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Review – Prostate Cancer

Genomic Markers in Prostate Cancer Decision Making

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Abstract

Context: Although the widespread use of prostate-specific antigen (PSA) has led to an early detection of prostate cancer (PCa) and a reduction of metastatic disease at diagnosis, PSA remains one of the most controversial biomarkers due to its limited specificity. As part of emerging efforts to improve both detection and management decision making, a number of new genomic tools have recently been developed.
Objective: This review summarizes the ability of genomic biomarkers to recognize men at high risk of developing PCa, discriminate clinically insignificant and aggressive tumors, and facilitate the selection of therapies in patients with advanced disease.
Evidence acquisition: A PubMed-based literature search was conducted up to May 2017. We selected the most recent and relevant original articles and clinical trials that have provided indispensable information to guide treatment decisions.
Evidence synthesis: Genome-wide association studies have identified several genetic polymorphisms and inherited variants associated with PCa susceptibility. Moreover, the urine-based assays SelectMDx, Mi-Prostate Score, and ExoDx have provided new insights into the identification of patients who may benefit from prostate biopsy. In men with previous negative pathological findings, Prostate Cancer Antigen 3 and ConfirmMDx predicted the outcome of subsequent biopsy. Commercially available tools (Decipher, Oncotype DX, and Prolaris) improved PCa risk stratification, identifying men at the highest risk of adverse outcome. Furthermore, other biomarkers could assist in treatment selection in castration-resistant PCa. AR-V7 expression predicts resistance to abiraterone/enzalutamide, while poly(ADP-ribose) polymerase-1 inhibitor and platinum-based chemotherapy could be indicated in metastatic patients who are carriers of mutations in DNA mismatch repair genes.
Conclusions: Introduction of genomic biomarkers has dramatically improved the detection, prognosis, and risk evaluation of PCa. Despite the progress made in discovering suitable biomarker candidates, few have been used in a clinical setting. Large-scale and multi-institutional studies are required to validate the efficacy and cost utility of these new technologies.
Patient summary: Prostate cancer is a heterogeneous disease with a wide variability. Genomic biomarkers in combination with clinical and pathological variables are useful tools to reduce the number of unnecessary biopsies, stratify low-risk from high-risk tumors, and guide personalized treatment decisions.

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1. Introduction

Prostate cancer (PCa) is the most frequent urological malignancy and the fifth leading cause of cancer death in men worldwide [1].

Prostate-specific antigen (PSA) is the most extensive screening biomarker adopted for PCa diagnosis and tumor monitoring. However, use of PSA testing in PCa screening is still controversial due to the absence of definitive data from randomized trials, and the lack of specificity between benign and malignant disease. Risk stratification based on traditional clinical parameters can stratify patients' risk of progression with relatively good reliability, but substantial heterogeneity persists within standard risk groups [2].

PCa genomic biomarkers include tools and technologies able to predict the likelihood of an initial positive biopsy; reduce the number of unnecessary repeat biopsies; substratify low-, intermediate-, and high-risk tumors; classify the extent of the disease; and predict and monitor clinical response to an intervention.

The widespread adoption of new biomarkers offering improvements in the discrimination of various disease-related outcomes need to match with a rigorous evaluation of their real benefit. To be clinically helpful, putative pre- and postdiagnosis biomarkers need to provide additive and independent information to clinical parameters. The use of prediction models obtained by adding genomic scores may be justified if, for any given risk defined by one of a number of validated multivariable instruments, they are able to better stratify PCa patient risk and prognosis than clinical variables alone.

The aim of this review is to critically examine the clinical and cost-related utility of novel PCa genomic biomarkers.

2. Evidence acquisition

A PubMed-based literature search was conducted up to May 2017. We selected the most recent and relevant original articles and clinical trials that have provided the most relevant information to guide treatment decisions.

Keywords included "biomarker," "genomic," "susceptibility," "stratification," "predictors of response," "treatment response," and "cost effectiveness." References cited in selected articles and review articles acquired in our search were also used to identify other papers not included in the initial search. The articles that provided the highest level of evidence were then evaluated and selected as the result of an interactive peer-reviewing process by the panel of coauthors.

According to their potential contribution to PCa decision making, we divided our findings into four categories: susceptibility biomarkers, biomarkers of disease risk, risk stratification biomarkers, and biomarkers for prediction of treatment response (Fig. 1).

3. Evidence synthesis

3.1. Susceptibility biomarkers

Family history, age, and race, with the additive role of the environment and lifestyle, have been considered the most relevant risk factors for PCa [3]. Although extensive resources have been invested in identifying the basis of genetic predisposition to PCa, the development of clinically available genomic biomarkers for predicting the susceptibility to the disease has only recently begun to gain traction.

3.1.1. Rare germline mutations

Rare and highly penetrant genetic variants have been studied to identify specific loci that can confer high risk for developing the disease, but difficulty persists in attributing significant value on susceptibility to common diseases to rare variants. Ewing et al [4] reported the association of the "G84E" germline mutation in the homeobox gene HOXB13, a regulator of growth in healthy and cancerous prostate biology, with a higher risk of hereditary PCa. G84E was observed in 0.6% of the control population and in 3.1% of patients with familiar and early-onset PCa (odds ratio 5.1).

Rare germline aberrations in DNA damage repair genes have been associated with higher rates of PCa diagnoses. Although mutations in *BRCA1* and *BRCA2* genes confer a 3.8- and 8.6-fold increased risk of developing PCa, respectively, there is an open debate on how to manage these men and about the impact of DNA repair defects on PCa outcome [3]. Castro et al [5] in a cohort of 2019 PCa patients (18-BRCA1 carriers, 61-BRCA2 carriers, and 1940 noncarriers) confirmed that BRCA1/2 mutations are associated with more aggressive disease ($p = 0.00003$), higher probability of nodal involvement ($p = 0.00005$), distant metastasis at diagnosis ($p = 0.005$), and shorter life expectancy (12.9 vs 8.1 yr; $p = 1 \times 10^{-7}$).

Although the IMPACT study [6] showed higher accuracy of biopsy for detecting intermediate/high-grade PCa in BRCA2 relative to controls (2.38% vs 0.71%; $p = 0.04$), further strong data supporting a change in PSA screening and biopsy recommendations are needed [7].

3.1.2. Single nucleotide polymorphisms

Numerous large genome-wide association studies, using high-throughput technologies and involving thousands of patients, have been conducted to simultaneously scan single nucleotide polymorphisms (SNPs) of various genes or loci associated with PCa. Although these common variants (>5% population frequency) confer relatively small increments in risk for developing the disease (1.1–1.5-fold), their risk levels increase multiplicatively [8]. More than 100 statistically significant PCa-associated loci, which explain 33% of PCa susceptibility, have been identified, but unfortunately, the power of the associations is often too weak to be introduced in a clinical setting [9].

Zheng et al [10] evaluated 16 SNPs from five chromosomal regions in a Swedish population. In men who had five or more of the germline genetic markers correlated to PCa, the odds ratio was 9.46 in relation to men without any of the factors.

Genotyping 25 PCa susceptibility SNPs in more than 40 000 cases and controls, Al Olama et al [11] estimated that PCa risk for men in the first percentile of the polygenic risk score distribution increases 30.6-fold compared with men

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