Molecular Updates in Prostate Cancer

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KEYWORDS

• Prostate cancer • *PCA3* • Carcinogenesis • Genomic classification

ABSTRACT

A wide array of molecular markers and genomic signatures, reviewed in this article, may soon be used as adjuncts to currently established screening strategies, prognostic parameters, and early detection markers. Markers of genetic susceptibility to PCA, recurrent epigenetic and genetic alterations, including *ETS* gene fusions, *PTEN* alterations, and urine-based early detection marker *PCA3*, are discussed. Impact of recent genome-wide assessment on our understanding of key pathways of PCA development and progression and their potential clinical implications are highlighted.

OVERVIEW

Deciphering the molecular pathways of prostate cancer (PCA) development has facilitated the pursuit of molecular biomarkers that would soon help refine early detection strategy, accurately predict outcome, and serve as potential targets of therapy.[1–3] Such efforts have gained an unprecedented momentum from the staggering amount of information that has been brought to light evaluating datasets of genomic, transcriptomic, and proteomic analyses using sophisticated bioinformatics tools.[4–6] Furthermore, genomic studies have been instrumental in identifying germline (host) markers of genetic susceptibility associated with risk of developing early and aggressive disease. The latter will in turn help refine the current "one-size-fits-all" screening strategy.

The recent debate questioning whether current serum prostate-specific antigen (PSA)-based screening strategies are potentially leading to "overtreatment" of at least a subset of patients with PCA[7–10] has further emphasized the need to identify molecular markers of biologically "significant" PCA that would merit "definitive" therapy. Currently used clinicopathologic algorithms and National Comprehensive Cancer Network guidelines that define "insignificant" very low risk (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp) PCA are in dire need of being buttressed by molecular signature(s) that will enhance confidence in accurately assigning the right patients to such approach while vigilantly monitoring using molecular imaging tools and signatures of molecular biologic progression in tissue samples.

CARCINOGENESIS AND GENETIC SUSCEPTIBILITY

The variation in PCA incidence among geographic populations has long pointed to differences in ethnic genetic determinants as well as environmental causes as significant etiologic factors. Although higher incidence of the disease in African American individuals compared with Asian American individuals is likely genetically based,[11] the alteration in risk on migration in a given ethnic group strongly suggests environmental and lifestyle factors as additional contributing determinants of risk.[1,2,12–14]

ENVIRONMENTAL FACTORS

Lifestyle and dietary habits have long been linked to PCA risk.[15–17] Accumulating evidence points to glandular epithelial cell injury by dietary carcinogens, estrogens, or oxidants as a trigger for a chronic inflammatory milieu that set the stage for cancer development.[12,13,17,18] Pinpointing the exact culprit environmental carcinogen(s) has proven to be a difficult endeavor; however, epidemiologic dietary association data and animal model studies[19,20] have strongly supported dietary intake of red meats and animal fats as risk factors. Cooking with high temperature and char-broiling

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of red meat result in the formation of heterocyclic aromatic amine (eg, 2-amino-1-methyl-6-phenylimidazopyrine) and polycyclic aromatic hydrocarbon carcinogens, some of which have been linked to disease pathogenesis in animal models.[21–23] Other cited environmental risk factors include exposures to sex steroid hormones and infectious agents. Animal data link estrogen to prostate epithelial cell damage and inflammation potentially though induction of autoimmunity.[24,25] Likewise, sexually transmitted infections (eg, trichomonas, chlamydia, and gonorrhea) have been cited as potential initiators of predisposing chronic inflammation of the prostate (**Fig. 1**).[26–29] Epithelial damage and ensuing inflammation is the common pathogenic link between environmental "carcinogens" and PCA development. Faced with persistent oxidative stress, the epithelial cells mount a genome damage defense and cell survival response by initially inducing their expression of α and π class glutathione S-transferases, cyclooxygenase-2, and other mediators.[15,30–32] Ultimately, this is followed by epigenetic silencing of hundreds of genes, including the crucial caretaker gene *GSTP1* that persists throughout subsequent cancer progression phases. Proliferative inflammatory atrophy (PIA) has been forwarded by some as the earliest histologic manifestation of the injury response exhibiting increased epithelial proliferation and inflammation. That view is supported by the fact that PIA shares many of the somatic genetic and epigenetic alterations that are exhibited by prostatic intraepithelial neoplasm (PIN) and PCA.[33–35]

GENETIC SUSCEPTIBILITY

PCA has increasingly been recognized as one of the most heritable cancer types driven by numerous common and few rare inherited germline genetic variants of risk (**Figs. 2** and **3**). Family pedigree and twin studies have consistently supported genetic predisposition as a risk factor for PCA.[11,36,37] Men with a first-degree relative diagnosed with PCA are at twice the risk (more than fourfold if diagnosed before age 60).[38,39]

Early linkage analysis studies suggested various inheritance models (eg, dominant, X-linked) and numerous chromosomal loci of association that failed to be consistently validated.[38,40–47] Evidence supporting the initial suggestion that inflammatory and infection response gene loci (*ELAC2*, *RANSEL*, and *MSR1*) are associated with risk have not been consistently replicated.[48–51] In the largest linkage study performed by the international consortium of PCA genetics, only one locus (22q) stood out.[52] Subsequent studies also pointed to 8q24[53–55] as a region harboring genetic risk variants. The detection of far more common germline genetic variants with only low to moderate penetrance had to await the advent of Genome-Wide Association Studies (GWAS). GWAS that are able to assess millions of single nucleotide polymorphisms (SNPs) in a given individual for disease risk association were first used to assess PCA risk variants in 2006.[56] To date, at least 92 SNPs associated with PCA risk (**Table 1**) have been established by such studies (A catalog of published genome-wide

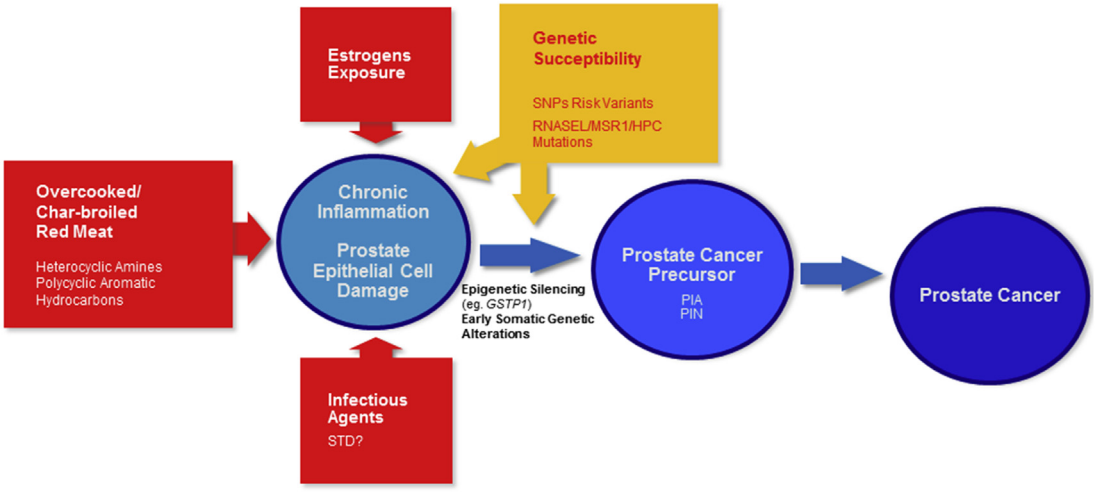

Fig. 1. Etiologic factors implicated in PCA development: chronic inflammation triggered by environmental and lifestyle exposures leads to persistent prostate epithelial cell damage. Inherited genetic predisposition also plays a determining factor in promoting oncogenesis.