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Review Article

Molecular mechanisms involving prostate cancer racial disparity

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Abstract: Prostate cancer (PCa) is the second leading cause of cancer-related deaths in the United States. The African (AA) descent has greater incidence and mortality rates of PCa as compared to Caucasian (CA) men. While socioeconomic differences across racial groups contribute to disparity in PCa, increasing evidence points that genetic and molecular alterations play important roles in racial disparities associated with PCa. In this review, we focus on genetic and molecular influences that contribute to racial disparity between AA and CA men including: androgen and estrogen receptor signaling pathways, growth factors, apoptotic proteins, genetic, genomic and epigenetic alterations. Future translational studies will identify prognostic and predictive biomarkers for AA PCa and assist in the development of new targeted-therapies specifically for AA men with PCa.

Keywords: Prostate cancer, racial disparity, African American, Caucasian, molecular markers

Introduction

Prostate Cancer (PCa) is one of the most frequently diagnosed cancers in men and is the second leading cause of cancer-related deaths in the United States [1]. According to the American Cancer Society report, there will be an estimated 180,890 newly diagnosed PCa cases and about 26,120 deaths due to PCa in 2016 [1]. Uniquely, several epidemiological studies show that compared to Caucasian (CA) men, African American (AA) men have a notably higher PCa prevalence and mortality rate [2, 3]. In AA men, PCa presents itself at a younger age and at a more advanced stage than with men in other ethnicities [3-5]. Even among the patients with low risk PCa, studies for PCa outcomes in different racial backgrounds reported adverse clinicopathologic factors such as higher positive surgical margins, pathologic upgrading, and upstaging in AA men after prostatectomy. Close monitoring and modified management options have been suggested for these patients [6, 7]. Factors which may contribute to the disparity in PCa incidence and outcome are multifactorial including socioeconomic differences and tumor biology [8-14]. In this review, we summarize previously published and recent studies highlighting molecular differences in PCa of AA and CA men (**Table 1**).

Androgens, androgen receptor (AR), and involved pathways

The crucial role of androgens and the androgen receptor mediated signaling pathway in PCa is well established. There are several aspects of this pathway which contribute to the racial disparity of PCa.

Serum androgen level

The role of sex steroid hormone levels on PCa racial disparity has been investigated in several studies [15-19]. Studies investigated the role of sex steroid exposure on the racial disparity of PCa. Young AA men had 15% higher testosterone levels than young CA men [20]. Other authors have shown higher active 5-alpha reductase levels in black men than in white men, suggesting that hormonal differences may have an impact in increased risk of PCa among AA men [21, 22]. Although there is no clear relationship between circulating androgen levels and PCa, high levels of androgens have long been considered as risk factors.

Table 1. Summary of studies showing altered genetic alterations and cancer gene pathways related to the racial disparity of PCa

Gene	Cancer Pathway	Racial Heterogeneity of Gene Mutations and Expressions	References
Serum Androgen		-High testosterone levels in young AA men	[20]
		-5-alpha reductase levels in AA men	[21, 22]
CYP17	Androgen synthesis	-A1 and A2 alleles may have a role in PCa susceptibility in AA men	[26, 31, 32]
CYP3A4	Androgen deactivation	G variant	
		-More common among AA men than white, Hispanic or Asian men	[36, 37]
		-Significantly associated with poor recurrence-free survival and aggressive PCa among black men	[37, 39]
AR		-Increased epithelial AR expression in tumoral prostate tissue	[50, 51]
		-Decreased stromal AR in PCa in AA vs CA patients	[53]
		-High germline and somatic mutations in AR in AA patients than in CA patients	[54]
		-Short CAG and CCG repeat length in AA patients	[44, 46]
		-Mutant AR-protein complexes unique to AA patients included ERCC1, ERCC2, ERCC3, ERCC5 and FEN1	[55]
		-Gene expression profiling identified AR-target genes: RHOA, ITGB5 and PIK3CB were associated with AA PCA cells	[57]
ER	Gene transcription	-Increased ER levels and decreased testosterone/ER ratio in black men than in white men	[59]
		-Increased estradiol and SHBG levels in AA men	[60, 61]
		-Polymorphism of 5 ER related genes with PCa risk in AA Patients	[62]
		-Elevated E2 and ERβ levels in both benign and tumor samples of AA men	[63]
EGFR	Growth factors	-Major racial differences in CA repeat polymorphism	[68, 69]
		-EGFR expression more common in AA than in CA patients	[72]
EphB2	Tyrosine kinase receptor	-1p36 linked with hereditary PCa in racially diverse families including AA	[75-77]
		-K109X mutation, more frequent in AA men and associated with increased risk of PCa	[78]
		-Genetic variation at EphB2 play a role in increased risk of PCa in AA men	[79]
Bcl-2/Survivin	Apoptosis	-Increased Bcl-2 expression and high proliferation in PCa tumors in AA but not in CA patients	[82, 83]
		-AA patients with PCa contained higher amounts of Survivin in extracellular vesicles from PCa patients	[84]
Chromosome 8	Tumor suppressor	-Gain of 8q24 and loss of 8p associated with metastatic disease in AA than in CA patients	[108]
		-The association between 8q24 and AA ancestry in patients with PCa	[110, 111]
miRNAs	Regulation of transcription and translation	-miR-30c-1, miR-1b-1, miR-219, miR-26a are differentially expressed among EA and AA racial backgrounds	[126]
		-Significant miR-26a expression in AA cell lines	[127]
		-Resiprocal regulation of miR152 in AA patients	[128]
		-Downregulation of miR-21 and miR-30c in AA patients	[129]
		-Increased activation 10 AA specific target genes in AA samples	[130]
		-Loss of miR-34b in AA samples which was inversely correlated with high AR and increased proliferation	[131]
		-Reciprocal regulatory relation of miR-24 in AA patients with PCa	[132]
Methylation		-RARβ2, SPARC, TIMP3, and NKX2-5 genes are highly methylated in AA tumors than in CA tumors	[133]
		-RARB methylation is associated with increased risk of PCa in black men compared to white men	[134]
		-Higher methylation prevalence of SNRPN and ABCG5 genes in AA vs CA samples	[135]
		-CD44 was differentially hypermethylated in AA vs CA samples and this was correlated with tumor grade	[136, 137]
		-Significant differences in methylation levels of ZFR2, MAST1, CDH18, MAP2K5 and PRDM13 in AA patients with metastasis	[139]

Biosynthetic enzymes affecting androgen

There are several genes involved in androgen biosynthesis that determine the activation or inactivation of androgens, thus they may have a potential role in PCa racial disparity.

SRD5A2: Studies have suggested that genetic mutations in 5α-reductase (encoded by the SRD5A2 gene) converting testosterone to dihydrotestosterone (DHT), may be involved in racial disparities in PCa [23]. It has been reported that certain SRD5A2 polymorphic alleles are restricted to AA men [24] such as *121-131-bp* allele.

CYP17: The CYP17 gene is located on chromosome 10 and encodes the cytochrome P450-c17a enzyme that is a catalyzer in the steroid biosynthesis pathway [25, 26]. T-to-C polymorphism in the 5' promoter region results in A1 (T) and A2 (C) alleles [23]. Some studies suggested that the A1 allele was associated with increased PCa risk [27, 28]; while other groups reported that the A2 allele was associated with a greater risk of PCa [29, 30]. A study that investigated CYP17 polymorphism in three different populations showed that AA men with A2 (C) allele had an increased risk for PCa. The A2 allele was associated with higher grade and stage PCa [26]. The authors conducted a meta-analysis from seven published and two unpublished studies that included 1580 subjects. Overall, there was no association between CYP17 and PCa; however, the analysis showed a significant association between CYP17 and PCa in AA men [31]. In another study, stratified analysis according to ethnicity showed a borderline association between CYP17 and an increased risk in AA men [32].

CYP3A4: The CYP3A4 gene belongs to the cytochrome p-450 family and functions in the oxidative deactivation of testosterone to biologically less active metabolites [33, 34]. A germline genetic variant in the 5' regulatory region of the CYP3A4 gene on chromosome 7 (A to G transition at position -293 from the ATG start site), referred to as "CYP3A4*1B or CYP3A4-V", has been reported and was found to be associated with a higher clinical grade and stage of PCa in CA men [35]. Several subsequent studies found that the CYP3A4 G variant is much more common among AA men than White, Hispanic, or Asian men [36, 37]. This association was found to be even stronger if PCa was diagnosed at an older age (>64) [36]. Researchers studied a large series of patients (428 white and 309 black men) who underwent prostatectomy and investigated the impact of CYP3A4 polymorphism on the risk of recurrence. The results showed a significant association between the CYP3A4 G variant and poor progression-free survival among black men [37]. Significant differences in the CYP3A5 and CYP3A43 genes have been reported in AA men compared to CA men [38]. A separate case control study evaluated the link between CYP3A4 variant alleles and the diagnosis and clinical presentation of PCa. Race-stratified analyses showed that CYP3A4*1B was associated with aggressive PCa in AA men, which was consistent with several other previous studies [39]. Overall, while several studies indicate differences in CYP3A4 among AA and CA patients further studies are needed to understand the effect of the CYP3A4 polymorphism in AA racial background.

Androgen receptor and target genes

The first exon of AR consists of two polymorphic nucleotide repeats; CAG and GGN. Studies found that the transcriptional activity of an AR is inversely correlated with CAG repeat length [40] and that short CAG and GGN repeat length was associated with increased risk of PCa [41-43]. AA men tend to have fewer CAG repeats than CA men [44-46]. The relation between GGN and PCa is controversial. One meta-analysis study reported that people with less than 16 GGN repeats have a higher risk of PCa [47]. However, other studies have not found an association between GGN repeat length and PCa risk in AA population [48, 49].

ARs have been evaluated at the protein level in benign and malignant prostatic tissue using immunohistochemistry [50]. Nuclear AR expression was significantly increased in black patients (p=0.048). Kim et al. reported higher expression levels of ARs and proliferation markers in AA patients who underwent radical prostatectomy [51]. In contrast, stromal AR levels are decreased in PCa and there is a greater level of decrease in AA compared to CA PCa [52, 53]. The contrasting expression of epithelial and stromal AR in PCa may be one of the leading cause of castration resistance in PCa

treatment. Occurrences of unique AR mutations and polymorphisms related to racial disparity have been investigated using 200 AA and 100 CA prostate tumor samples. High frequency of germline and somatic mutations in AR were observed more frequently in AA than in CA patients. This indicates the potential role of AR specific hypermutations in racial disparities in PCa [54]. One of the most common somatic mutations that occurs in PCa AR mutation is Thr877Ala. A recent mutation study characterized AR interacting proteins known to bind T877A-AR, in different racial groups. The AR-interacting proteins that were unique to the AA group included proteins which are required for DNA damage excision repair such as ERCC1, ERCC2, ERCC3, ERCC5, and FEN1 [55].

Consistent with higher epithelial AR levels in AA PCa, the expression of AR target genes is increased. In several studies, serum PSA levels have been seen to be significantly higher in black patients than in white patients [50, 56]. Interestingly, one study considered the differences between initial presenting serum (iPSA) levels between AA and CA men through time. They found greater difference of PSA between AA and CA PCa. Between 1990 and 1996, the average iPSA level was 10.5 and 14.6 for CA men and AA men, respectively. However, the difference is decreased between 1997 and 2001 with iPSA levels 9.5 and 10.8 for CA men and AA men, respectively. Using gene expression profiling, Wang et al. identified 1188 genes that are differentially expressed between AA and CA PCa samples. Among them AR-target genes RHOA, ITGB5, and PIK3CB are associated with increased invasion activity of PCa cells have been suggested as promising drug targets for the management of PCa in AA patients [57].

Estrogen and its receptor

Many reports have shown that estrogens, alone or synergistically, play a critical role in normal prostate growth as well as PCa [15]. Bosland et al. studied the biological role of estrogen and progesterone in PCa in animal models [58]. Testosterone caused low incident tumor development in rat models. However, combination treatment with estradiol (E2) caused nearly 100% tumor development [58]. Although the role of estrogens in PCa has been investigated, their potential role in racial disparity of PCa remains unclear. A study of 5003 men older than 65 years of age showed an increased estrogen level and a decreased testosterone/estrogen level ratio in Black men when compared to White and Asian men [59]. Likewise, several other studies reported increased estradiol and sex hormone binding globulin levels in AA men [60, 61]. A more recent study reported the association of polymorphisms of five estrogen related genes with PCa risk in two different populations with African ethnical background [62]. Another ethnicity-based study evaluated serum estrogen and tissue ERβ levels in matched normal and tumor prostate samples. Elevated circulating E2 levels and increased ERβ expression were found in all PCa patients in comparison to their benign matched counterparts. Moreover, blood E2 and tissue ERβ levels were significantly higher in AA men, in both benign and PCa samples than in CA men [63].

Although the role of hormones in PCa racial disparity needs to be further investigated, these findings support the suggestion that androgens, synergistically with estrogens and their receptors, may have an important role in racial disparity in PCa [15, 64-66].

Growth factors and receptors

The best studied growth factors regarding the racial disparity in PCa cases include EGFR and EPHB2.

Epidermal growth factor receptor (EGFR)

EGFR plays a role in cell proliferation, promotion of tumor cell invasion, and avoiding apoptosis. This makes it a target of anticancer agents [67]. Studies have shown major racial differences in dinucleotide (CA)n repeat polymorphism in intron 1 of the EGFR gene [68, 69]. The numbers of CA repeats (which range from 14 to 21) have been found to be correlated with transcriptional activity [70, 71]. The longer allele is significantly more common in Asian individuals [68] and is associated with an 80% reduction in EGFR protein expression compared with the shorter allele [70]. EGFR overexpression in PCa is seen to be more common in AA patients than in CA patients [72]. We have seen a significant correlation between EGFR overexpression and AA race (45% in AA versus 18% in CA) [72]. There has been one group that

reported no correlation between EGFR expression and race [73], however, their conclusion was based on a small number of AA patients.

EPHB2

The EphB2 gene encodes the EphB2 receptor tyrosine kinase. EphB2's location near a suspected PCa locus and its characteristics make it a possible candidate gene for PCa susceptibility. Several lines of evidence, including its inactivation in the DU145 PCa cell line and growth inhibition from its overexpression, suggest that EphB2 may be a tumor suppressor gene [74]. EphB2 maps to 1p36, which has been shown to be linked with hereditary PCa in racially diverse families including AA [75-77].

One study investigated the role of EphB2 in PCa susceptibility in AA men by screening for germline polymorphisms in the EphB2 gene. Ten sequence variants were identified including the nonsense mutation, K1019X, which is common among AA PCa patients. The K1019X mutation was shown to be more frequent in AA men, and is associated with increased risk for PCa [78]. The risk for PCa was seen to increase 3-fold among AA men who carried the K1019X allele and had a family history of PCa. It is likely that K1019X is associated with familial PCa in AA men.

A later study evaluated the relationship between genetic variation at the EphB2 locus and the risk of sporadic PCa in AA men. They genotyped 341 single nucleotide polymorphisms (SNPs) in a population of AA men which included 490 sporadic cases and 567 matched controls. It was indicated that genetic variation at the EphB2 locus has been seen to play a significant role in increased disease risk of sporadic PCa in AA men. These studies indicate the importance of the EphB2 gene in both AA men with familial PCa and also AA men with sporadic PCa [79].

Differences in apoptotic genes in relation to prostate cancer racial disparity

Anti-apoptotic Bcl-2/survivin

Studies have investigated the incidence of the expression of the Bcl-2 gene in AA and CA patients with PCa, to identify potential differences in tumor growth and aggressiveness between the two ethnic groups. Bcl-2 is an anti-apoptotic mediator that has been linked to a variety of human cancers including PCa [23, 80, 81]. Guo et al. conducted a study including 44 AA and 35 Ca patients who underwent radical prostatectomy. The apoptotic status and proliferation of the tumors were evaluated using immunohistochemistry and the TUNNEL assays. Apoptosis was significantly higher in AA patients; however, the rate of cell proliferation was similar in both groups [82]. In a larger sized study of 117 PCa patients, tissues from AA and CA patients have been evaluated for proliferation and p53 and Bcl-2 expression. The study results showed a significant association between Bcl-2 positivity and proliferation in AA patients [83]. The shift in the balance of apoptosis and proliferation in black men suggests that this pathway may contribute to the aggressive behavior of PCa in AA men.

A recent study evaluated the expression differences of the apoptosis inhibitor protein "Survivin" in blood-derived exosomal vesicles of AA and CA PCa patients. AA patients had significantly increased levels of exosomal vesicles, which contained the highest anti-apoptotic Survivin protein levels, compared to CA patients. All these findings indicate a possible link between apoptosis and increased risk and aggressiveness of PCa in AA racial background [84].

MDM2

The human mouse double-minute 2 protein (Mdm2) is a ubiquitin ligase that binds to and promotes the degradation of the tumor suppressor protein, p53 a protein involved in cell cycle arrest, DNA repair, and apoptosis [85, 86]. Mdm2 overexpression is associated with tumor aggression and lack of response in a wide variety of human cancers [86]. Our lab has shown that increased Mdm2 expression is associated with advanced-stage PCa [87]. Several other subsequent studies supported this finding showing an association between increased Mdm2 and increased risk of PCa [88-90]. A single nucleotide polymorphism was found, which is located 309 bp downstream from intron 1 in the promoter of the MDM2 gene (SNP309, T>G) [91]. SNP309 can enhance the affinity for promoter protein binding and results

in increased transcriptional activation of Mdm2 and increased suppression of the p53 pathway [91]. A number of studies assessed the association of SNP309 and tumor risk in different cancers and patient populations and have shown an association of SNP309 with several types of cancer [92-96]. Our lab has also evaluated the association between SNP309 and PCa in patients with different ethnic backgrounds [97]. Our results did not show any difference in the level of SNP309 between AA and CA PCa patients. Interestingly, Mdm2 expression was significantly higher in CA than in AA patients [97]. Another group performed a meta-analysis on seven published studies that included 5151 PCa cases and 1003 controls. In the overall analysis, SNP309 was significantly associated with a decreased risk of PCa, and with lower degrees of PCa malignancy. Furthermore, a meta-analysis between different ethnic groups showed that SNP309 in Caucasians was significantly associated with a decreased risk for PCa and lower degree of PCa malignancy [98]. The authors did not found any association in Asian group [98]. In summary, despite several studies indicate the role of Mdm2 overexpression and SNP309 in cancer progression, their impact on PCas with different ethnic groups is limited and needs to be further investigated.

Genetic, genomic and epigenetic variations between AA and CA prostate cancer

Copy number variation

Recently, genome-wide copy number variation between AA and CA PCa has been studied [99]. 27 chromosomal regions with significantly different copy number changed between AA and CA patients has been seen. Copy number changes have also been significantly associated with gene expression changes. The copy number in the 27 regions was significantly associated with gene expression changes. aCGH was performed in a larger cohort of AA and CA tumors which indicated that there were 4 validated regions of DNA copy number changes and revealed enrichment of genes to immune response [99]. This suggests that there are distinct genetic differences contributing to racial differences in PCa characteristics.

Chromosome 8

Several studies indicated that the short arm of chromosome 8 has an important role in PCa carcinogenesis [100-104]. Genetic variation at 8q24 is an important contributor for PCa [105-107]. Studies also have shown that a gain of 8q24 is commonly seen in PCa, and often accompanied by 8p loss [108]. Amundadottir reported that an allelic variant of 8q24 has a role in the risk PCa. Allele -8 of the microsatellite DG8S737 was associated with PCa in three case-control series of European ancestry from Iceland, Sweden, and the US. They found that about 195 of affected men and 13% of the general population carried at least one copy of allele -8, with a population attributable risk (PAR) of about 8%. [109]. Furthermore, the association was almost twice as high in AA case-control group, in which 41% of affected individuals and 30% of the population were found to be carriers. This leads to a greater PAR (16%) and higher incidence of PCa in AA men rather than in men with European ancestry [109]. Another study, which used whole-genome admixture mapping analysis, showed the role of 8q24 in risk of PCa in young AA patients [110]. They also identified a 3.8 million base pair (Mb) region on chromosome 8q24 and it was associated with the risk for PCa in AA men. The 3.8 Mb interval had a single admixture peak containing nine genes [110]. A follow-up study identified seven SNPs at the 8q24 region, which were associated with higher risk of PCa among AA, rather than CA men [111]. Additionally, several studies also confirmed the association between PCa susceptibility loci on 8q24 and AA ancestry [107, 108, 112, 113].

HPC1

PCa is caused by multiple genes via complex interaction with environmental factors [114-117]. The genetic basis of PCa has been investigated using linkage studies. Results suggested that hereditary PCa 1 (HPC1) susceptibility locus contributes to the early onset and familial forms of PCa [118, 119]. The prevalence of this susceptibility locus was higher in AA families than in CA families that have multiple members with PCa [8, 120].

MicroRNAs

MicroRNAs (miRNAs) are short non-coding RNAs that regulate gene expression at the transcriptional and post-transcriptional level [121]. miRNAs behave either as tumor suppressors or oncogenes and change the tumor dynamics

[122-125]. The effect of miRNA's on racial disparities in patients with PCa has been an area of intensive investigation in recent years. Five miRNAs, miR-30c-1, miR-26a, miR-1b-1, miR-219, and miR-301, were differentially expressed among the AA and EA racial backgrounds [126]. Theodor et al. studied miR-26A expression using benign, malignant, and metastatic AA and CA prostate cell lines. The results showed the most significant difference of miR-26A expression in AA cell lines. Furthermore, there was a trend of increased miR-26A expression in aggressive cell lines in both the AA and CA group [127]. Another study from the same author showed that the reciprocal regulation of miR152 may contribute to aggressive PCa in AA patients [128]. Our lab investigated miRNA profiles in tissue samples of 27 PCa patients. miR-21 and miR-30c were significantly downregulated in PCa in AA patients as compared to CA patients. In addition, the reduction of miR-21 and miR-30c, let-7c and miR-219 was significantly associated with metastasis [129]. Using integrative genomic analysis, Wang et al. identified 22 AA-specific and 18 CA specific miRNAs in patients with PCa when compared to their matched normal tissues. They also found an increased activation of 10 AA-specific miRNAs along with the target genes in AA samples compared to that in CA samples [130]. Shiina et al. investigated miRNA-34b expression in AA and CA derived PCa cell lines and tissue samples. There was a significant loss of miR-34B in AA vs CA patient samples and this loss was inversely correlated with high AR level and cell proliferation [131]. Same group studied miR-24 in AA and CA PCa patients. Treatment of AA derived PCa cells with 5Aza-CdR restored miR-24 activity however, this was not seen in CA derived PCa cells. Based on their qPCR based analysis, AR, IGF-1, IGFBP5, and ETV1 gene expression markedly decreased in AA derived PCa cells compared with CA PCa cells [132].

Epigenetic changes

Several recent studies showed that different epigenetic changes are involved in PCa between AA and CA men. Kwabbi-Addo et al. analyzed the methylation status of six genes in benign and malignant prostate tissue specimens from AA and CA patients. The genes RARβ2, SPARC, TIMP3, and NKX2-5 genes are highly methylated in AA tumor samples in comparison to that from CA samples ($p<0.005$). Furthermore, NKX2-5 and TIMP3 were found to be hypermethylated, even in benign prostate tissues of AA samples. This was not found in CA patients [133]. Tang et al. found higher frequency of RARB methylation in the benign prostate tissue which was highly associated with increased risk of PCa in white and black patients but the risk was more than doubled in black men [134]. In a recent study by the same author, they used the Illuminia 450K methylation platform to investigate the methylation status of 485,577 CpG sites. DNA from AA and CA men were used in the analysis to compare different methylation patterns and corresponding functional changes not only in human samples but also in AA and CA PCa cell lines. They identified higher methylation prevalence of SNRPN and ABCG5 genes in AA vs CA samples. The knockdown of those genes resulted in a significant decrease in invasion and proliferation in CA but not in AA PCa cell lines [135]. Differences in the DNA hypermethylation of the genes GSTP1, CD44, RARβ2, EDNRB, E-cadherin, Annexin, and Caveolin have been evaluated in prostate tumors of AA and CA patients in two different subsequent studies. They have found that only CD44 was differentially hypermethylated in AA patients compared to CA patients and this difference was positively correlated with tumor grade [136, 137]. In contrast, another study did not find any significant differences in the GSTP1 gene- and CD44 gene-specific methylation pattern between AA and CA patients [138]. A recent study examined the correlation between DNA methylation, aggressive clinical features, and recurrence only in AA PCa patients. They found significant differences in the methylation level of five ion binding genes, ZFR2, MAST1, CDH18, MAP2K5, and PRDM13 in patients with metastasis but not in patients without recurrence [139]. Despite limited evidence, it is suggested that, epigenetic changes play a role in the racial disparity of PC.

Conclusion

Although a number of genetic and molecular based studies highlight different pathways and biological events which may contribute to PCa disparities, efforts remain to develop molecular markers of predictive and prognostic values and therapeutic targets for men of African descent.

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