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Review Article

Molecular mechanisms involving prostate cancer racial disparity

David Hatcher, Garrett Daniels, Iman Osman, Peng Lee

Department of Pathology and Urology, New York University School of Medicine, New York, NY

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Abstract: African American (AA) men with prostate cancer (PCa) have worse disease, with a higher incidence, younger age and more advanced disease at diagnosis, and a worse prognosis, compared to Caucasian (CA) men. In addition to socioeconomic factors and lifestyle differences, molecular alterations contribute to this discrepancy. In this review, we summarize molecular genetics research results interrelated with the biology of PCa racial disparity. Androgen and androgen receptor (AR) pathways have long been associated with prostate growth. Racial differences have also been found among variants of the genes of the enzymes involved in androgen biosynthesis and metabolism, such as SRD5A2, CYP17, and CYP3A4. The levels of expression and CAG repeat length of AR also show racial divergence and may be critical molecular alterations for racial disparity. Growth factors and their receptors, which promote cancer cell growth, are another potential cause of the disparity; both EGFR and EPHB2, two of the most studied receptors, show interethnic differences. Differences have also been found among genes regulating cell apoptosis, such as BCL2, which is increased in PCa in the AA population. Recent developments in genetics, proteomics, and genomics, among other molecular biotechnologies, will greatly aid the advancement of translational research on PCa racial disparity, hopefully culminating in the discovery of novel mechanisms of disease, in addition to prognostic markers and novel therapeutic approaches.

Key words: Prostate cancer, disparity, incidence, prognosis, molecular genetics, SRD5A2, CYP17, CYP3A4

Introduction

The incidence of prostate cancer (PCa) varies widely between ethnic populations and countries. PCa is the most common male-specific cancer in most Western countries [1-3]. In the US, there were an estimated 186,320 new cases in 2008 [4], and it was the second leading cause of cancer related deaths after lung and bronchus carcinoma [4]. PCa disproportionately affects African American (AA) men, who have a higher incidence of PCa, present at a younger age and with more advanced disease, and have a worse prognosis than men of other ethnicities [5-8].

Along with positive family history and older age, African ancestry has long been recognized as an important risk factor for PCa [2, 9]. The underlying reasons for this disparity are not well understood, although existing evidence implicates important genetic components. While it has been argued that racial variation may be largely due to lifestyle, dietary, socioeconomic [10, 11], or clinical factors, these cannot fully explain the discrepancy [6-8, 12] or the results of migration studies, and consequently, genetic parameters may be important. Studies of the pathology and recurrence of tumors in AA and CA men have suggested that racial differences in the biology of PCa tumors may explain observed differences in outcome [13, 14]. We studied men treated with radical prostatectomy at an equal-access-to-care facility and found AA men continue to have higher PSA levels and Gleason scores than CA men in the 2000s, despite a narrowing of the differences in pathologic stage [15]. Our data also suggests that socioeconomic factors have limited impact on PSA recurrence in AA men treated with radical prostatectomy [16] in this

group of patients. Thus, the distinct behaviors of AA and CA PCa might be biologically or genetically encoded. This article summarizes the previous and current molecular research findings related to PCa racial disparity (**Table 1**).

Androgens, androgen receptor, and involved pathways

Androgens and the androgen receptor pathway constitute the most intensely studied field in PCa. Several aspects of the pathway are related to the racial disparity of PCa.

Serum androgen levels

Young AA men were shown to have higher mean serum testosterone levels (about 15%) than CA men [17], and another study of men aged 31 to 50 also showed a significantly higher mean serum testosterone level among AA men [18], which may be related to the higher risk of PCa in AA men. There is conflicting evidence on the role of androgens in the growth and differentiation of prostate tumors. Elevated testosterone and dihydrotestosterone (DHT) have not been persuasively shown to increase the risk of PCa, with some groups reporting that serum hormones levels are higher in PCa patients while others found no differences [1, 3]. Although there is no clear relationship between circulating androgen levels and PCa [19-21], high levels of androgens have long been considered as risk factors [19, 22].

Androgen receptors

The human androgen receptor (AR) is a ligand-dependent nuclear transcriptional factor that regulates the expression of genes necessary for the growth and development of both normal and malignant prostate tissue. In a study of malignant and benign prostate tissue from AA and CA men who underwent radical prostatectomy for PCa, expression of AR protein was 22% higher in the benign prostate and 81% higher in PCa of AA patients by immunohistochemistry [23]. This suggests that differences in androgenic stimulation may have an important role in racial disparity.

The AR gene is over 90 kb in length and is located on chromosome Xq11-12 and consists of eight exons. Exon 1 of the gene entirely encodes the N-terminal (transactivation) domain, which controls transcriptional activation of the receptor, as well as two polymorphic trinucleotide repeats (CAG and GGC), which code for polyglutamine and polyglycine tracts, respectively, in the N-terminal domain. Prior studies indicate that this CAG repeat varies in length from 11 to 31 repeats in normal men [24], and an inverse relationship has been demonstrated between CAG repeat length and AR transcriptional activation ability [25]. Short CAG and GGC repeat lengths have been associated with an increased risk of developping PCa [26-28], specifically individuals with CAG repeat length less than 20 and GGC repeat length less than 16 [26, 28-30]. Striking differences in CAG repeat lengths have been observed between populations. AA men tend to have significantly shorter repeat length than CA men [24, 31, 32]. One study examining men at low risk for PCa (normal PSA and prostate examination) found that nearly twice as many AA men have a CAG repeat length less than 20 compared with CA men [31].

Biosynthetic enzymes affecting androgen

Variants in the genes of the enzymes involved in androgen biosynthesis and metabolism are compelling candidates for susceptibility factors in PCa pathogenesis.

SRD5A2: It has been suggested that intraprostatic DHT levels may be integral to racial variations in risk [33]. Testosterone is converted to the more active metabolite, DHT, by 5α-reductase [154]. DHT binds to the AR, and the DHT-AR complex transactivates genes with AR-responsive elements [154]. Two isozyme forms of 5α-reductase have been reported, with the type II enzyme (encoded by the SRD5A2 gene) primarily expressed in genital skin and the prostate [34]. One study revealed that this gene is more polymorphic than previously assumed, and that certain polymorphisms are restricted to AA men [35]. This was supported by the finding of SRD5A2 TA repeat alleles that are only present in high-risk AA men and not in lower risk CA and Asian men [155]. Thus, it has been proposed that certain steroid 5α-reductase enzyme variants encoded by SRD5A2 genes marked by particular TA repeat alleles may result in an elevation of enzyme activity, leading to an increased prostatic level of DHT, which may increase the risk for developing PCa.

Table 1. Summary of altered genetic polymorphisms and variants of key genes in cancer pathways, changing susceptibility to prostate cancer across race

Gene	Cancer Pathway	Racial Heterogeneity of Gene Mutations and Expressions	References
Serum Androgen		– AA shown to have higher mean serum testosterone levels (about 15%) than CA	17, 18
AR	Gene transcription	CAG and GGC repeat length	
		– expression of AR protein was 22% higher in the benign prostate and 81% higher in PCa in AA than CA	23
		– AA men tend to have significantly shorter repeats than CA men	24, 31, 32
		– among low risk of PCa (normal PSA and prostate examination), nearly twice as many AA have a CAG repeat length less than 20 compared with CA men	
SRD5A2	Androgen conversion (DHT)	TA repeat alleles	
		– present in only AA, not in CA or Asian	155
		A49T variants	
		– increase DHT production, particularly in AA and Hispanic	39
CYP17	Androgen synthesis	A1 and A2 alleles	
		– polymorphisms may have a role in PCa susceptibility in AA but not CA	52
		– A2 allele was slightly less frequent in AA versus CA, but another study had the opposite finding	39
CYP3A4	Androgen deactivation	G variant	
		– considerably more common among AA (>50%) than CA (<10%), Hispanic, or Asian	58 – 61
		– in CA, associated with a higher clinical grade and stage, especially if PCa was diagnosed at an older age (≥ 64), and is predictive of progression	
		– in AA strongly associated with PCa that had aggressive characteristics at diagnosis	67
		– after prostatectomy, increasing copies were found to be associated with worse progression-free survival among CA but had virtually no impact on AA	71
IGF-1 and IGFB-3	Growth factors	– AA men have been found to have higher IGF-1 and lower IGFB-3 levels	72
EGFR	Growth factor receptor/Signal transduction	CA repeat length	
		– the longer allele is significantly more common in Asian individuals and is associated with an 80% reduction in EGFR protein expression compared with the shorter allele	82, 83
		– EGFR overexpression in PCa is more common in AA (45%) than CA (18%)	80, 86
		– no correlation found in another study	87
		TK domain	
		– 4 novel missense mutations found: 3 in Koreans and 1 in CA but none in AA	88
EphB2	Tyrosinne kinase receptor/Tumor suppressor	K1019X mutation	93
		– higher in AA with a family history of PCa (15.3%) than CA controls (1.7%)	
		– associated with increased risk for PCa in AA with a family history	
		– risk for PCa was increased 3-fold among AA who carried at least one copy of the allele and had a family history of PCa	
BCL-2	Apoptosis	– linkage between increased cancer proliferation and BCL-2 positively seen in prostate tumors in AA but not in CA	94
MDM2	p53 regulator	– expression was significantly greater in CA than AA patients (78% CA, 45% AA)	110
short arm of chromosome 8 (8p22-23)	(potential) Tumor suppressor	short arm deletion	128 – 130
		– conflicting findings	
miRNAs	Regulation of transcription and translation	let-7c and miR30c	D. Hatcher and P. Lee, unpublished data
		– higher let-7c and 30c expression in PCa tissue in AA than in CA, but only let-7c remained statistically significant after normalization	
MSR1		common MSR1 sequence variants	
		– in AA, germline mutations was associated with an increased risk of PCa	152
		– in CA, five common sequence variants had significantly different allele frequencies among men with PCa compared with unaffected men, with each, except INDEL7, associated with an elevated risk for PCa	153
		– in AA, Asp174Tyr mutation is nearly twice as common among PCa patients compared with controls; however, none were associated with a significantly increased risk of PCa	112

Furthermore, the V89L and A49T variants of the SRD5A2 gene have been shown to alter the conversion of testosterone to DHT [36, 37]. While the V89L polymorphism is believed to decrease the production of DHT [38], the A49T variant is thought to increase its production, particularly in AA and Hispanic men [39].

CYP17: Located on chromosome 10, the CYP17 gene encodes the cytochrome P450c17a enzyme [40], which mediates both 17α-hydroxylase and 17,20-lyase activities at key points in testosterone biosynthesis in the gonads and adrenals [40]. The 5'-untranslated promoter region of CYP17 contains a polymorphic T-to-C substitution that gives rise to A1 (T) and A2 (C) alleles [41]. Some studies have indicated that the A2 allele may be associated with an increased risk of PCa [42-47]; however, other results have either been inconclusive [48, 49] or showed a possible increased risk from the A1 allele [50, 51]. The results of a meta-analysis suggest that CYP17 polymorphisms may have a role in PCa susceptibility in AA but not CA men [52]. The A2 allele was slightly less frequent in AA versus CA men, but a different study had the opposite finding [53]. Ultimately, there may be little difference in A2 frequency and a null effect of the CYP17 polymorphism on androgen levels.

CYP3A4: Cytochrome P450 3A4 (CYP3A4), a protein in the cytochrome P-450 supergene family, facilitates the oxidative deactivation of testosterone to biologically less active metabolites [54-56], the inhibition of which would result in increased levels of testosterone. CYP3A4 also has a role in the oxidative metabolism of finasteride [57] and could impact its effectiveness in PCa treatment. Studies of the CYP3A4 variant indicate that it may be a determinant of PCa risk. A germline genetic variant in the 5' regulatory region of the CYP3A4 gene (A to G transition) on chromosome 7 has been reported. This variant G allele (referred to as CYP3A4 G variant) was found to be considerably more common among AA men (gene frequency >50%) than CA (<10%), Hispanic, or Asian men [58-61]. Previous studies found little evidence of altered function in the CYP3A4 G variant [62-64], but studies later found it was associated with a higher clinical grade and stage, especially if PCa was diagnosed at an older age (≥ 64), and is predictive of progression among CA men. They expected to see a similar impact among AA men but did not [58-60]. In other research, the G variant was inversely associated with risk among men with less aggressive PCa [65, 66]. Another study found that among AA men, the CYP3A4 variant was strongly associated with PCa that had aggressive characteristics at diagnosis [67].

Although these observations support a role for the CYP3A4 variant as a biologic marker of the aggressiveness of PCa, laboratory investigations have found relatively little evidence of functional effects from this polymorphism [62-64, 68, 69]. However, among certain patients with PCa, several other SNPs in CYP3A4 and CYP3A5 are associated with risk [66, 70]. Elsewhere, in a follow-up study of men who underwent prostatectomy, increasing copies of the CYP3A4 variant were found to be associated with worse progression-free survival among CA men but had virtually no impact on AA men [71]. While the above data indicate that differences in CYP3A4 exist between AA and CA patients, a better understanding of androgen metabolism and signaling pathways is needed to understand the effect of the G variant in AA men.

Growth factors and receptors

The most studied growth factor receptors concerning the racial disparity of PCa are EGFR and EPHB2. In addition, AA men have been found to have higher IGF-1 and lower IGFB-3 levels, which may cause higher tumor growth with lower anti-tumor activity [72].

EGFR

The epidermal growth factor receptor (EGFR) plays a critical role in cellular proliferation, escape from apoptosis, and promotion of tumor cell invasion and is the target of anticancer agents, based on evidence that increased EGFR signaling is crucial for prostate carcinogenesis [73]. Both in vitro and in vivo studies have demonstrated that the EGFR signaling pathway is critical in the progression to androgen-independent disease [74, 75]. Moreover, studies have shown that EGFR inhibitors effectively hinder the growth of both androgen-dependent and androgen-independent PCa xenografts [76-78]. Several

studies have found an increase of EGFR expression in androgen-independent and metastatic PCa [79, 80] as well as after androgen ablation [81].

EGFR is shown to be related to PCa racial disparity through intronic dinucleotide (CA) repeats and EGFR overexpression [82, 83]. Studies have demonstrated major racial differences in a dinucleotide (CA)n repeat polymorphism in intron 1 of the EGFR gene [83, 84]. The number of CA repeats (which ranges from 14 to 21) has been found to be correlated with transcriptional activity [82, 85]. Specifically, it was shown that the longer allele is significantly more common in Asian individuals [83] and is associated with an 80% reduction in EGFR protein expression compared with the shorter allele [82].

EGFR overexpression in PCa is more common in AA than CA patients [80, 86]. We reported a significant association between EGFR overexpression and AA race (45% in AA versus 18% in CA) [86]. Although one group reported no correlation between EGFR expression and race [87], their conclusion was based on a small number of AA patients. In addition to its overexpression, we identified 4 novel missense mutations in the EGFR TK domain, 3 in Koreans and 1 in CA but none in AA patients [88]. Three of the four EGFR kinase domain mutations are oncogenic in nature.

EPHB2

The EphB2 gene encodes the EPHB2 receptor tyrosine kinase. The characteristics of EphB2 and its location near a suspected PCa locus make it a potential 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 EphB2 may be a tumor suppressor gene [89].

EphB2 maps to 1p36, which was previously shown to be linked with hereditary PCa among racially diverse families [90, 91], including AA [92]. One study evaluated the role of EphB2 in PCa susceptibility in AA men by screening the EphB2 gene for germline polymorphisms. They identified ten sequence variants in the EphB2 gene, including a common nonsense mutation, K1019X, among AA PCa patients. Their data show that the K1019X mutation in the EphB2 gene differs in frequency between AA and CA men and is associated with increased risk for PCa in AA men with a positive family history [93]. This variant was observed in much higher frequency among AA PCa patients than among healthy AA men. In fact, the risk for PCa was increased 3-fold among AA men who carried at least one copy of the K1019X allele and had a family history of PCa. Given its high frequency in hereditary cases, K1019X likely is associated with familial PCa in AA men.

Differences in apoptotic genes in relation to prostate cancer racial disparity

Anti-apoptotic Bcl-2

Studies show that altered expression of the BCL-2 gene may be an important factor underlying the greater aggressiveness of PCa in AA men [94]. This gene has a central role in preventing cancer cells from dying, via its anti-apoptotic effect, and its up-regulation in AA men may be responsible for PCa cell survival and resistance to therapies. Thus, the connection between BCL-2 positively and increased proliferation seen in prostate tumors in AA but not in CA men may contribute to the aggressive behavior of PCa in AA men [94].

MDM2

In response to stress, cells activate a complex pathway involving tumor suppressor p53 that is responsible for cell cycle arrest, DNA repair, and apoptosis as protection from the deleterious effects of mutation [95]. MDM2 is a key negative regulator of tumor suppressor p53, by targeting p53 for proteasomal degradation [96-98]. We previously reported that MDM2 overexpression was significantly associated with advanced stage PCa [99], a finding later reproduced by other investigators [100, 101]. Recent studies have also shown that inhibiting MDM2 expression enhances the effects of radiation and chemotherapy on PCa cells [102-104]. A single nucleotide polymerphism in the MDM2 promoter, SNP309, enhances transcriptional activation of MDM2 and has been associated with early onset of several types of cancer [105-109].

To determine if the MDM2 SNP309 polymorphism plays a role in the aggressive phenotype

seen in AA PCa, we examined the association between MDM2 SNP309 and MDM2 protein levels in PCa patients of different racial backgrounds [110]. Somewhat surprisingly, we found MDM2 protein expression was significantly greater in CA than AA patients (78% versus 45%, respectively). While MDM2 and AA ethnicity have both been associated with poor prognosis, the relationship between the two variables in our study was neither causative nor correlative. Thus, while MDM2 expression in PCa differs between AA and CA patients, the data does not support a role for the MDM2 SNP309 polymorphism in the development of aggressive PCa in AA patients.

Genetics variations between AA and CA prostate cancer

Evidence that PCa may be caused by multiple genes, interacting in complex manners, possibly with environmental factors, has continued to grow [1, 2, 9, 39, 46, 58, 71, 111-114]. There may be ethnic variation in the frequency of alleles that may be associated with PCa risk and/or progression. Although the incidence and mortality for PCa may differ among different racial groups, the increased risk for PCa attributed to family history of this disease is consistent across different racial backgrounds, supporting the possibility of a common genetic basis of disease [115]. The analysis of genetic alterations in PCa is challenging because PCa often has genetic and morphological heterogeneity and multifocality, the presence of more than one lesion of independent origin [116-119]. Linkage studies, to determine if the tumors in AA men are different from those in CA men, have identified susceptibility loci for PCa on several chromosomes and several candidate genes [9, 120].

Chromosome 8

The short arm of chromosome 8 (8p22-23) has been proposed as a potential location for one or more genes important in the development of PCa [121, 122]. The short arm of chromosome 8 is frequently deleted in both adenocarcinomas and PINs [123, 124], which has lead to the assumption that the inactivation of an unidentified tumor suppressor gene on 8p is involved in prostate tumor initiation [125-127]. Studies of chromosome 8p loss in AA and CA men have generated conflicting findings. One group [128] reported a racial difference in the distribution of 8p loss, but another group reported none [129]. Another group found no differences during both tumor initiation and progression, suggesting similar molecular events between CA and AA men [130]; however, they did find racial differences in the association between disease recurrence and several prognostic factors of cancer progression, including Gleason score, surgical margin, and TNM stage. This was a significant finding given the similar baseline profiles of the two groups.

miRNA

MicroRNAs (miRNAs) are a class of small, endogenous, non-coding RNAs that regulate gene expression at the levels of transcription and translation [131, 132]. miRNA inhibits translation of target genes involved in a variety of fundamental cellular processes including organ development, differentiation, and cancer formation [133-136]]. Functional studies of individual miRNAs have since shown that miRNAs can act as oncogenes or tumor suppressor genes [137-141]. We showed that miRNAs are differently dysregulated in neoplasms other than PCa, such as uterine leiomyomas between AA and CA women, indicating that miRNA expression is associated with the racial disparity of cancer [142]. In prostate, the expression of 5 miRNAs, miR-30c, miR-301, miR-219, miR-261, and miR-1b1, were reported racially different in benign prostate tissue [143]. We recently examined the expression of commonly dysregulated miRNAs in PCa in relation to race and revealed racial difference for the expression of let-7c and miR30c in AA prostate tissue (D. Hatcher and P. Lee, unpublished data). Thus, miRNA might play a role in the racial disparity of PCa.

Distinct gene expression and genome-wide copy number variation between AA and CA prostate cancer

Currently, we are taking a genome-wide approach to studying the more aggressive clinical behavior of PCa in AA patients compared to CA patients. Gene expression profiling with Affymetrix microarray revealed distinct clustering of patients by racial group (I. Osman, unpublished data). We also identified 27 chromosomal regions with significantly

different copy number changes between AA and CA patients. Copy number changes were also significantly associated with gene expression changes. 28 chromosomal regions were significantly different between the AA and CA PCa. 11 regions were more commonly altered in AA patients compared to CA patients [144]. This data further suggests there are distinct genetic differences contributing to racial difference in PCa.

PSA levels in AA and CA prostate cancer patients

The PSA test, approved by the FDA in 1986 for monitoring disease status and in 1992 for disease diagnosis, is performed on symptomatic and asymptomatic men in an effort to diagnose PCa early and to monitor disease recurrence and progression [145]. Past surveys of urologists revealed significant variation in the use of the PSA test [146], including racial disparities in PSA surveillance, with AA men half as likely as CA men to receive annual monitoring [147]. After the 1995 publication of clinical guidelines from the National Comprehensive Cancer Network, the American Urological Association, and the American College of Radiology, however, there has been an increase in evidence-based staging techniques and a decrease in racial disparities [148]. A recent study concluded that PSA testing is probably not able to explain current racial differences in PCa mortality rates [149].

Interestingly, recently a relationship was reported between serum PSA levels and polymorphisms in the PSA and AR genes [150]. Specifically, serum PSA levels increased by 7% with each decreasing AR CAG repeat allele size among individuals homozygous for a single nucleotide polymorphism in the PSA gene promoter. A recent study of the ERDA1 locus revealed that large CAG repeats are more common among Asian populations, less common in populations of European ancestry, and least common in African populations [151]. This pattern is very similar to that which was observed in the study of the AR trinucleotide repeats.

Other genes potentially involved in PCA racial disparity

MSR1

Recently, the macrophage scavenger receptor 1 (MSR1) gene has been proposed as a link between germline alterations in 8p and PCa [152, 153]. Both common sequence variants and rare germline mutations have been suggested as potential PCa susceptibility factors. Several rare germline mutations of the MSR1 gene were found to cosegregate with PCa, and at least one of the germline mutations was associated with an increased risk of PCa among AA men [152]. In a subsequent study of CA men, the same authors examined five common sequence variants of MSR1 and reported significantly different allele frequencies for each of the variants among men with PCa compared with unaffected men [153], with each, except INDEL7, associated with an elevated risk for PCa. An ensuing study examined each of these five common MSR1 sequence variants in AA men [112]. They found that the Asp174Tyr mutation is nearly twice as common among PCa patients compared with controls; however, after adjusting for age, none of the sequence variants were associated with a significantly increased risk of PCa, providing limited support for an association in AA men.

Conclusion

Though studies show a biological basis behind the racial disparity of PCa, more studies are needed. Current technologies will allow a more focused approach towards identifying those genetic and biological factors involved in the racial disparity of PCa, leading to the discovery of new prognostic markers and novel therapeutic approaches to this disease.

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Please address correspondences to: Peng Lee, MD, PhD, Department of Pathology, New York University School of Medicine, New York Harbor Healthcare System, 423 E. 23rd Street, 6139N, New York, NY 10010, (Tel)(212)951-3418, (Fax)(212)951-6341, E-mail: Peng.Lee@nyumc.org

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