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Prostate Cancer: An Update on Molecular Pathology with Clinical Implications

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Abstract

Recent advances in sequencing technologies, proteomics, and metabolomics have led to the identification of numerous molecular alterations across solid tumors including prostate cancer. The delineation of various genetic and epigenetic events involved in tumor progression have facilitated the development of novel diagnostic tests and the successful therapeutic targeting of key oncogenic events in prostate cancer. The most common genomic aberrations in prostate cancer include gene fusions, amplification, deletion, and mutations. In addition, up and down regulation of gene expression in critical cellular pathways is also at play. A series of long noncoding RNA expression changes have been also unveiled from transcriptome sequencing data. They play a regulatory role in prostate cancer and are promising diagnostic and potentially prognostic markers. In this review, we summarize recent advances in molecular pathology of prostate cancer and their emerging clinical utility.

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1. Introduction

The unprecedented advances in sequencing technologies, proteomics, and metabolomics have helped unravel numerous driver molecular alterations and key oncogenic pathways across solid tumors including prostate cancer (PCA). These technologies helped identify dysregulation in multiple genetic and epigenetic events during tumor progression. The monumental amount of information garnered by evaluating datasets of genomic, transcriptomic, and proteomic analyses using sophisticated bioinformatics tools [1–3] has allowed for the development of novel diagnostic tests and molecularly targeted therapeutic strategies [4–6].

Trials such as "PLCO" evaluating the outcome benefit of screening strategies in prostate, lung, colorectal, and ovarian cancers have fueled a raging debate on whether current serum prostate-specific antigen (PSA)-based screening strategies are justified or potentially leading to overtreatment, in at least a subset of PCA patients [7–10]. Genomic studies may soon help refine the current "one size fits all" screening strategy for PCA through the identification of germline (host) biomarkers of genetic susceptibility that stratify risk of developing early and aggressive disease. Identification of molecular biomarkers

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of biologically *significant* PCA would help further refine the current clinical and pathologic input based management algorithms. Such biomarkers will enhance confidence in accurately assigning patients with *insignificant* PCA categorized as very low risk in National Comprehensive Cancer Network guidelines (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp) to active surveillance approach that is coupled with active monitoring by molecular imaging and ongoing look out for genomic signatures of biologic progression using tissue samples.

2. Pathogenesis of prostate cancer: genetic risk and environmental factors

The interplay between genetic determinants of risk and environmental factors is responsible for the long-observed variation in PCA incidence among geographic populations. The higher incidence of PCA in African-Americans compared with Asian-Americans is thought to be only partially driven by genetic predisposition [11]—the fact that such risk is modulated upon migration in a given ethnic group points to environmental and lifestyle factors as additional contributing determinants of risk [4,5,12,13].

2.1. Inherited genetic risk factors

Twins and family pedigree studies have long supported genetic predisposition as a risk factor for PCA [11,14,15]. Men with a first degree relative affected by the disease are at twice the risk for developing PCA. The risk is even higher (> 4-fold) if a relative was diagnosed with PCA at a younger age (< 60 yr) [16,17].

PCA is now recognized as one of the most heritable cancer types driven by numerous inherited germline genetic variants of risk ranging from those that are more common with a weak risk effect to the rare variants that are associated with a stronger risk for PCA. While earlier linkage analysis studies pointed to numerous chromosomal loci of association, such claims have failed to be consistently validated [16,18–25]. The same is true for the initial suggestion that inflammatory and infection response gene loci (*ELAC2*, *RANSEL*, and *MSR1*) were associated with higher risk of PCA [26,27]. In the largest linkage study performed by the international consortium of PCA genetics only one locus (22q) stood out [28]. Subsequent studies also pointed to 8q24 [29–31] as a region harboring genetic risk variants.

In the last decade, the application of Genome Wide Association Studies that enables assessment of millions of single nucleotide polymorphisms (SNPs) in a given individual for disease risk association to PCA [32] has allowed for the detection of far more common germline genetic variants with only low-to-moderate penetrance. To date, over 280 SNPs associations with PCA risk have been established by 30 such studies (A Catalog of Published Genome-Wide Association Studies (https://www.ebi.ac.uk/gwas/search?query=Prostate%20cancer#association). Collectively, these SNPs may account for up to one-third of PCA familial risk. Regions such 8q24 region [33,34] containing SNPs exerting a modifier effect on neighboring *MYC* oncogene, a recognized player in PCA pathogenesis [31] and SNP variants located on chromosomes 19 q13 that harbor kallikrines *KLK2* and *KLK3* (*PSA*) genes are of particular interest [35,36]. Although each susceptibility SNP allele individually carries only a small risk, multiplicatively, a subject SNP profile can be deduced from risk algorithms models that will identify individuals in the upper 1% risk tier with approximately 5-fold the risk of the general population [37,38]. It is such an approach that have the potential to refine the best groups of men to be targeted for screening and prevention strategies and help address the current concerns of overdiagnosis and overtreatment of PCA [8,9].

The detection of the more rare but strongly penetrant germline variants (> 5% frequencies) requires exhaustive case/control direct sequencing that was only achievable with more recently propagated massively parallel next generation sequencing technologies. Given their rarity, such variants account for only a minute fraction of PCA incidence but importantly impart a high risk in carrier individuals for early onset (5—7-fold) and at times more aggressive PCA. Most established among these are germline mutations in the *BRCA 2* tumor suppressor gene [39] and *HOXB13 (G84E)* [40,41]. A 5% germline carrier frequency for *HOXB13 (G84E)* mutation was shown in families of PCA of mostly European descent [41]. Men with the *BRCA2* germline mutation were found to be at 5-fold the risk for PCA (7-fold the risk of early disease) in the Breast Cancer Linkage Consortium study [42]. The evidence for *BRCA1* [43] and other DNA repair genes such as *PALB2*, *CHECK2*, *BRIP1*, and *NBS1* remains less robust [44–47].

Finally, molecular risk studies support increased susceptibility for PCA in Lynch syndrome. A recent meta-analysis of 12 risk studies showed a 2.28-fold (95% confidence interval [CI]: 1.37–3.19) increased risk of PCA for all men from mismatch repair genes mutation-carrying families. In another study, the relative risk was greatest for MSH2 carriers (5.8, 95% CI: 2.6–20.9) where PCA was the first or only diagnosed tumor in 37% of carriers [48–50].

Several multinational consortia (PCA Association Group to Investigate Cancer Associated Alterations in the Genome, http://practical.ccge.medschl.cam.ac.uk/; International Consortium for PCA Genetics, http://www.icpcg.org/?q=content/about-icpcg; Elucidating Loci Involved in PCA Susceptibility, http://epi.grants.cancer.gov/gameon/personnel.html#ellipse) are investigating the important clinical impact of genetic susceptibility to PCA in order to address the potential screening, risk management guidelines and functional and treatment implications of the growing list of identified germline genetic variants.

2.2. Environmental risk factors

A body of evidence points to glandular epithelial cell injury resulting from chronic exposure to dietary carcinogens, estrogens, or oxidants as a trigger for a chronic inflammatory milieu that set the stage for cancer development [12,51–55]. Epidemiologic and animal model studies [56,57] strongly support the dietary intake of charred red

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