chemopreventive agent. Criteria for the ideal study population include: (1) a rapidly identifiable high-risk profile;