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Genetic susceptibility to prostate cancer in men of African descent: implications for global disparities in incidence and outcomes

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Abstract

Introduction—Disparities in prostate cancer incidence and outcomes are a hallmark of the global pattern of prostate cancer, with men of African descent suffering disproportionately from this disease. The causes of these disparities are poorly understood.

Methods—A review of the literature was undertaken to evaluate the role that genetic susceptibility may play in prostate cancer etiology and outcomes, with a particular emphasis on disparties.

Results—The genetic contribution to prostate cancer is well established, and a number of candidate prostate cancer genes have been identified. Significant differences in the frequency of risk alleles in these genes have been identified across the major races. These allele frequency differences may in part explain an increased susceptibility to prostate cancer in some populations. In addition, non-genetic factors contribute significantly to prostate cancer disparities, and the cumulative contribution of both genetic and non-genetic factors to poor-prognosis prostate cancer may explain the poorer outcomes experienced by men of African descent.

Conclusions—Prostate cancer disparities are a function of genetic susceptibility as well as environment, behavior, and health care factors acting in the context of this genetic susceptibility. Elimination of global prostate cancer disparities requires a full understanding of the effects of all of these factors on prostate cancer etiology and outcomes.

Keywords

prostate cancer; African descent; genetics; disparities

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Introduction

Prostate cancer disproportionately affects men of African descent in terms of incidence, morbidity, and mortality. There are significant gaps in our knowledge about the factors that predict disparities in prostate cancer incidence and outcomes between men of African and European descent. This is true both in the United States as well as other geographic locations, including Africa and the Caribbean. In order to fully understand the source and solution to these disparities, it is imperative to integrate diverse scientific disciplines, methods, and analytic approaches to understand the multiple contributions to disparities in prostate cancer, including factors associated with the social environment (e.g., economic status, access to health care, social isolation), the physical environment (e.g., location or type of residence or medical care setting), behavior (e.g., attitudes, beliefs, and practices associated with prostate cancer screening), and biology (e.g., inherited genotypes that may affect the development of prostate cancer or predict the aggressiveness of a prostate tumor).

Evidence of global prostate cancer disparities

Prostate cancer has one of the highest incidences and prevalences of any cancer in the world, accounting for 6.9% of all cancers diagnosed. Prostate cancer accounts for 9.7% of all cancers in men, including 15% of cancers in developed countries and 4% of cancers in less developed areas of the world. It is also responsible for almost 6% of cancer deaths in men worldwide. About 600000 new cases of prostate cancer are diagnosed each year, and approximately 200000 deaths are attributed to prostate cancer. Three-fourths of prostate cancer cases occur in men over the age of 64 years.[1]

Prostate cancer rates vary significantly by geographical region, Table 1. The incidence of prostate cancer is highest in countries where prostate-specific antigen (PSA) screening for prostate cancer is common.[1] These rates are influenced greatly by the detection of latent or asymptomatic prostate cancers through the use of screening modalities. Screening with PSA has not been applied in all regions, including Africa, to the same degree as in the United States.

While rates of prostate cancer are high in Europe and North America, the incidence of prostate cancer is highest among men of African descent in North America and the Caribbean. African American men are at particularly high risk for prostate cancer. Recent SEER data (2006) indicate that the incidence of prostate cancer in African American men is higher than in any other group, with an age-adjusted incidence of 255.5 per 100000 versus 161.4 per 100000 in European Americans. African American men also present with more advanced disease at initial diagnosis,[2] and have a worse prognosis than white men.3 However, the reason for these differences is not completely understood. It has been hypothesized that genetics and environmental exposures may play a role in determining these high rates.4‚5

Like incidence, prostate cancer mortality rates are highest in populations of African descent. A study by Thompson et al[6] found that after controlling for prognostic variables, African American men were more likely than European American men to have inferior outcomes after receiving hormonal therapy for prostate cancer. This ethnic disparity suggests that there may be a biological difference in prostate cancer as it manifests in African Americans versus European Americans.

Reported prostate cancer rates are low in native Africans, perhaps due to underreporting of the disease. Although not reflected in many international reports, prostate cancer appears to be one of the most prevalent urological malignancies in native Africans.[7] Rates in East and West African populations have been reported to be higher than those in North Africa and

other developing countries. However, the validity of these rates in West African populations is not known, and it is possible that rates are substantially higher than those reported in the existing registries.[8]

Prostate cancer may pose a significant public health burden in some African countries, as the majority of newly diagnosed cases present with advanced disease, including poor differentiation of the tumor, metastasis, and neurological symptoms.[9-12] Diagnosis at this later stage of disease often is associated with poor prognosis, which has devastating effects in countries with limited medical resources.[9,12] Because of differences in screening practices which increase the number of low grade or asymptomatic cancers detected, prostate cancer survival is estimated at 80% in the United States compared to 40% in developing nations.[1] A combination of low socioeconomic status, late disease presentation, and limited health care access for prostate cancer treatment in many African countries may contribute to the poor prognosis that African men face after being diagnosed with prostate cancer.[13]

Because African and African American men have common ancestry, knowledge of prostate cancer in African men, and comparisons of prostate cancer in African American men and men of the African Diaspora may provide valuable clues about the causes, prevention and treatment of prostate cancer. International comparisons of prostate cancer rates are complicated by differences in prostate cancer screening, diagnosis and reporting systems.[11,14]

Research on prostate cancer disparities by ethnicity has revealed that there are ethnic differences across populations in terms of diagnostic characteristics and prognostic characteristics, with African Americans having an earlier age at diagnosis and higher PSA levels compared with European Americans.[10,15,16] However, these ethnic disparities are not explained entirely by inequities in socioeconomic status or access to an use of health care.[17]

Despite this evidence, the reasons for disparity in prostate cancer etiology and outcomes in men of African descent are not well understood. Previous research has largely identified individual factors that may be associated with prostate cancer risk or disparities, including family history, age, race, and possibly exposures. However, this research has not generally considered the interaction of multiple factors and the neighborhood context in which they act in determining the causes of disparities. A transdisciplinary approach that considers multiple causative agents may be required to fully understand disparities in prostate cancer and the translation of this information into meaningful disparities reduction approaches. Here, we focus on the possible role of genetic susceptibility in affecting prostate cancer disparities.

Genetic susceptibility

Genetic contribution to prostate cancer risk is well established. Men with one, two or three first-degree affected relatives have a 2-,5- and 11-fold increased risk of developing prostate cancer, respectively.[18] In a study of the risk of prostate cancer among 44788 pairs of twins in the Scandinavian countries, 42% of cases were attributed to inheritance, with the remainder considered to be most likely due to environmental factors.[19] These findings have been confirmed by other studies as well.[20,21] Epidemiological studies also suggested that about 9% of familial prostate cancer cases diagnosed by age 85 are caused by transmission of a rare high risk allele, and that this allele accounts for approximately half of the prostate cancer cases diagnosed before age 55.[18] Examples of the genes that may explain these effects are provided below.

Candidate androgen metabolism genes

Of the potential candidate gene pathways, a substantial amount of work has been focused on androgen metabolism genetics. Testosterone is a major determinant of prostate growth and differentiation. There are numerous lines of evidence that support the role of androgen metabolism in prostate cancer etiology. Circulating levels of androgens have been reported to be higher in populations at increased prostate cancer risk, including African American men,22 and lower in populations at decreased prostate cancer risk, such as Chinese men.23 Although serum levels of testosterone do not correlate well with prostate cancer risk,[24], serum levels of dihydrotestosterone (DHT) and other testosterone metabolites do correlate with prostate cancer risk.[22,]24 Second, there is abundant clinical evidence that androgens are related to the growth and development of prostate cancers. Androgen ablation in men with hormone-sensitive prostate cancer reduces tumor size, and decreases the associated disease burden.25 This evidence suggests that the disposition of testosterone may be important in determining prostate cancer risk.

There are several enzymes that determine the activation or inactivation of testosterone, which subsequently influences the signaling capability of testosterone metabolites in androgen-sensitive cells. These genes include the 5 alpha-reductase type II (SRD5A2) and the cytochromes p450 CYP3A4, CYP3A5 and CYP3A43. In addition, the androgen receptor (*AR*) gene encodes a ligand-activated receptor that mediates androgen signaling response.

The SRD5A2 gene encodes the steroid 5α-reductase type II, which converts testosterone to DHT. The valine to leucine missense variant at codon 89 (V89L) and the alanine to threonine missense variant at codon 49 (A49T) are common SRD5A2 variants that have been associated with prostate cancer etiology or severity.[26-]31 The V89L polymorphism on the SRD5A2 is believed to decrease the conversion of testosterone to DHT32 while A49T is believed to increase the conversion of testosterone to DHT.30 However, associations of prostate cancer risk involving these variants have not been consistent in all studies.[29,33-40]

The CYP3A multigene family lies in a region of chromosome 7q21-q22, which includes CYP3A4, CYP3A5, CYP3A7 and CYP3A43 in addition to pseudogenes. Only CYP3A4, CYP3A5, CYP3A7, and CYP3A43 are expressed in adults. Previous reports suggested that linkage disequilibrium exists at the CYP3A locus.[41-43] Linkage disequilibrium between CYP3A4 and CYP3A5 in particular, suggests that associations at one locus could be the result of causative effects at the other locus.[42]

The CYP3A genes are involved in the metabolic deactivation (hydroxylation) of testosterone.[44,]45 These genes convert testosterone to 2β-, 6β-, or 15β-hydroxytestosterone, and therefore shunt testosterone away from the more biologically active DHT. However, the function of CYP3A4*1B has been controversial. In addition to epidemiological evidence that CYP3A4*1B is associated with prostate cancer, the basic science literature has not consistently supported a functionally significant effect. A number of authors have studied the relationship of CYP3A4 expression or function of CYP3A4*1B.46-52 Most of these authors concluded that no biologically meaningful effects existed given the small magnitude of effects that were observed. However, almost all studies have reported consistent elevations in expression associated with CYP3A4*1B in the range of 20%-200% increase over the consensus CYP3A4*1A.

CYP3A5*1 is the only CYP3A5 allele to date that produces high levels of full length CYP3A5 mRNA and expresses CYP3A5.[41] The more common CYP3A5 polymorphism in European Americans, CYP3A5*3, produces an aberrantly spliced mRNA with a premature stop codon. Therefore, there is ample reason to believe that the CYP3A5 alleles studied here

could have a functionally meaningful effect on disease etiology. CYP3A5*1 has been inversely associated with prostate cancer.[43]

In addition, reports have shown a significant association of CYP3A4 and CYP3A43 with occurrence of prostate cancer.[42] While CYP3A5*1 had no effect on disease occurrence alone in that study, CYP3A43 increased risk of disease in men with a family history of disease, while CYP3A4*1B had an overall protective effect. It is unclear why CYP3A43 is associated with prostate cancer when examined alone. CYP3A43 is preferentially expressed in the prostate,[53] but it has rarely been studied. As a result, there is not enough basic science about these genes that can explain the associations with family history-positive prostate cancer. However, one might speculate that this variant is more commonly inherited in men who have a family history of prostate cancer and may be a candidate hereditary gene for prostate cancer.

When CYP3A4 and CYP3A43 were considered in pairwise interactions in our earlier study to determine the effect of having genotypes with at least one CYP3A4*1B and at least one CYP3A43*3 allele, there were highly significant protective effects for early onset prostate cancer.[42] This is an interesting finding, as it suggests an association that may have its greatest impact in African Americans. While only 4% of European Americans carry this allelic combination, it was a more common haplotype observed in our African American sample (35%). Therefore, a subset of men who carry the CYP3A4*1B and CYP3A43*3 combination and are likely African American are significantly less likely to have been diagnosed with prostate cancer before age 60. The reasons for this association are not understood, as African Americans, in general, are at high risk to be diagnosed with prostate cancer prior to the age of 60 years.

The androgen receptor (AR), located on the X chromosome, plays a major role in the development and functioning of the prostate gland. AR is expressed in all histologic types and stages of prostate cancer and its transactivation domain is highly polymorphic.[54] Several regions of repetitive polymorphic DNA sequences exist in AR, including CAG trinucleotide repeats encoding polyglutamine residues and GGN repeats encoding polyglycine residues. Several studies have demonstrated an inverse association between the number of CAG and GGN repeats and risk of prostate cancer, advanced cancer, and risk of associated mortality.[55-62] Still, some studies suggest that a postivie association exists between prostate cancer and long GGN repeats in combination with short CAG repeats62 Vijayalakshmi.[63] The combination of GGN/CAG repeats may be the key to understanding how the AR is functioning to promote or inhibit prostate cancer development and progression.[62-64]

Race-specific effects

Genotypes involved in prostate cancer etiology differ significantly across ethnicities. For example, the allele frequencies in candidate prostate cancer susceptibility genes such as CYP3A4 and SRD5A2 differ substantially by ethnicity. We have reported a 4-5-fold higher rate of this CYP3A4 vriant in African Americans relative to European Americans.65 Similarly, Ross et al66 and Jaffe et al29 have reported significant ethnic variation in SRD5A2 genotype frequencies that rack with race-specific differences in prostate cancer risk. More recently, Zeigler-Johnson et al[67] reported significant differences in the frequency of V89L variant in the SRD5A2 gene by ethnicity, with an L allele frequency of 30% in European Americans, 27% in African Americans, 19% in Ghanaians, and 18% in Senegalese ($p = 0.002$). Differences were also observed for CYP3A4*1B, with *1B frequencies of 8% in European Americans, 59% in African Americans, 81% in Ghanaians, and 78% in Senegalese ($p = 0.0001$). When these data were pooled with data from previous studies, significant ethnic differences were observed for each of the polymorphisms. Overall, Asians were least likely to have SRD5A2-V89L and CYP3A4*1B while Africans,

followed by African Americans, were most likely to have those alleles. These results suggest that ethnicity-specific differences in allele and genotype frequencies exist for candidate prostate cancer genes. They further suggest that prostate cancer risk across ethnicity (lowest in Asians and highest in African Americans) may be correlated with allele frequencies at candidate prostate cancer susceptibility genes. It remains unknown whether or how these inherited genotypes may explain prostate cancer risk and variability in that risk across racial or ethnic groups. However, these findings suggest that African populations may be at genotypically increased prostate cancer risk, even though the actual magnitude of risk is not well characterized. Because so little is known about the genetics of prostate cancer in Africa, research in this area will provide insight into disease etiology and ethnic disparities worldwide that are associated with prostate cancer incidence and mortality.

Non-candidate susceptibility genes identified by other methods

Family-based studies have yielded numerous prostate cancer susceptibility genes, including ELAC2/HPC2 at 17p (MIM 605367),68 2′-5′-oligoadenylate-dependent RNase L (RNASEL/HPC1) (MIM 180435)69 and macrophage scavenger receptor 1 (MSR1) (MIM 153622).70 Two of these genes, RNASEL and MSR1 have been shown to play a major role in inflammation and innate immunity.

2′-5′-oligoadenylate-dependent RNase L (RNASEL) is a constitutively expressed latent endonuclease that mediates the antiviral and proapoptotic activities of the interferon-inducible 2-5A system.[71,72] Initial linkage analysis studies revealed the presence of two deleterious mutations, Met1Ile and Glu265X in African American and European American families, respectively, that segregated with the disease.69 Glu265X was also associated with hereditary prostate cancer in other patients from European origin,73 while Met1Ile was not found in other studies. Two additional deleterious frameshift mutations, 471delAAAG and 147dupCAAT, in this gene was detected in Ashkenazi Jewish and Asian Indian men, respectively.[74] Several missense variants in RNASEL have also been detected.[73,75] One of these variants, Arg462Gln, was implicated in up to 13% of prostate cancer cases using a family-based case-control study.[76] Although there is a low frequency of deleterious mutations in RNASEL, functional studies strongly implicate this gene in the disease. Prostate cancer patients carrying the Glu265X or the 471delAAAG mutation showed loss of heterozygosity of the wild type allele in microdissected tumor DNA,[69,74] while the Arg462Gln had a significantly lower RNASEL enzymatic activity compared to the normal protein.[76]

Macrophage scavenger receptor 1 (MSR1; Chromosome 8p22) is a member of an expanded family of membrane receptors collectively termed scavenger receptors. MSR1 can bind many chemically modified molecules ranging from bacteria to modified lipoproteins. Correspondingly, MSR1 has been associated with a wide variety of normal and pathological processes, including inflammation, innate and adaptive immunity, oxidative stress and apoptosis.[77] MSR1 maps to the 8p22 chromosome region, wich is commonly deleted in prostate cancer.78 Six rare missense variants and one nonsense mutation within MSR1 were observed to co-segregate with the disease in hereditary prostate cancer families.70 Furthermore, the prevalence of MSR1 mutations in prostate cancer cases of European and African American descent was substantially higher compared to unaffected men.70 Arg293X and Ser41Tyr were the most common mutations detected among prostate cancer patients of European and African American descent, respectively.[79]

ELAC2/HPC2 was predicted to encode an evolutionarily conserved, metal-dependent hydrolase, which could partially explain environmental effects on human prostate epithelial cells by postulating differential interactions with environmental exposures.[68] ELAC2 was also shown to encode a 3′ processing endoribonuclease, an enzyme responsible for the

removal of a 3′ trailer from precursor RNA[80] and to interact with γ-tubulin, a component of the mitotic apparatus,[81] suggesting a possible role for ELAC2 in cell cycle control. Initial sequence analyses of the ELAC2 gene identified rare mutations and two common missense changes, Ser217Leu and Ala541Thr that were reported to be associated with prostate cancer risk.[68,82,83] However, confirmation of these results has been difficult with only weak consensus among studies.[84 85]

Race-specific effects

Rennert et al[86] observed significant differences in ELAC2, RNASEL and MSR1 allele frequencies by race. Although no significant association has been found with prostate cancer risk overall, certain effects for MSR1 IVS7delinsTTA and RNASEL Arg462Gln were observed when stratified by race, family history or disease severity in both African American and European American men. No association between the common ELAC2 Ser217Leu and Ala541Thr sequence variants and prostate cancer risk was found. Moreover, Ala541Thr was rare among African Americans compared to European Americans, and therefore was unlikely to explain the higher rate of prostate cancer in the African American racial group. RNASEL Arg462Gln gene variation is of particular interest since it was clearly associated with reduced functional activity, and although not statistically significant, it was more common among African American cases compared to controls (0.12 versus 0.16), Table 2. When stratified by prostate tumor characteristics, Arg462Gln was associated with low-grade (OR = 1.5, 95% CI 1.04-2.2) and early-stage (OR = 1.5, 95% CI 1.02-2.1) disease in family history negative European Americans, while in family history positive individuals, Arg462Gln was inversely associated with low grade (OR = 0.43 95% CI 0.21-0.88) and low stage (OR = 0.46 95% CI 0.22-0.95) disease. In African Americans however, Arg462Gln was associated with positive family history high stage disease (OR = 14.8 95% CI 1.6-135.7).[86]

These conflicting associatons among the different studies may be explained by clinical and genetic heterogeneity of prostate cancer, heterogeneity of study populatons, incomplete penetrance, or non-genetic etiologies (e.g., environmental factors). Screening practices for prostate cancer and the inclusion of patients with clinically insignificant disease probably play a role as well. Follow-up meta-analysis studies on the association of prostate cancer with ELAC2, RNASEL, or MSR1 variants found no association or very weak effects of gene variations in these genes with prostate cancer risk overall in either European Americans or African Americans.[84,85,87-90] However due to power constrains, these studies did not evaluate gene variation effects by disease or prostate tumor characteristics. Taken together, these results suggest that although MRS1 and RNASEL do not seem to be associated with disease risk overall, they may still influence disease severity and that this effect possibly varies by family history of cancer and by racial background.

8q24 locus

Recently, a genome-wide linkage study in Iceland91 and an admixture study among African Americans[92] independently detected markes associated with prostate cancer risk on chromosome 8q24. Of these, a signel nucleotide, rs1447295, at 8q24.21 (denoted region1) was most strongly associated with prostate cancer risk in pooled case-control studies of Caucasians from several countries.[91].93-95 Weaker effects, however, were noted for this SNP among African American men.93 SNP marker rs1447295 was also reported to be associated with prostate cancer aggressiveness, but this effect varied widely by popylation and study group.[96,97] Moreover, a second region approximately 350 kb upstream to the previously reported rs1447295, denoted region 2, also demonstrated strong association with prostate cancer[93,94] in both Caucasians and African Americans. These effects were independent of those detected for region 1. Finally, a third region located between region 1

and region 2 approximately 70 kb centromeric to rs1447295 was also found to be strongly associated with prostate risk in alarge nested case-control study of Caucasians, suggesting the presence of at least two independent loci within 8q24 that may contribute to prostate cancer riks in this population.[95]

Relationship of genotypic susceptibility and other factors

Genetic susceptibility represents only one piece of the very complex nature of prostate cancer etiology. Underlying differences in susceptibility to develop prostate cancer is manifest through exposure to environmental agents, social environmental and neighborhood context, behavior, access to quality health care, and other factors. To fully understand the causes of prostate cancer diparities across groups, a comprehensive approach to the study of many factors involved in prostate cancer causation is required.

Environmental exposure

Relatively few exposures have been consistently associated with prostate cancer risk, and very little information about the role of exposures in establishing prostate cancer disparties is available. Thus, expanded definitions of “the environment” could be developed to include social environment (e.g., socioeconomic status, access to health care, social isolation, cultural beliefs and values); physical environment (e.g., location or type of residence, access to computer and internet resources, or medical care); and behavioral facrtors (e.g., attitudes, beliefs and practices associated with cancer screening). Thus “environment” could include both individual-level factors as well as neighborhood- or community-level factors using a multilevel approach. For example, neighborhood-level factors could include housing density, measures of social captical such as cultural/civic participation or neighborhood cohesiveness, neighborhood stability such as the percent of rental housing, measures of deprivation such as violent crime rate, and social conditions such as violent crime rate, and social conditions such as percent of individuals in the neighborhood who live below the poverty level or average educational attainment. Similarly, institutional factors such as health care patterns, access to care, insurance, and type and quality of health care that has been accessed could also be considered. In general, research has focused on individual-level variables, and therefore has not been able to address the larger context in which genes, biological factors, or individual environmental exposures are acting.

Health care

Access to and choice of prostate cancer treatment may have a profound effect on disparities in outcome.[98] African American men are more likely than European American men to undergo watchful waiting instead of aggressive therapy for localized prostate cancer[99-101] and differences in treatment and mortality persist after adjusting for individual factors such as stage, grade, and socioeconomic status.[99] This remains true despite the observation that mortality differences can be explained by lower rates of aggressive treatment in African American men.[102,103] A strong relationship exists between cancer outcomes and hospital and provider characteristics, prevalent distrust of research/teaching hospitals among African Americans, and links between residential segregation and racial alienation.[98] However, there remain little data about the role of social environment, including factors that affect access to care, contributes to racial disparities in access to quality prostate cancer treatment.

Social environment and behavior

Social environment, including culture, is increasingly recognized as having an important impact on cancer outcomes in ethnically diverse population.[98] Environmental stressors such as life stress, racism, and discrimination may have a deleterious impact on physiological (i.e., immune functioning, cardiovascular reactivity) and behavioral (i.e., coping efforts,

dietary behaviours, smoking) responses to prostate cancer.[104] While African ancestry is a marker for other factors that might better explain quality of life, ethnicity alone does not provide information on the causes of these disparities. Incorporating biological and other factors into the application of assessment of risk and outcomes could improve interventions that could be addressed through psycho-educational approaches designed to facilitate stress reduction and increased confidence to cope with treatment-related side effects98.

Implications for prostate cancer disparities

Our limited knowledge about the genetic and other biological events that cause prostate cancer disparities presents a major barrier to eliminating these disparities. The accumulating knowledge of the human genome provides an opportunity to apply knowledge of carcinogenic mechanisms to the problem of prostate cancer disparities. The incorporation of biomarkers in cancer disparties research provides new opportunities for clinical and public health research and practice, and has the potential to catalyze needed improvements in the prevention and management of cancer to eliminate cancer disparities.

Prostate cancer may be a major cancer burden in African men, so it will be important to understand etiological factors including inherited genotypes that confer risk of developing prostate cancer. Understanding prostate cancer in Africa may inform us about inherited predisposition, modifiable risk factors, and disease prevention in the high risk African American population. Additionally, knowledge of the interactions of prostate cancer susceptibility genes, environment, and behavior could be used to identify individuals at risk of developing prostate cancer with poor outcomes for heightened screening or prevention modalities, and to identify optimal treatment strategies for men of African descent.

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TABLE 1

Sample prostate cancer incidence and mortality rates (per 100000)

Region	Subgrouping	Age-specific incidence	Age-specific mortality	Source
World		25.3	8.2	
Developed countries		56.2	13.5	IARC[105]
Developing countries		9.4	5.2	
Africa	Eastern Africa	13.8	11.8	
	Middle Africa	24.5	21.1	
	Northern Africa	5.8	4.9	IARC[105]
	Southern Africa	40.5	22.4	
	Western Africa	19.3	16.0	
Americas	The Caribbean	52.4	28.0	IARC[105]
	Brazil	53.2	15.8	
	United States: all races	168.0	27.9	
	African American	255.5	62.3	
	European American	161.4	25.6	SEER, 2004
	American Indian/ Alaskan Native	68.2	21.5	
	Asian or Pacific Islander	96.5	11.3	
	Hispanic	140.8	21.2	
Asia	Eastern Asia	3.8	1.9	
Europe	Northern Europe	57.5	19.7	IARC[105]
	Western Europe	61.6	17.5	
Oceania	New Zealand	79.9	18.1	

TABLE 2

Allele frequencies and SIFT analysis of missense polymorphisms in ELAC2, MSR1 and RNASEL genes

Gene	Nucleotide sequence variant	Amino acid change	Substitution probability (Pi)	Allele frequency (total no. of alleles in sample)			
				African American		European American	
				Controls	Cases	Controls	Cases
ELAC2/	650C > T	Ser217Leu	0.15	0.228 (254)[a]	0.211 (180)	0.296 (656)	0.301 (1020)
HPC2	1621G > A	Ala541Thr	0.26	0.004 (268)[a]	0 (190)	0.027 (698)	0.033 (1072)
MSR1	520G > T	Asp174Tyr	0.13	0.015 (266)[a]	0.022 (186)	0 (696)	0 (1064)
	876C > T	Arg293X	0	0 (262)	0 (166)	0.012 (694)[b]	0.007 (994)
	−14,742A > G	None	N/A	0.269 (260)[ab]	0.253 (186)[b]	0.105 (686)	0.105 (1060)
	IVS5-59C > A	None	N/A	0.012 (246)[a]	0.006 (170)	0.059 (628)	0.050 (968)
	IVS7delTTA	None	N/A	0.264 (220)[a,b]	0.218 (156)	0.057 (562)	0.045 (894)
RNASEL/	793G > T	Glu265X	0	0 (268)	0 (188)	0.001 (714)	0.003 (1080)
HPC1	354C > T	None	N/A	0.004 (266)	0 (182)	0.003 (682)	0.002 (1002)
	1385G > A	Arg462Gln	0.02	0.119 (252)[a]	0.159 (176)	0.361 (642)	0.370 (1010)

[a] Frequency in control groups differs by race (two-sided Fisher's exact tests: $p < 0.05$).

[b] Deviations from Hardy-Weinberg proportions based on $\chi 2$. Test at $p < 0.05$.