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Review

The Role of Genetic Polymorphisms in the Diagnosis and Management of Prostate Cancer: An Update

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Abstract. *Prostate cancer (PCa) is the most common non-cutaneous tumor among men worldwide and, if diagnosed late, it exhibits a high mortality representing the sixth most lethal tumor in men. The main method to detect PCa is the prostate-specific antigen (PSA) level followed by direct rectal examination (DRE). Unfortunately, the PSA test has limited accuracy, as it does not provide information on disease outcome leading to the overtreatment of benign tumors. Thus, PSA analysis does not allow for stratifying PCa patients in high or low risk groups for disease recurrence or distant metastasis. Currently, the detection of several genetic markers might improve the risk stratification, addressing patients with PCa to the best therapeutic option. Here we describe the current clinical practice for PCa patients, the possible genetic polymorphisms associated with diagnosis, prognosis and therapy response as well as variants linked to familial PCa. The use of genetic markers could be routinely introduced in clinical practice leading to improvements in the management of PCa.*

Prostate cancer (PCa) is the second most common malignant tumor and the fifth regarding cancer-related mortality in the world, counting 1,414,259 new cases (7.3% of all cancer associated diseases) with 375,304 deaths (3.8% of all deaths caused by cancer in men) in 2020 (1). The most frequent genetic mutation related with prostate cancer is the fusion of the oncogenic E26 transformation-specific (ETS) family of transcription factors (ERG) with the androgen-regulated TMPRSS2 gene that is detected in about the 50% of all prostate tumors (2). Other lesions commonly observed in PCa disease include mutations in SPOP, TP53, FOXA1 and IDH1 genes as well as PTEN loss of function, PI3K-related pathway activation and MYC oncogene amplification (2). These mutations may affect cancer progression and therapy response. Early detection of PCa is crucial because when this cancer is diagnosed at a late stage, in most cases, it has already developed metastases that dramatically reduce the overall survival of PCa patients (3). Early detection of PCa was mainly carried out by the analysis of prostate-specific antigen (PSA) that is the most used biomarker for PCa screening. However, PSA blood levels are affected by individual variations such age, prostate volume and androgen levels (4). Therefore, this biomarker does not lead to the appropriate diagnosis or prognosis for this disease. The absence of specific prostate cancer prognostic biomarkers in current diagnostics prevents us from distinguishing benign and aggressive tumors, as well as to formulate specific therapeutic treatments (5). Therefore, the identification of novel genetic markers which could be used in clinical practice as indicators to predict the outcome of the disease would be extremely important to enhance the overall survival and the quality of life of PCa patients.

Current Clinical Practice

PCa is usually an asymptomatic disease at the initial stage and may require minimal or no treatment at all, except active surveillance. However, the frequent criticisms are uncomfortable urinary symptoms, such as urine flow blockage out of the bladder and nocturia. These symptoms are also found in benign prostatic hyperplasia (BPH) (6). Advanced stages of the tumor may occur with bone metastatic disease, urine retention and hematuria. Therefore, new markers for PCa detection and risk stratification are needed (1, 7). There is no single specific test for PCa;

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however, it is usually diagnosed by a digital rectal examination (DRE) and the prostate specific antigen (PSA) test that remain the keystone for PCa diagnosis (8).

PSA is a glycoprotein produced by the glandular cells of the prostate. Patients with PSA levels between 4 and 10 ng/ml have approximately 1 in 4 probabilities of having PCa. If the PSA levels are >10 ng/ml, the possibility of having PCa is over 50% (9). PSA is a prostate gland specific antigen and not a PCa specific antigen; consequently, elevated PSA levels can indicate benign pathologies such as prostatic hypertrophy or prostatitis, and are not always associated with the presence of malignancy (9). A prostate biopsy is frequently performed to confirm the diagnosis of the tumor. The biopsy can be performed through the skin between the anus and scrotum (known as a transperineal biopsy) or through the rectal wall (known as a transrectal biopsy) (10). During a prostate biopsy, the gland is usually visualized with instruments including magnetic resonance imaging (MRI) and ultrasound (11). An MRI scanner produces detailed images of organs tissues utilizing a magnetic field and radio waves (12). MRI results can be utilized for precisely targeting irregular areas of the prostate during the bioptic procedures (11, 12). A multiparametric MRI (mpMRI) can also be a triage test performed without a biopsy if the results are negative for irregular area detection. Biopsy analysis is currently the most reliable method for PCa diagnosis. The analysis of prostate biopsy is usually reported as follows: Negative for PCa; positive for PCa; or Suspicious for PCa, abnormal cells present, but may not be tumor cells.

In recent years, the availability of novel molecular markers, as well as the introduction of advanced imaging techniques such as mpMRI has changed the diagnosis and treatment of patients affected by PCa to a more tailored approach (13). According to the latest guidelines, any man at risk of prostate cancer should have an MRI of the prostate performed before obtaining a prostate biopsy (12, 13). This development in PCa diagnosis has improved clinicians' capacities to categorize patients by risk and propose a treatment constructed on tumor prognosis and patient predilection (11). Active surveillance, radical prostatectomy and radiotherapy are accepted as the standard treatments for stage I-III PCa. Furthermore, pharmacological castration can bring on lasting remission in all stage IV and high-risk stage III PCa. However, the small and selected number of biopsy cores obtained with a fusion biopsy technique is connected to a higher risk of complications such as bleeding (rectal bleeding, hematospermia) and acute urine retention (14). Based on recent evidence, some genetic markers could help in discriminating between aggressive and non-aggressive cancers with an additional significance compared to the prognostic parameters currently used by clinicians (11, 13). Furthermore, in men with an elevated risk of PCa with a prior negative biopsy or biopsy naïve with mpMRI negative, additional information may be added by biomarkers in deciding on whether to take a repeat biopsy.

Susceptibility Polymorphisms

As the early diagnosis of PCa is necessary to prevent metastasis and promote treatment, research of new efficient predictive biomarkers is essential to select risk patients. Different genetic polymorphisms linked to prostate cancer susceptibility have been found; the variant (rs1805087) in *METH* gene codifying for the methionine synthase, a key enzyme in the folate pathway, seems to be associated with increased prostate cancer risk. In fact, a positive association between the *METH* rs1805087 A/G variant and prostate cancer susceptibility has been found. This enzyme shows a critical role in the synthesis, repair, and methylation of DNA. This polymorphism is the most common mutation of the *METH* gene and involves the A2756G substitution, which leads an aspartic acid to glycine transition at position 919 of the protein. Therefore, subjects carrying the *METH* G-allele might have an increased PCa risk (15, 16). Another study reported that different SNPs are correlated with PCa predisposition; in particular, the variants rs7000448, rs1048169, rs2961144, rs4430796, rs12500426, rs2066827 and rs114798100 seem to correlate with PCa incidence (17). These polymorphisms are located in genes such as *HNF1B*, *CASC8*, *CDKN1B* and others that are implicated in the regulation of cell cycle, metabolic pathways and cell division. These variants are more frequent in African population that show a greater risk of PCa compared with other ethnic groups (17).

It has also been reported that variants in apoptotic gene regulators and tumor suppressor genes could be associated with PCa susceptibility. In this context, polymorphisms in the pro-apoptotic genes *CASP3* (rs4647603) and *CASP9* (rs1052571) as well as in the tumor suppressor gene *NKX3-1* (rs11781886) have been linked with a greater risk of developing PCa (18). In addition, the interleukin-6 (IL-6) gene could be involved in the development of multiple tumors, including prostate cancer. The analysis of the variant rs1800795 located in the promoter of IL-6 gene revealed no important association between this polymorphism and PCa risk in the general population. However, the rs1800795 polymorphism in *IL-6* might enhance the susceptibility to PCa in African and American people (19).

Interestingly, different studies have verified the possible relationship between SNPs in non-coding microRNAs (miRNAs) and cancer predisposition. In this regard, the polymorphism rs3746444 of miR-499 is significantly associated with PCa risk in general population. The variants rs2910164 of miR-146a and rs11614913 of miR-196a2 represents a risk factor especially for Asian people (20).

Taken together these observations indicate that the introduction of SNPs in clinical practice could help clinicians select risk patients for prostate cancer screening.

Prognostic Variants

The identification of risk groups for the development of disease relapse or distance metastases is essential for formulating accurate prognosis and the most appropriate therapy. There are different available putative genetic polymorphisms related to prostate cancer prognosis that could be used in clinical practice. The polymorphism rs1400633 in *MSH2* gene is significantly associated with more aggressive disease characteristics; therefore, it may represent an independent prognostic biomarker for PCa survival. This gene codifies for a core protein involved in the DNA mismatch repair pathway that recognizes and removes base pair mismatches due to incorrect replication. The variant rs1400633, located in a regulatory region of the promoter, could affect the expression of this gene that is associated with poor prognosis (21).

The variant rs4648302 was found to be associated with disease recurrence in PCa. This SNP is localized in the 3'-untranslated region of the *PTGS2* gene that codes for the enzyme prostaglandin-endoperoxide synthase 2. The polymorphism rs4648302 could be used as an independent risk marker for PCa recurrence (22). In addition, we have found that variants of *ATM* (rs587781894), *TP53* (rs786203436 and rs587780075), *SPOP* and *FOXA1* genes correlate with poor prognosis (3). Mutations of these genes are associated with tumor development and progression including prostate tumor, therefore, SNPs localized in these genes could be promising prognostic biomarkers to improve the management of PCa patients. Other studies report that the polymorphism rs1203072 of *YB-1* gene is linked with the clinical outcome of PCa. This gene codifies for the Y-box binding protein-1 (YB-1) and is involved in resistance to hormone therapy, regulating the expression of androgen receptor (AR) variants. The polymorphism rs1203072 is located in the intron of *YB-1* gene and could affect its expression by intron-mediated enhancement (23). This SNP might be considered a promising predictive biomarker in metastatic PCa and be useful in identifying high-risk patients that require more intensive therapeutic interventions. It is known that the downregulation of growth arrest-specific 5 (*GAS5*) gene expression is correlated with enhanced cell proliferation and poor prognosis of prostate cancer. The SNP rs145204276 lying in the *GAS5* gene is linked to metastasis development in PCa patients. In fact, patients carrying the genotype ins/del or del/del at SNP rs145204276 have decreased risk of lymph node metastasis; therefore, this polymorphism could represent a further prognostic biomarker for PCa (24). Finally, it has been found that rs35148638 and rs78943174 polymorphisms located close to genes involved in vascular disease are associated with the Gleason score in prostate tumors. Therefore, these SNPs that correlate with prostate cancer aggressiveness could be useful as prognostic biomarkers (25).

SNPs Linked to Hereditary Cancer Syndrome

Genomic variations have been found to be associated with hereditary PCa; in this context, we have observed that the germline variants R3008H (rs587781894) and R805X (rs780619951) in the *ATM* gene as well as the substitution P1275L (rs34070318) in *CDK12* gene correlate with cancer familiarity (3). ATM is one of the DNA damage response regulators and functions as a tumor-suppressor gene. Mutations of this gene have been found in different cancer types including prostate cancer. In particular, the variant rs587781894, located in the PI3-kinase regulatory domain (PRD) of the protein is the most common cancer-associated ATM missense mutation (26). Other studies report that the polymorphic homozygote genotype of the SNP rs7931342 was five times more frequent in patients with familial PCa than in subjects with sporadic PCa. This SNP consists of a *G/T* variation located on human chromosome 11, which was first reported in early-onset disease and familial prostate cancer (27). Interestingly, three SNPs (rs183373024, rs188140481 and rs138042437) localized on chromosome 8q24.21 correlate with high-risk of PCa development. SNP rs188140481 had already been found to be associated with prostate cancer in a study conducted on the population of Iceland. The other two SNPs (rs138042437 and rs183373024) lie in the oncogenic long non-coding RNA (CASC9) and prostate cancer associated non-coding RNA 1 (PRNCR1), respectively. These rare alleles are strongly associated with prostate cancer familiarity (28). An interesting study reported that the four variants rs116890317, rs79670217, rs73000144 and rs118004742 show a statistically significant association with prostate cancer predisposition. The first two variants were found in both familial and sporadic PCa patients. These mutations are intronic polymorphisms located in the *ZNF652* gene that codes for a DNA-binding transcriptional repressor protein that is downregulated in different tumors including prostate cancer (29). The SNP rs73000144 is a missense polymorphism lying in the *HDAC4* gene, a transcriptional repressor, and correlates with familial prostate cancer (29). Finally, the variant rs118004742 is a nonsense mutation located in the *EFCAB13* gene that encodes for the EF-hand calcium binding domain 13 and may contribute to hereditary PCa (29). These and other polymorphisms associated with hereditary prostate cancer could be used for the selection of patients for PCa screening and monitoring.

Genetic Polymorphisms and Therapy Response

Metastatic prostate carcinoma is a lethal disease that is difficult to treat; in fact, the treatment of advanced PCa may be ineffective due to therapy resistance. Therefore, the detection of specific genetic variations associated with therapy response might lead to the selection of patients who could benefit from

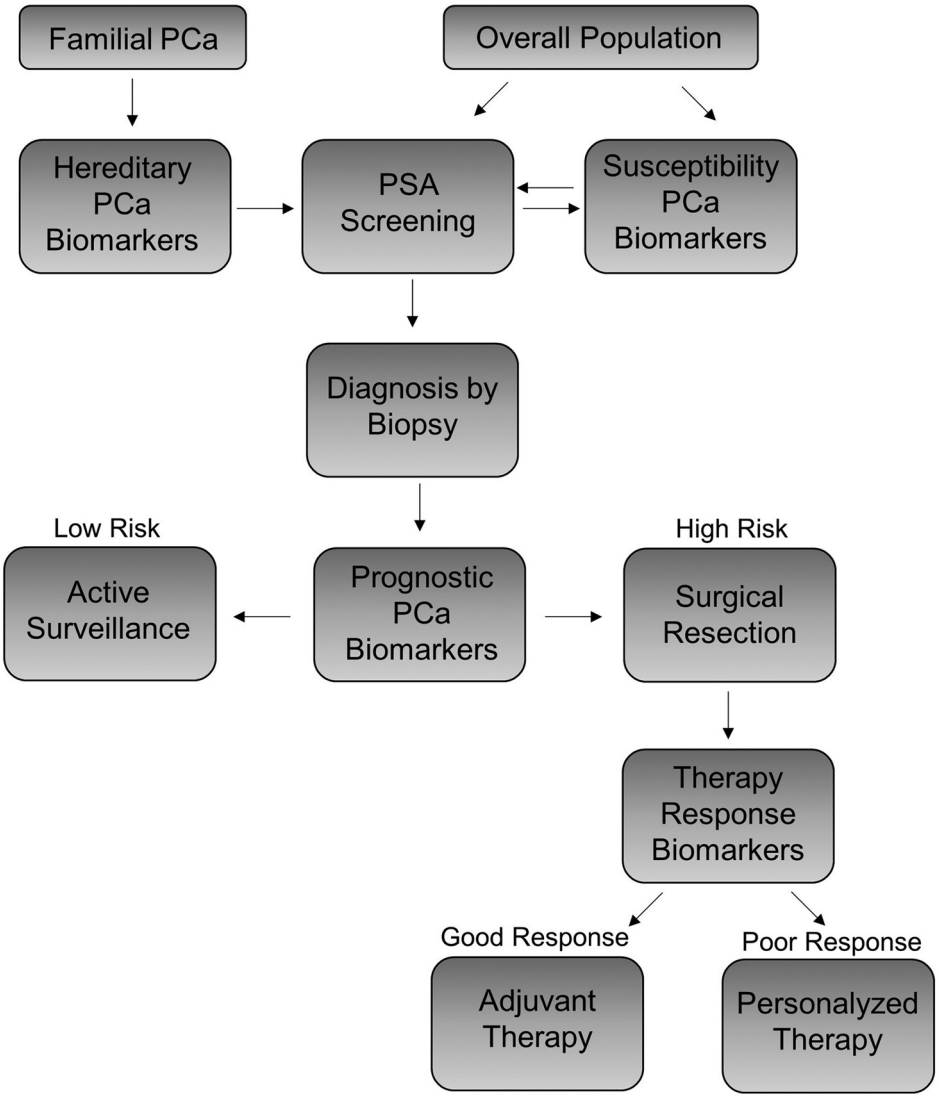

Figure 1. *Flow chart for the use of genetic polymorphisms in clinical practice. Based on age, general population could enter in screening programs using predictive biomarkers. Subjects with prostate abnormalities subjected to PSA test could benefit from susceptibility biomarkers. After diagnosis, the analysis performed by prognostic markers could identify low- and high-risk patients. Following surgical resection performed in high-risk patients, the use of therapy response biomarkers could recognize groups with good therapy response from those associated with drug resistance.*

adjuvant therapies or other therapeutic interventions. In this regard, it has been reported that the variant rs10420407, an intronic polymorphism located in the *PTBP1* gene, is associated with poor clinical outcomes in patients with PCa receiving androgen deprivation therapy (ADT) (30). This polymorphism lies in a region linked to histone modifications and could affect the expression of this gene. *PTBP1* is a regulator of post-transcriptional gene expression and the upregulation of this gene was associated with advanced tumor stage and worse survival after pharmacological treatment (30). Interestingly, it was reported that genetic variants might have a different impact on therapy response. In fact, the 1245 A/C substitution in *HSD3B1* gene encoding for the enzyme 3β-hydroxysteroid dehydrogenase-1 is associated with poor response to ADT in a Japanese cohort of PCa patients (31). Conversely, this variant correlates with a good therapeutic response in PCa patients treated with Abiraterone (31). 3β-hydroxysteroid dehydrogenase-1 is an enzyme required for dihydrotestosterone synthesis and the mutation described above makes it constitutively active. Therefore, prostate tumors linked to this variant show higher enzymatic activity of 3β-hydroxysteroid dehydrogenase-1 becoming resistant to ADT but more vulnerable to Abiraterone (31). In addition, Hahn and colleagues have reported that patients treated with first-line

abiraterone acetate for metastatic castration-resistant prostate cancer (mCRPC), who carry the heterozygous rs12422149 variant, had a significant improvement in progression free survival (PFS) compared with the homozygous wild-type group (32). The mutation rs12422149 is a polymorphism located in *SLCO2B1* gene that encodes for a transporter protein involved in cellular uptake of different hormones such as testosterone, DHEA sulfate and abiraterone acetate (32). Finally, it has been described that the polymorphism rs11549465, localized in the hypoxia inducible factor 1 alpha (*HIF1A)* gene, is associated with a greater risk for developing distant metastasis and resistance to ADT (33). HIF1a is a key regulator of tumor cell response to hypoxia and is involved in mechanisms linked to cancer aggressiveness and metastasis development. This genetic polymorphism may predict more aggressive PCa and ADT resistance, supporting the involvement of HIF1a in the biology of this tumor (33).

Conclusion

The incorporation of genetic biomarkers into the clinical practice, as proposed in Figure 1, could lead to important advances in the diagnostic, prognostic, and therapeutic field, helping clinicians in the management of PCa patients. This investigation does not take into account environmental factors such as lifestyle, smoking, diet, alcohol abuse and other conditions reported by PCa patients. However, the analysis of genetic variations should be integrated with environmental information, since they could affect the development and outcome of PCa.

The use of genomic information to select patients for predisposition, prognosis and best therapeutic interventions could become routinely feasible. Interactions between clinical and molecular parameters will lead to improvements in the patients' management, minimizing adverse effects and increasing the quality of life of PCa patients.

Conflicts of Interest

The Authors declare no conflicts of interest related to this study.

Authors' Contributions

Study design: LD. Data analysis: all Authors. Article writing: LD, GA. Data check: all Authors. Final approval: all Authors.

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