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REVIEW ARTICLE

Genetic alterations in prostate cancer as diagnostic and prognostic markers

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Abstract

Prostate cancer is the second-most frequently diagnosed cancer in men worldwide. Serum prostate-specific antigen is currently used for the early detection of prostate cancer. However, new biomarkers are needed to decrease over diagnosis and over treatment of prostate cancer due to limitations of prostate-specific antigen. Recently, molecular biomarkers have shown promising results for diagnosis and prognosis of prostate cancer. Molecular biomarkers have improved the sensitivity and specificity of prostate-specific antigen and studies are ongoing to identify molecular biomarkers as a replacement for prostate-specific antigen. This review aims to give an overview of emerging molecular biomarkers for diagnosis and prognosis of prostate cancer.

Keywords: Prostate cancer, genetic alterations, diagnostic markers, prognostic markers

INTRODUCTION

Prostate cancer (PC) is the second most frequently diagnosed cancer in men and the fifth leading cause of cancer death in men. [1]Serum prostate specific antigen (PSA) is widely used as a biomarker to diagnose PC.[2] However, PSA is a prostate but not cancer-specific marker.[3] The level of serum PSA could be increased in prostatitis or benign prostatic hypertrophy,[4] whereas some drugs such as finasteride could reduce PSA in the blood.[5] Patients with high levels of PSA may undergo prostate biopsy, and Gleason scores are used to assess prostate biopsy samples.[6] Nevertheless, prostate biopsy is an invasive procedure that may lead to fever, infection, urinary retention, rectal bleeding, and macroscopic hematuria.[7] Moreover, a negative biopsy does not reassure patients and clinicians of not having PC,[8] and a positive biopsy result does not guarantee an accurate diagnosis of PC to prevent overtreatment.[6] Thus, novel markers for PC detection are required due to limitations of PSA. [9,10,11]

Molecular biomarkers are one of the emerging biomarkers that potentially can be used to improve the limitations of PSA or even take the place of it. It has been suggested that several genetic alterations in PC can be used as potential molecular biomarkers for diagnosis, namely, PCA3, and TMPRSS2: ERG (T2: ERG) gene fusions[12] as well as prognosis purposes including, PTEN,[13] DNA repair genes,[14,15] AR,[16,17] HOXB13,[18] and TP53,[14,19,20] SPOP.[20] Studies are ongoing to confirm the usefulness of these molecular markers and to identify new genetic alterations as molecular markers for diagnosis and prognosis in PC. So far, the PCA3 test has been approved by FDA for diagnosis purposes in PC patients. PCA3, and TMPRSS2: ERG (T2: ERG) gene fusions are considered as the most advanced urine-based PC specific early detection biomarkers. Both Biomarkers have shown increased specificity for PC detection compared with PSA.[12] In this review, we have highlighted some of the genetic alterations in PC with potential prognosis and diagnosis value.

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PCA3

Prostate Cancer Gene 3 (PCA3) is highly over-expressed in PC.[21] The Progensa *PCA3* assay has been approved by FDA for PC diagnosis. This test can be considered to avoid repeated biopsy in men with a previously negative biopsy.[22] The PCA3 score is calculated as the ratio of PCA3 mRNA to PSA mRNA in urine (PCA3/PSA ×1000).[23]

It has been shown that urinary T2: ERG test in combination with PCA3 test improves specificity of detecting aggressive PC from 17% to 33% with preserved 95% sensitivity.[22] Recently, in a recent systematic review and meta-analysis of PCA3 evaluation for PC detection, the sensitivity and specificity of 0.65 (95% confidence interval [CI]: 0.63–0.66) and 0.73 (95% CI: 0.72–0.74) were reported, respectively for the urine PCA3 test.[24] More recently, in systematic review and meta-analysis consisting 1721 PC patients, the sensitivity and specificity of 0.83 and 0.40 were reported, respectively when the PCA3 cutoff value of 35 was used.[25]

Merola *et al*. in a study of 407 men with previous negative biopsies reported the superiority of PCA3 to total PSA and free PSA test in PC diagnostic. Furthermore, the study correlated higher PCA3 score to greater PC aggressiveness.[26]

HOXB13

HOXB13 G84E variant is linked to the early-onset and elevated risk of hereditary PC.[27] It has been found that HOXB13 G84E variant is associated with a 2.93-fold elevated risk of PC.[18] HOXB13 overexpression is associated with high Gleason grade, early PSA recurrence, high-level AR expression, advanced pathological tumour, positive lymph node statue, PTEN deletions, TMPRSS2: ERG fusion, and has been suggested as an independent prognostic factor in PC.[18] In one study, while the specificity and sensitivity of HOXB13 as an immunohistochemical marker for metastatic prostate cancer were 94% and 100%, respectively, the specificity and sensitivity of PSA were 100% and 53%, respectively.[28]

Recently, Park *et al*. examined clinicopathologic characteristics of HOXB13 expression in PC. The authors found an association between high level of HOXB13 expression and prostate ductal type adenocarcinoma, advanced pathologic T stage, occurrence of biochemical recurrence, and higher Gleason score. The study suggested HOXB13 as a diagnostic and a prognostic marker for prostate ductal type adenocarcinoma.[29]

PTEN

PTEN loss has been found in almost 20% of primary prostate tumour samples and in approximately 50% of castration-resistant tumours.[13] Loss of PTEN is associated with an elevated risk of tumour upgrading at radical prostatectomy from biopsy to radical prostatectomy,[30] adverse surgical findings and progression on active surveillance,[31] lethal PC progression,[32] biochemical recurrence after prostatectomy,[33] shorter progression-free survival, shorter overall survival,[34] and improved radiographical progression-free survival in mCRPCs patients treated with Ipatasertib plus abiraterone in PC patients.[35] Moreover, PTEN loss is associated with increased risk of metastasis and death in PC,[36] and has been suggested as an independent prognostic biomarker for death and metastatic disease after surgery.[13]

Ferraldeschi *et al*. found an association between PTEN loss and shorter time on abiraterone treatment as well as worse survival in a study of PC patients who had hormone-sensitive PC and had treated with abiraterone.[37]

Gao *et al*. in a meta-analysis of 26 published studies found that PTEN deletion in PC patients is associated with increased risk of aggressive Gleason score, ERG rearrangements, and PC replace.[38]

TP53

TP53 mutations are common in different types of human cancer.[39] TP53 gene aberrations in PC are linked to the development of aggressive PC,[40] poor metastasis-free survival,[41] increased risk of relapse,[42] shorter OS,[20] and shorter radiographic progression-free survival (rPFS).[43] Moreover, TP53 gain of function mutations are associated with PC progression and drug resistance after enzalutamide or abiraterone treatments in men with metastatic castration-resistant PC.[44] Maxwell *et al*. found an association between germline TP53 variants and aggressive prostate cancer in a study of 6850 men with PC. Germline TP53 variants were identified in 38 (0.6%) men with PC and were associated with aggressive PC.[40]

Lin *et al*. investigated the association between SNPs in TP53 binding sites and PC in a large cohort of 1,024 patients with PC. This study suggested some SNPs within TP53 binding sites as biomarkers for prognosis of disease progression, PC-specific mortality, and all-cause mortality after androgen deprivation therapy in PC.[19]

Huang *et al*. examined the correlation between TP53 and immune-related genes with PC. The results of study linked mutations in TP53 and some immune-related genes to poor prognosis in PC patients.[45]

Maughan *et al*. in a retrospective analysis of 309 CRPC patients treated with enzalutamide or abiraterone reported overall survival of 16.7 months for men with p53 nuclear accumulation and 31.2 months for men without p53 nuclear accumulation. Progression-free survival for men with p53 nuclear accumulation was 5.5 months and was 10.9 months for men without p53 nuclear accumulation. Moreover, p53 status was correlated with progression-free survival.[46]

TMPRSS2: ERG fusions

The transmembrane protease serine 2:v-ets erythroblastosis virus E26 oncogene homolog TMPRSS2: ERG gene fusion, is reported in almost 50% of patients with PC.[47] Recently, TMPRSS2: ERG fusion has been considered as a new biomarker in PC.[48]

TMPRSS2-ERG fusion transcripts have shown a sensitivity of 37% and a specificity of 94% for the diagnosis of PC.[49] It has been demonstrated that the utility of serum PSA is increased by combination of urine TMPRSS2: ERG and PCA3.[50, 51]

TMPRSS2-ERG fusion gene is associated with a more aggressive PC phenotype[52] and an increased risk of PC metastases in bone.[53] Pettersson *et al*. investigated the association between ERG overexpression and lethal disease as well as biochemical recurrence in a study of 1,180 PC patients treated with radical prostatectomy. The results of the study correlated ERG or TMPRSS2: ERG overexpression with stage at diagnosis. However, no association was found between ERG, or TMPRSS2: ERG overexpression and biochemical recurrence.[53]

DNA Repair

DNA Repair gene alterations have been identified in approximately 23% of patients with advanced PC. BRCA2 is the most frequently mutated gene among the DNA repair genes in PC.[54] Pritchard *et al*. studied the frequency of 16 DNA-repair genes in 692 cases with metastatic PC. Deleterious germline DNA-repair gene mutations were found in 82 cases (11.8%). The most frequently mutated genes were BRCA2, ATM, CHEK2, BRCA1, RAD51D, and PALB2 with 5.3%, 1.6%, 1.9%, 0.9%, 0.4%, 0.4%, respectively.[55]

BRCA2 mutations [56] as well as alterations in the other DNA repair gene including CHEK2,[57] PALB2, ATM,[58] BRCA1[59] are associated with an increased risk of PC development, and genetic aberrations in BRCA2, PALB2, ATM, MLH1, MUTYH, CHEK2, MSH2,[58] BRCA1, *BRCA2*,[60] CDK12,[61] ATM, NBN, BRCA2, and PALB2[62] are associated with more aggressive PC. Moreover, genetic alterations in some DNA repair genes including BRCA1/2, ATM[64] CDK12[65] are associated with shorter survival time.

Matejcic *et al*. screened 2,098 PC patients and 1,481 controls with African origin for pathogenic variants in 19 DNA repair genes. Of 2,098 PC patients and 1,481 controls, pathogenic variants were identified in 75 cases (3.6%) and in 31 controls (2.1%). Further analysis revealed that pathogenic variants in the BRCA2, ATM, NBN, and PALB2 genes are associated with increased risk of aggressive PC.[63]

Darst *et al*. found an association between DNA repair genes alterations namely, BRCA2, ATM, PALB2, CHEK2, MUTYH, MSH2 as well as MLH1 and an elevated risk of metastatic and aggressive PC in a large cohort study of 5545 men with PC.[58]

Castro *et al*. in a prospective cohort study (PROREPAIR-B) screened 419 mCRPC patients for DNA damage repair (DDR) genes to assess the effect of germline DDR (gDDR) mutations on mCRPC outcomes. gDDR mutations were found in 68(16.2%) patients. Further analysis suggested gBRCA2 mutations as an independent prognostic factor for cause-specific survival (CSS) (hazard ratio [HR], 2.11; $P = .033$).[65]

Kimura *et al*. sequenced gDNA from 549 Japanese men with metastatic and/or mCRPC to evaluate the prognostic significance of germline variants in HRR genes in advanced PC. BRCA2, HOXB13, PALB2 and ATM alterations were found in 19, 9, 5, and 5 patients, respectively. The study reported short overall survival and short time to castration resistance for the patients harboring ATM, BRCA1, BRCA2, and PALB2 variants.[66]

Antonarakis *et al*. investigated the effect of gDDR mutations status on PSA progression-free survival (PSA-PFS), ≥50% and ≥90% PSA responses, OS, and clinical/radiologic progression-free survival (PFS) in 172 mCRPC patients receiving abiraterone and enzalutamide treatment. gDDR mutations were found in 12% (22/172) of mCRPC patients. In this study, patients with germline BRCA/ATM mutations (9/172) responded better to abiraterone and

enzalutamide.[67] By contrast, poor response to abiraterone and enzalutamide was reported in a study of 319 mCRPC patients by Annala *et al*. In this study, 24 (7.5%) out of 319 patients had deleterious germline mutations in DDR.[68] However, Mateo *et al*. found no association between gDDR mutations and clinical outcomes in a study of 60 gDDR mutations carriers and 330 non-carriers treated with standard therapies including abiraterone/enzalutamide.[69]

Recently, olaparib and rucaparib have been approved by the FDA for the treatment of mCRPC with at least one altered gene among 14 of 15 DNA repair genes screened in the trial, and mCRPC with BRCA1/2 mutations, respectively.[70]

Androgen Receptor

AR Overexpression has been reported in almost 80% of patients with CRPC.[71] Both AR gene amplification and mutations have been identified in almost 60% of the patients with metastatic tumors.[72] It has been suggested that differential AR expression might predict clinical relapse after treatment of PC with external beam radiotherapy (EBRT).[73]

Androgen receptor splicing variant 7 (AR-V7) aberrations are associated with a higher Gleason score[74], site metastases and bone metastases.[74,75] enzalutamide and abiraterone resistance,[76-78] superior survival on taxane therapy compared to enzalutamide or abiraterone therapy.[79,80] Moreover, AR-V7 positive PC can be targeted by niclosamide.[81]

Pacheco-Orozco *et al*. suggested AR-V7 as a biomarker for resistance to enzalutamide and abiraterone in a study of PC patients from three Latin American countries, namely Colombia, Mexico, and Argentina.[78]

Recently, Li *et al*. investigated the association between androgen receptor splicing variant 7 (AR-V7) alterations and clinicopathological characteristics of castration resistant PC in meta-analysis and a systematic review. This study correlated AR-V7 expression to a higher Gleason score, metastasis, and more aggressive PC cancer. [74]

More recently, Khan *et al*. in a systematic review and meta-analysis investigated the prognostic and predictive value of AR-V7 in liquid biopsy of PC patients. In this study, the presence of AR-V7 in PC patients was correlated with worse OS, PFS, and PSA-PFS. Poorer OS, PFS, and PSA-PFS were reported in patients treated with abiraterone and enzalutamide. Moreover, significant association with OS was found in taxane-treated patients, and patients with AR-V7 who were treated with taxane had better OS outcomes than abiraterone and enzalutamide.[16]

SPOP

SPOP mutations have been reported in about 8% of localised[82] and mCRPC.[54] SPOP mutations are associated with better prognosis in several studies.[20,83,84]

Swami *et al*. in a study of 25 PC patients with SPOP mutation and 96 wild type SPOP found that SPOP mutation is associated with better overall survival (97 vs 69 mo; adjusted HR 0.32; p = 0.027) and median progression-free survival (35 vs 13 mo; adjusted hazard ratio [HR] 0.47; p = 0.016) in mCRPC patients with SPOP mutation who received androgen deprivation therapy.[83]

Nakazawa *et al*. investigated genomic and clinical characteristics of 72 PC patients with somatic SPOP mutations. They found that SPOP mutations are associated with durable responses to androgen deprivation therapy (ADT) with a median time-to-castration-resistance of 42.0 (95% confidence interval [CI], 25.7-60.8) months, and PC patients with concurrent TP53 and SPOP mutations have shorter time-to-castration-resistance. In this study, median progression-free survival was 7.3 (95% CI, 3.2-NR) months and 8.9 (95% CI, 6.7-NR) months on enzalutamide and abiraterone, respectively.[84]

Zhou *et al*. analysed 2,172 patients with PC to investigate the effect of SPOP and TP53 mutations on OS in lethal metastatic PC. While SPOP mutations were associated with better prognosis, TP53 mutations were associated with poor prognosis in metastatic PC. In this study, PC patients with both TP53 and SPOP mutations had shorter OS.[20] However, Mangolini *et al*. in a study of 48 paraffin-embedded PC cases and normal paired tissues reported that SPOP is associated with biochemical recurrence or lymph node metastasis.[14]

CONCLUSION

The approval of PCA3 test by FDA for diagnosis purposes in PC patients has highlighted the importance of molecular biomarkers in the management of PC. Recently, several studies have investigated the genetic alterations of AR, DNA Repair, PTEN, TP53, HOXB13, SPOP in PC as potential molecular biomarkers for PC. The results of these studies have been promising and further studies might lead to the clinical usage

of them as molecular biomarkers in the future. However, the usefulness of many identified altered genes as a potential diagnosis and prognosis biomarkers, alone or in combination has not been well studied. Therefore, further studies are required to investigate the potential usefulness of genetic alterations in PC as potential diagnostic and prognostic molecular biomarkers.

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