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OVERVIEW

# Markers of Premalignant and Early Malignant Lesions

Prostate cancer is the most common clinically manifest cancer in U.S. males (22% of new cancer cases in 1991); however, this is far exceeded by the presence of histological tumors. It has been estimated that almost one-third of men over 50 years of age have microscopic or early malignant lesions; an even larger number may also harbor premalignant lesions. The problem is to identify the fraction of these early lesions with the potential for development of more advanced tumors.

Biological alterations in tissue have been associated with the process of carcinogenesis, *i.e.*, markers. When the alterations occur between initiation and malignant tumor development, they are called "intermediate biomarkers." In the prostate, however, an additional step may be required for microscopic tumors to progress; biological alterations associated with this process will also be included under this term.

Markers may be grouped as biochemical, histological, genetic, proliferative, or differentiation-related. Biochemical markers include increased levels of enzymes and other proteins, such as prostate specific antigen (PSA), which have been associated with early cancer. PSA is a protease which is produced exclusively by prostatic tissue, benign or malignant. Elevated serum levels of PSA have been detected in some men with noncancerous lesions [benign prostatic hyperplasia (BPH)], premalignant lesions (PIN) and organ-confined prostate cancer. Although serum PSA can identify some cancers which are not detected by other methods, the specificity is not high. Dr. Oesterling discusses the use of PSA density and the rate of change of PSA as improvements in this marker.

The accumulation of genetic changes within a single cell has been theorized to be responsible, at least in part, for the development of cancer. A genetic marker, DNA ploidy, is assessed in both premalignant and early malignant lesions in this session. Dr. Montironi discusses alterations in ploidy with increasing grades of PIN. Dr. Lieber discusses the association of increasing aneuploidy with clinical stage of prostate cancer. Early malignant lesions which are diploid may be at lower risk of progression.

Histological alterations may also serve as markers of prostate premalignancy and early malignancy. Dr. Montironi has improved some of the traditional histological markers, as well as discovered more subtle markers, by the use of quantitative, rather than subjective, analysis of PIN lesions. For example, quantitation of some nuclear and nucleolar alterations differentiates between BPH, two grades of PIN and adenocarcinoma.

Angiogenesis, the induction of vascularization, is an area of new research which may be grouped with histological markers. Dr. Brawer has investigated the distribution and density of microvessels using a computerized image analysis system. These measurements are discussed as morphometric markers of growth potential and tumor progression.

Since growth factors have been associated with neovascularity, a related proliferation-type marker may be expression of transforming growth factor β (TGF-β1). Dr. Thompson discusses the correlation between malignant potential and elevation of this marker in the mouse prostate reconstitution model system. The distribution of TGF-β1 in human prostatic tissue appears to differ in benign and cancerous lesions.

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