INTRODUCTION

Prostate cancer (CaP) is the most common solid tumor in American males (1). The wide spectrum of biological behavior (2) exhibited by prostatic neoplasms poses the difficulty of predicting the clinical course in the individual patient (3,4). Because of increasing public awareness and screening efforts, the enhanced incidence has translated into a large increase in the use of radical prostatectomy as well as four other treatment modalities for localized disease (5). With this incremental rise in surgical intervention has come the frustrating realization of the inability to predict organ-confined disease and clinical outcome for a given patient (5,6). Traditional markers, such as grade, clinical stage, and pretreatment prostate-specific antigen (PSA), are of limited prognostic value for individual men. There is clearly a need to recognize and develop molecular and genetic biomarkers to improve prognostication and the management of the patient with clinically localized CaP. As with other common human neoplasia (7), the search for molecular genetic markers to better define the genesis and progression of CaP, is the key focus for cancer research investigations worldwide.

The new wave of research addressing molecular genetic alterations in CaP is primarily the result of increased awareness for this disease and the development of newer molecular technologies. Until today, the search for a precursor to prostatic adenocarcinoma has focused largely on the spectrum of microscopic changes referred to as prostatic intraepithelial neoplasia (PIN). Bostwick defines this entity as a histopathologic continuum.

*The opinions and assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the US Army or the Department of Defense.

From: Current Clinical Urology: Management of Prostate Cancer
Edited by: E. A. Klein © Humana Press Inc., Totowa, NJ

47
that culminates in high-grade PIN and early invasive cancer (8). The morphologic and molecular changes include the progressive disruption of the basal cell layer, changes in the expression of differentiation markers of the prostatic secretory epithelial cells, nuclear and nucleolar abnormalities, increased cell proliferation, DNA content alterations, and chromosomal and allelic losses (8–10). This progressive gain or loss of a variety of biomarkers helps trace the etiology of prostate carcinogenesis. Foremost among these would be the molecular and genetic markers associated with histological phenotypes in transition between normal prostatic epithelium and cancer. The innovative armamentarium of genetic analysis tools that are available for the genome-wide screening of genetic abnormalities together with the study of genetic polymorphisms, genetic susceptibility, and molecular epidemiology are beginning to uncover gene alterations that could define the events leading to the transformation of normal prostatic epithelial cells to preneoplastic cells and malignant prostate cells. Most studies so far seem to concur that PIN and prostatic adenocarcinoma cells have a lot in common with each other. The invasive carcinoma more often reflects a magnification of some of the events already manifest in PIN.

Early detection of CaP is possible today because of the widely propagated and recommended blood PSA test that provides a warning signal for CaP if high levels of serum PSA are detected. More reliable tumor cell-specific biomarkers are needed that can distinguish between normal and hyperplastic epithelium, and the preneoplastic and neoplastic stages of CaP. When used alone, PSA is not sufficiently sensitive or specific to be considered an ideal tool for the early detection or staging of prostate cancer (11). Combining PSA levels with clinical staging and Gleason scores is, however, more predictive of the pathological stage of localized CaP (12). New molecular techniques, such as reverse transcriptase polymerase chain reaction (RT-PCR), which measures PSA of circulating prostate cells in blood and bone marrow of CaP patients, are being used for improved molecular staging of CaP (13,14).

The science of molecular epidemiology is simultaneously gaining momentum to help in our understanding of genetic predispositions and susceptibilities to CaP. It has been reported that the incidence of prostate cancer in African-American men is higher than in other races, and most studies also report a higher recurrence rate and poorer survival (15). Even with localized cancers, these men have higher PSA levels, since their tumors are larger. There is also a subset among this population that tend to have their cancers diagnosed at a younger age, and these young blacks harbor more high-grade PIN than their Caucasian counterparts. Whether these observed differences are attributable to environmental or biological factors, or a combination of the two is an open question. A comprehensive study of CaP-prone men of predominantly Caucasian origin has actually led to the identification of a familial prostate cancer susceptibility locus, HPC1, on chromosome 1q24–25 (16, reviewed by Isaacs et al. in this volume). Other molecular epidemiologic studies have shown that polymorphisms of the CAG repeats in the androgen receptor (AR) gene (17) and increased plasma insulin-like growth factor 1 (IGF-1) levels are indicative of a higher risk for CaP (18). Mutational analyses for the detection of allelic imbalances (AI) or microsatellite imbalances (MSI) are critical to our understanding of the role of genes/loci involved in CaP. Comparative Genomic Hybridization (CGH) and classical cytogenetics have helped uncover locations for putative tumor suppressor genes (TSGs) and/or proto-oncogenes and critical losses and gains. Methodologies like microcell-mediated chromosome transfer (MMCT), fluorescent in situ hybrid-