Genetic variations in androgen metabolism genes and associations with prostate cancer in South African men

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Background. In South Africa white men have the highest incidence of prostate cancer (PCa), coloured (mixed ancestry) men have an intermediate incidence, and low incidences are reported for black and Asian men. It has been suggested that ethnic differences in incidence and mortality of PCa are related to genetic variations in genes that regulate androgen metabolism. We investigated the role of genetic variants in the androgen metabolism genes and the probability of developing PCa in South African coloured and white men.

Methods. Genotype and allele counts and frequencies of single nucleotide polymorphisms (SNPs) in *CYP3A5*, *CYP3A4* and *CYP3A43* were assessed in coloured men (160 case individuals, 146 control individuals) and white men (121 case individuals, 141 control individuals).

Results. A genetic association indicating an increased probability of developing PCa was observed with the G allele of the SNP rs2740574 in *CYP3A4* in coloured men, the A allele of rs776746 (*CYP3A5*) and the G allele of rs2740574 (*CYP3A4*) in white men, and the G allele of rs2740574 and the C allele of rs501275 (*CYP3A43*) in the combined ethnic groups analysis. In addition, we identified allele combinations (termed haplotypes) with significantly higher frequencies in the PCa case individuals than in the control individuals.

Conclusions. The findings support the role of variants in genes that regulate androgen metabolism and the probability of developing PCa. The study paves the way to identify other genetic associations in South African men, and to establish genetic profiles that could be used to determine disease progression and prognosis.

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Prostate cancer (PCa) is the second most common histologically diagnosed malignancy in South African men, with an estimated annual incidence rate of 17.8/100 000.[1] The age-standardised incidence rate (ASIR) of PCa in South African men in the 55 - 59-year age range is 56/100 000; this figure rises to 455/100 000 in men older than 75 years.[1] In North America, incidences of PCa are the highest in black men, intermediate in white men and the lowest in Asian men.[2] In South Africa, the highest incidence is reported in white men (Northern European ancestry) and the lowest in black and Asian men, with an intermediate incidence reported for coloured (mixed ancestry) men.[1] However, substantial under-diagnosis and under-reporting may be the reason for the low incidence in South African black men.[3]

It has been suggested that ethnic differences in incidence and mortality of PCa are related to genetic variations in genes that regulate androgen metabolism. Studies addressing this hypothesis have demonstrated that genes that regulate androgen metabolism are associated with PCa susceptibility. Findings include genes that encode proteins belonging to the cytochrome P450 (CYP) family (a group of enzymes that are involved in the metabolism of xenobiotics, steroids, vitamins and sex hormones).[4] The CYP3A subfamily is a group of enzymes that are key deactivators of testosterone. The CYP3A locus consists of four genes, *CYP3A5*, *CYP3A7*, *CYP3A4* and *CYP3A43*, each gene containing 13 exons and located on chromosome 7q21-22.1. We did not screen *CYP3A7* because it is predominantly expressed in fetal stages of development[4] and we therefore considered it unlikely to play a role in the pathogenesis of PCa.

The CYP3A5 enzyme catalyses the 6β-hydroxylation of testosterone, producing a less biologically active form of testosterone that is more readily eliminated.[4] The single nucleotide polymorphism (SNP) rs776746 (6986A>G; in some publications the A allele = *CYP3A5*1* and G allele = *CYP3A5*3*) in intron 3 creates a cryptic splice site resulting in a messenger ribonucleic acid (mRNA) that is more unstable and more rapidly degraded than the mRNA formed by the wild-type A allele.[4] In Finnish men, the rs776746 A allele was significantly associated with PCa bone metastases.[5]

The CYP3A4 enzyme is involved in the oxidation of testosterone to 2β-, 6β- or 15β-hydroxytestosterone. For the SNP rs2740574 (-392A>G; the A allele = *CYP3A4*1A* and G allele = *CYP3A4*1B*) in the 5′ regulatory region of the gene, the G allele was initially shown to be associated with PCa in white and black American men,[6] which was replicated in subsequent investigations. In black American men, no association was found between the rs2740574 A or G alleles, or other SNP alleles in *CYP3A4*, and the probability of developing PCa.[7]

CYP3A43 is expressed predominantly in the prostate and less significantly in the testis, kidney and pancreas.[8] The CYP3A43 enzyme is inactive, but splicing of *CYP3A43* exon 1 to *CYP3A4* and *CYP3A5* exons produces hybrid mRNA products, of which the longest *CYP3A43*/*CYP3A4* chimeric isoform can hydroxylate testosterone.[8] An association was demonstrated between the G allele of rs680055 (60084G>C [Pro340Ala]) and the probability of developing PCa in white American men with a positive family history of the disease,[6] while an association was observed between the G allele and probability of PCa in black American men, after adjusting for age and pack-years of cigarette smoking.[9] A significant association was demonstrated between the rs680055 G allele and probability of

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developing PCa in white American men with a history of benign prostatic hyperplasia (BPH).[10] We did not screen rs680055 and chose to screen the SNP rs501275 (75726T>C) in *CYP3A43* because we considered it to be more polymorphic in our screening population of coloured and white men.

Little PCa genetic research has been undertaken in South Africa. We have reported associations between SNP alleles in a gene involved in mediating inflammatory responses and the probability of developing PCa in South African men.[11] In the present study, we screened genetic variants in the androgen metabolism genes *CYP3A5*, *CYP3A4* and *CYP3A43* to determine whether these play a role in the development of PCa and report findings of our case-control genetic association study of self-reported South African coloured and white men.

Methods

Study population

Unrelated men from the South African coloured and white ethnic groups were enrolled in the case-control study to determine genetic factors associated with the probability of developing PCa. The study comprised 160 coloured individuals (mean age 69 (range 47 - 88) years) and 121 white individuals (mean age 71 (range 48 - 90) years) with histologically confirmed PCa. All were from the Western Cape province of South Africa and had undergone radical prostatectomy, transurethral resection of the prostate or prostatic biopsy in the Department of Urology at Tygerberg Hospital. Control individuals were selected from subjects admitted to the same hospital during the same period and comprised 146 coloured men (mean age 65 (range 52 - 91) years) and 141 white men (mean age 67 (range 52 - 88) years) from the same geographical region.

Blood samples were collected from each subject. Clinical characteristics, including prostate-specific antigen (PSA), Gleason grade, tumour node metastasis (TNM) stage, age at diagnosis and family history, were obtained from medical records. Controls had PSA levels ≤2.5 ng/ml and normal findings on digital rectal examination (DRE). Subjects were informed and gave written consent to participate and allow their biological samples to be genetically analysed, according to the Helsinki Declaration. The study was approved by the Faculty of Health Sciences Human Research Ethics Committee, Stellenbosch University.

SNP genotyping

Genomic deoxyribonucleic acid (DNA) was extracted from whole blood using a QIAamp DNA kit (Qiagen, GmbH). The polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) method used to determine the *CYP3A4* rs2740574[12] and *CYP3A5* rs776746[13] genotypes has been reported previously. For PCR amplification of the *CYP3A43* rs501275 polymorphism we used the primers F 5′-GTCAATGGCAATTTTCTGTT-3′ and R 5′-CTGTCTTCACAAACCAGATG-3′ in a 50 µl reaction mix containing 50 ng of genomic DNA, 120 ng of each of the forward (F) and reverse (R) primers, 200 µM of dATP, dCTP, dGTP and dTTP, 1.5 mM $MgCl^2$, 1 µl 10 × Taq DNA polymerase buffer, and 0.5 U Taq DNA polymerase. PCR conditions were as follows: 7 minutes at 94°C; 30 cycles of 30 seconds at 94°C, 30 seconds at 52°C, and 45 seconds at 72°C; and finally 5 minutes at 72°C. The 210 base pair (bp) PCR amplification product was digested with the restriction enzyme RsaI (Promega, USA) in a volume of 10 µl for 2 hours at 37°C. The restriction fragments were analysed in a 3% agarose gel stained with ethidium bromide. A fragment at 210 bp corresponds to a homozygous wild-type genotype (TT) and two fragments at 119 bp and 91 bp correspond to the homozygous variant genotype (CC). Three fragments at 210 bp, 119 bp and 91 bp represent the heterozygous genotype (TC).

Statistical analysis

Genotype and allele counts and frequencies were calculated for each SNP. Haplotype frequencies were inferred for a haplotype consisting of allele combinations, one allele from each gene. Each polymorphism was tested in the control individuals to confirm that they were in Hardy-Weinberg equilibrium (HWE). Linkage disequilibrium (LD) (the concept of alleles inherited together at a frequency higher than by chance) between adjacent polymorphisms was assessed. We tested each SNP for an ethnic-genetic interaction for probability of developing PCa. For each SNP in each ethnic group, we tested additive allelic association with PCa, adjusted for age. This provided *p*-values and estimated allelic odds ratios (ORs), which are the number with which the odds are multiplied, for each additional copy of a specific allele. We adjusted for ethnicity and age in the combined group, and because the South African coloured population is mixed, we corrected for their population stratification by multiplying the obtained *p*-values by an inflation factor (λ) of 3.06, which we had determined previously in a study on the same group.[11] We used the same inflation factor to correct the *p*-values for the combined ethnic groups, which is very conservative because it is only required for the coloured individuals in the combined group. PCa ORs (and 95% confidence intervals (CIs)) for specific haplotypes compared with the reference (highest frequency) haplotype were estimated, as previously described.[11] We used logistic regression models to test the additive allelic association with PCa and estimate the ORs (with corresponding 95% CIs), while adjusting for age by including it as a covariate in the models. Logistic regression was used to test genotype-ethnicity interaction on the probability of developing PCa, and to test haplotype association with PCa. Analyses were done in R, a language and environment for statistical computing available from http://www.R-project.org. The R packages genetics, LDheatmap and haplo.stats were used.

Results

Genotypes were compared within each of the two ethnic groups for rs776746, rs2740574 and rs501275. All three SNPs were in HWE among the controls in both populations (results not shown). For the purpose of this study, the rs776746 A allele was considered the variant allele because it occurred at a lower frequency in both populations, although biologically it produces the wild-type protein product.

For the coloured group, after adjusting for age, a significant association with PCa was observed for the rs2740574 G allele (OR 1.93; 95% CI 1.29 - 2.95; p=0.0014) (each G allele almost doubles the odds of PCa) and the rs501275 C allele (OR 1.52; 95% CI 1.01 - 2.31; p=0.0429) (Table I). However, after correcting for population stratification, only the effect of the rs2740574 G allele remained significant (p=0.0043) (Table I). For the white group, after adjusting for age, a significant association with PCa was observed for the rs776746 A allele (OR 1.87; 95% CI 1.04 - 3.80; p=0.0358) and rs2740574 G allele (OR 5.11; 95% CI 2.50 - 11.44; p<0.0001). There was no significant interaction between ethnicity and genotype on case-control status. We could therefore combine the two ethnic groups, which showed significant associations with PCa with the variant alleles of all three SNPs, although only the association of the rs2740574 G allele and rs501275 C allele remained significant after correcting for the effect of population stratification in the coloured group (Table II). Across the case and control groups in both ethnic groups we observed statistically significant LD between the SNPs (results not shown).

In the white group, a highly significant difference in frequency of the most common haplotype, GAT, was observed between case and control individuals (p<0.0001) (Table III). The inferred frequency was 88% in the control group versus 71% in the case group. In coloured

Table I. Genotype and allele count and frequency distributions and age-adjusted additive allelic ORs with 95% CIs and *p*-values for prostate cancer among *CYP3A5*, *CYP3A4* and *CYP3A43* SNPs in South African coloured and white men

		Coloured				White			
SNP	Genotype	Cases (*N*=160) *N* (%)	Controls (*N*=146) *N* (%)	OR (95% CI)	*p*-value	Cases (*N*=121) *N* (%)	Controls (*N*=141) *N* (%)	OR (95% CI)	*p*-value
CYP3A5	GG	46 (29)	55 (38)	1.00		94 (78)	125 (89)	1.00	
rs776746	GA	77 (48)	59 (40)			24 (20)	14 (10)		
	AA	37 (23)	32 (22)			3 (2)	2 (1)		
	A allele	151 (47)	123 (42)	1.26 (0.91 - 1.73)	0.1588 30 (12) 0.4859*		18 (6)	1.87 (1.04 - 3.80)	0.0358
CYP3A4	AA	63 (39)	87 (60)	1.00		84 (69)	131 (93)	1.00	
rs2740574	AG	82 (52)	56 (38)			35 (29)	10 (7)		
	GG	15 (9)	3 (2)			2 (2)	0		
	G allele	112 (35)	62 (21)	1.93 (1.29 - 2.95)	0.0014 39 (16) 0.0043*		10 (4)	5.11 (2.50 - 11.44)	<0.0001
CYP3A43	TT	79 (49)	89 (61)	1.00		98 (81)	124 (88)	1.00	
rs501275	TC	71 (45)	53 (36)			23 (19)	17 (12)		
	CC	10 (6)	4 (3)			0	0		
	C allele	91 (28)	61 (21)	1.52 (1.01 - 2.31)	0.0429 23 (10) 0.1312*		17 (6)	1.83 (0.92 - 3.74)	0.0869

*Corrected *p*-value for the effect of population stratification in coloured men obtained by multiplying age-adjusted value by an inflation factor λ = 3.06 (Fernandez *et al.*, 2008[11]).

Table II. Genotype and allele count and frequency distributions and age and ethnicity-adjusted additive allelic prostate cancer ORs with 95% CIs and p-values among *CYP3A5*, *CYP3A4* and *CYP3A43* SNPs in a combined group of coloured and white South African men

SNP	Genotype	Cases (*N*=281) *N* (%)	Controls (*N*=287) *N* (%)	OR (95% CI)	*p*-value
CYP3A5	GG	140 (50)	180 (63)	1.00	
rs776746	GA	101 (36)	73 (25)		
	AA	40 (14)	34 (12)		
	A allele	181 (32)	141 (25)	1.37 (1.04 - 1.82)	0.0262 0.0802*
CYP3A4	AA	147 (52)	218 (76)	1.00	
rs2740574	AG	117 (42)	66 (23)		
	GG	17 (6)	3 (1)		
	G allele	151 (27)	69 (13)	2.51 (1.76 - 3.61)	<0.0001 <0.0001*
CYP3A43	TT	177 (63)	213 (74)	1.00	
rs501275	TC	94 (33)	70 (24)		
	CC	10 (4)	4 (2)		
	C allele	114 (20)	78 (14)	1.60 (1.13 - 2.29)	0.0086 0.0263*

*Corrected *p*-value for the effect of population stratification in coloured men obtained by multiplying age-adjusted value by an inflation factor λ = 3.06 (Fernandez *et al.*, 2008[11]).

men, we observed the same trend, 44% in the control group and 40% in the case group, but it was not statistically significant (Table III). In the combined ethnic groups, haplotype GAT was also significantly less prevalent in the PCa case individuals (54%) than in the controls (67%) (Table III). In coloured men, haplotypes AGT, AGC and GCC were significantly more prevalent in the case group than in the control group (Table III). In white men, only haplotype GGT showed a highly significant difference, 11% in the case group and 1% in the control group (Table III). For the combined ethnic groups analysis, haplotypes GGT, AGT, AGC and GGC were significantly more prevalent in the case group than in the control group (Table III).

Discussion

Our findings support the involvement of *CYP3A5*, *CYP3A4* and *CYP3A43* alleles in the probability of developing PCa in South African men. We report a unique finding indicating increased PCa probability associated with the rs776746 A allele (*CYP3A5*1*). Additionally, we confirmed an association between the rs2740574 G allele (*CYP3A4*1B*) and PCa occurrence.[6]

We demonstrated that the rs776746 A allele was associated with developing PCa in South African white men, whereas in Finnish men the allele was not associated with development of PCa but was associated with bone metastases (disease progression).[5] The

Table III. Inferred haplotype frequencies, prostate cancer ORs and joint *p*-values for tests of association with prostate cancer for each haplotype in South African coloured and white men

	Haplotype frequency (%)						
	rs776746	rs2740574	rs501275	Controls	Cases	OR (95% CI)	*p*-value
Coloured	G	A	T	44	40	1.00	0.0975
	A	A	C	7	4	0.59 (0.22 - 1.58)	0.1076
	A	A	T	22	16	0.74 (0.43 - 1.29)	0.0709
	G	A	C	5	5	1.30 (0.52 - 3.25)	0.9193
	G	G	T	7	3	0.48 (0.17 - 1.36)	0.2537
	A	G	T	5	12	2.98 (1.29 - 6.88)	0.0067
	A	G	C	8	15	2.54 (1.28 - 5.03)	0.0011
	G	G	C	1	5	3.51 (0.83 - 14.87)	0.0383
White	G	A	T	88	71	1.00	<0.0001
	A	A	C	1	2	3.12 (0.36 - 27.01)	0.2878
	A	A	T	3	7	2.04 (0.87 - 4.82)	0.1571
	G	A	C	4	4	1.32 (0.51 - 3.41)	0.9519
	G	G	T	1	11	12.32 (3.56 - 42.58)	<0.0001
	A	G	T	1	2	2.39 (0.46 - 12.56)	0.2268
	A	G	C	1	2	2.37 (0.58 - 9.78)	0.2216
	G	G	C	0	1		
Combined	G	A	T	67	54	1.00	0.0000
	A	A	C	4	3	0.84 (0.37 - 1.88)	0.4284
	A	A	T	12	12	1.06 (0.70 - 1.60)	0.6206
	G	A	C	4	4	1.38 (0.72 - 2.65)	0.9954
	G	G	T	4	6	2.43 (1.26 - 4.68)	0.0108
	A	G	T	4	8	2.61 (1.38 - 4.94)	0.0014
	A	G	C	5	10	2.79 (1.59 - 4.92)	0.0001
	G	G	C	1	3	4.45 (1.32 - 15.00)	0.0055

Coloured men global *p*-value = 0.0004; white men global *p*-value <0.0001; combined global *p*-value <0.0001.

sample size of our case individuals limited the analytical power to test for associations between the SNP alleles and disease extent. Individuals harbouring at least one copy of the A allele express large amounts of CYP3A5, whereas having a copy of the variant G allele causes alternative splicing and protein truncation resulting in an absence of CYP3A5.[4] Men with the A allele would therefore have increased testosterone oxidation, which decreases the bio-availability of testosterone for conversion to 5α-dihydrotestosterone (5α-DHT), the principal androgenic hormone involved in regulating prostate cell growth (more testosterone oxidation = less 5α-DHT = less prostate cell growth). Our association with the A allele contradicts this hypothesis, although it might lend support to this variant being in LD with the causal variant in *CYP3A5* or a nearby gene.

The *CYP3A4* rs2740574 G allele has been associated with PCa aggressiveness.[6] We did not stratify the case individuals by disease aggressiveness because of our small sample size. No substantial effect of the G allele variant on *CYP3A4* expression has been identified.[14] However, it has been shown in white individuals that the *CYP3A4* rs2740574 polymorphism is in tight LD with the *CYP3A5* rs776746 polymorphism.[4,6,15] Furthermore, it has been suggested that reported associations between the variant G allele and PCa could be due to the polymorphic CYP3A5 expression.[15] We observed significant LD between rs776746 and rs2740574, lending support to possible synergistic interaction between their alleles in PCa development in South African men.

Associations have been reported with a specific allele of the *CYP3A43* coding SNP rs680055 and PCa, only after stratifying for a positive family history of PCa,[6] a history of cigarette smoking[9] or a history of BPH.[10] We observed a direct association with the *CYP3A43* rs501275 C allele and PCa probability only in our combined analysis. It is unclear why the C allele increased probability of the disease, given that *CYP3A43* has been suggested to be a pseudogene,[4] having a specific role of contributing exons to CYP3A5 and CYP3A4 transcripts to produce hybrid mRNAs.[8] Moreover, it is unclear how the rs501275 polymorphism in intron 4 of the gene could play a role in PCa causation as it is probably non-functional. Because the CYP3A locus exhibits significant LD, the association with *CYP3A43* might alternatively reflect the effect of another variant in the gene, or in *CYP3A5* or *CYP3A4*.

We report significant differences in haplotype frequency distributions by PCa case-control status, with and without stratifying by ethnicity. The higher frequency of haplotype GAT in the control individuals (Table III) might suggest that this haplotype is protective against developing PCa in white South African men. The *CYP3A5-CYP3A4-CYP3A43* haplotypes may contain additional information about disease probability prediction beyond single SNP analysis, suggesting that other variants in these genes or variants in other genes in the region may be involved in the development of PCa.

Limitations of our study include the small sample size, although it was sufficient to detect small to moderate associations. Additionally, the sample size limited our ability to test for associations with disease aggressiveness or disease extent. Cytochromes metabolise xenobiotics and an association with PCa and pack-years of cigarette smoking has been demonstrated.[9] Information related to cigarette smoking and alcohol use was occasionally omitted in medical records, and our control individuals were not obliged to indicate cigarette and

alcohol use; we were therefore unable to incorporate these data into our analyses. However, future studies with larger sample sizes and collection of all relevant covariates should address these limitations.

Conclusions

We detected variants in genes at the CYP3A locus that are associated with PCa in South African men. Our previous findings support the role of genes involved in inflammation and the development of PCa in South African coloured men.[11] This study supports the role of genetic variants in genes that regulate androgen metabolism in the development of PCa in South African men. It has been suggested that prostate tumours initiated under conditions of chronic inflammation are fed by exposure to androgens, resulting in clinically more severe tumours.[10] Our study does not conclusively identify a PCa causative variant, although it strongly suggests that the causative variant may lie within or closely adjacent to the CYP3A locus. Further studies in larger sample sizes and in other South African population groups should confirm the associations in *CYP3A5*, *CYP3A4* and *CYP3A43*, or identify associations in other genes in the region, which will allow stratified analyses by disease aggressiveness. This could lead to uncovering the genetic relationship between genotype and haplotype profiles associated with disease progression and prognosis.

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RESEARCH LECTURE

Should we be giving antiretroviral drugs to HIV-negative people?

The fourth prestigious Research Lecture hosted by the Faculty of Health Sciences Research Office, University of the Witwatersrand (Wits) will be held on 25 November 2010 in the Johannesburg Hospital Auditorium.

New results show that an antiretroviral vaginal gel can partially prevent HIV infection transmitted by vaginal intercourse. Other research studies that use antiretroviral drugs (ARVs) to prevent HIV infection are currently in the pipeline, with the results expected soon. Should these results show that ARVs can be used to prevent HIV, we will be faced with a number of financial, ethical and programmatic dilemmas.

At a time when South Africa is struggling to afford ARVs for treatment, should the use of ARVs for prevention be considered? If the answer is yes, can the country afford to offer these medications to anyone at risk of HIV, or will we have to decide which groups should be targeted for this intervention? If we roll out these medications widely, will the emergence of drug resistance become a problem among those who become HIV positive and in the broader community, and what impact will this have on the treatment programme?

These issues will be debated by Professor Helen Rees, Executive Director of the Wits Institute for Sexual and Reproductive Health, HIV and Related Diseases, Professor in the Wits Department of Obstetrics and Gynaecology and Honorary Professor in the London School of Hygiene and Tropical Medicine, and Professor Lynn Morris, Head of the AIDS Unit, Division of Virology and Communicable Disease Surveillance, National Institute for Communicable Diseases and Research Professor in the Faculty of Health Sciences at Wits.