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Association of Androgen Metabolism Gene Polymorphisms with Prostate Cancer Risk and Androgen Concentrations: Results from the Prostate Cancer Prevention Trial

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Abstract

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Background—Prostate cancer is highly influenced by androgens and genes. We investigated whether genetic polymorphisms along the androgen biosynthesis and metabolism pathways are associated with androgen concentrations or risk of prostate cancer or high-grade disease from finasteride treatment.

Methods—A nested case-control study from the Prostate Cancer Prevention Trial using cases drawn from men with biopsy-proven prostate cancer and biopsy-negative, frequency-matched controls was conducted to investigate the association of 51 single nucleotide polymorphisms (SNPs) in 12 genes of the androgen pathway with total, low-grade, and high-grade prostate cancer incidence and serum hormone concentrations.

Results—There were significant associations of genetic polymorphisms in *SRD5A1* (rs3736316, rs3822430, rs1560149, rs248797, and rs472402) and *SRD5A2* (rs2300700) with risk of high-grade prostate cancer in the placebo arm of the PCPT; two SNPs were significantly associated with increased risk (*SRD5A1* rs472402 [OR, 1.70; 95% CI, 1.05-2.75, $P_{\text{trend}}=0.03$]; *SRD5A2* rs2300700 [OR, 1.94; 95% CI, 1.19-3.18, $P_{\text{trend}}=0.01$]). Eleven SNPs in *SRD5A1*, *SRD5A2*, *CYP11B1*, and *CYP3A4* were found to be associated with modifying mean serum androgen and sex hormone-binding globulin concentrations; two SNPs (*SRD5A1* rs824811 and *CYP11B1* rs10012, $P_{\text{trend}}<0.05$) consistently and significantly altered all androgen concentrations. Several SNPs (rs3822430, rs2300700; *CYP3A4* rs800672; *CYP19* rs700519; $P_{\text{trend}}<0.05$) were significantly associated with both circulating hormone levels and prostate cancer risk.

Conclusion—Germline genetic variations of androgen-related pathway genes are associated with serum androgen concentrations and risk of prostate cancer. Further studies to examine the functional consequence of novel causal variants are warranted.

Keywords

androgen; metabolism; genetics; polymorphism; prostate cancer

Introduction

Androgens play a critical role in the etiology of prostate cancer, and binding of the potent androgen 5 α -dihydrotestosterone (DHT) to the androgen receptor drives the development and progression of the disease. Prostate cancer is highly influenced by genetic variations. Single nucleotide polymorphisms (SNPs) have been found in key regulatory genes involved in the steroid hormone pathway (biosynthesis, activation, metabolism, and degradation of androgens), androgen receptor (AR), and downstream AR effector pathways. These androgen-related SNPs and their putative roles in prostate cancer may contribute to susceptibility to the disease.

The androgen biosynthesis and metabolism pathway is shown in Figure 1. Testosterone is irreversibly converted to DHT by the enzyme steroid 5 α -reductase types I and II in the prostate tissue (encoded by the *SRD5A1* and *SRD5A2* genes, respectively)¹ and also by steroid 5 α -reductase type III (encoded by *SRD5A2L* or *SRD5A3*) recently identified in castration-resistant prostate cancer cells.^{2, 3} The cytochrome P450 family of enzymes (encoded by the *CYP* genes) are involved in metabolizing endogenous hormones and their biochemical intermediates.

We have previously demonstrated that there were no statistically significant associations of baseline serum testosterone, 5 α -androstane-3 α ,17 β -diol glucuronide (3 α -androstenediol glucuronide, 3 α -dG), androstenedione, or sex hormone-binding globulin (SHBG) concentrations with risk of total, low- or high-grade prostate cancer in the placebo^{4, 5} or finasteride^{4, 6} treatment arm of the Prostate Cancer Prevention Trial (PCPT), consistent with most results in the literature.⁷⁻⁹ Serum 3 α -dG, a distal metabolite of DHT, was used as a surrogate measure of intraprostatic DHT and marker for SRD5A activity¹⁰ and serum SHBG as a carrier protein for androgens. While evidence from the above studies has largely been null, others have suggested that genetic modulators of androgen metabolism may affect circulating serum androgen levels¹¹ and subsequently influence prostate carcinogenesis. Moreover, germline polymorphisms within key androgen regulatory genes may contribute to the risk of developing prostate cancer.^{12, 13}

Here, we investigate the association of genetic polymorphisms in genes of the androgen biosynthesis and metabolism pathway with prostate cancer risk using a nested case-control study of the PCPT population. In the PCPT, a randomized, placebo-controlled trial testing whether finasteride could reduce the 7-year period prevalence of prostate cancer, finasteride reduced the risk of prostate cancer by 25%, even though high-grade prostate cancer was more common in the finasteride group.¹⁴ Therefore, we genotyped a total of 51 SNPs in the 12 genes involved in the androgen metabolism pathway: *SRD5A1*, *SRD5A2*, *SRD5A2L*/*SRD5A3*, *HSD3B2*, *HSD17B2*, *HSD17B3*, *CYP11B1*, *CYP3A4*, *CYP3A5*, *CYP3A43*, *CYP17*, and *CYP19*. We also examine whether these polymorphisms are responsible for altering serum androgen concentrations. Findings from this study could provide further insight into the genetics of androgen metabolism, the role of genetics in the etiology of the increased risk of high-grade cancer among men treated with finasteride, as well as improve our understanding of the contribution of genetics to prostate cancer risk.

Methods

Participant and Study Description

All data for this study are from the PCPT (SWOG-9217).^{14, 15} Details of the trial and participant characteristics have been described previously.^{14, 15} All men signed informed consent and study procedures were approved by the Institutional Review Boards of the participating 221 study sites.^{14, 15} The study reported here is part of a large nested case-control study designed to examine multiple hypotheses about prostate cancer risk. Tumors were graded centrally and categorized as low grade = Gleason < 7; high grade = Gleason 7, retaining the definitions used in the original trial report. Cases were men with biopsy-determined prostate cancer identified either by a for-cause or end-of-study biopsy (N=1809) and controls were selected from men who completed the end-of-study biopsy procedure and had no evidence of prostate cancer (N=1809). All non-white controls were included, and the remaining controls were frequency matched to cases based on treatment arm (finasteride versus placebo), age (in 5-year groupings), and family history of a first-degree family member with prostate cancer. Serum steroid hormone concentrations were available from 1802 cases and 1800 controls. SNP data was available on 1,617 cases and 1,731 controls. The final SNP analysis included white men only as the sample size was too small for sub-

group analysis of SNP associations for other racial/ethnic groups (1,506 cases and 1,380 controls). Of these, the population used in the analyses with both serum measures and SNP data available included 1499 cases and 1373 controls.

Genotyping & Serum Measurements

DNA extractions were performed, as described previously.¹⁶ Genotyping was conducted by polymerase chain reaction amplification using the Sequenom, TaqMan (Life Technologies), or Illumina platform assays. Total testosterone, 3 α -dG, androstenedione and SHBG were quantified in serum by highly specific immunoassays as described previously.^{4, 6}

Statistical Methods

Logistic regression was used to calculate odds ratio (ORs) and 95% confidence intervals (CIs) for risk of total prostate cancer, and polytomous logistic regression was used to calculate ORs and 95% CIs of both low-grade and high-grade prostate cancers. To investigate a possible interaction between SNPs and serum androgen levels and their influence on prostate cancer risk, models were also stratified by androgen concentrations, using the observed median as cut-point. To determine the association between single SNP and androgen levels, mean concentrations of androgen were calculated for each allele, and p-values were calculated using linear regression adjusted for age and family history. For all SNP analyses, the major allele homozygote was used as the reference genotype, and minor alleles were compared to this reference. All statistical tests were two-sided with statistical significance set at $p < 0.05$ and carried out using SAS statistical software (version 9.4, SAS Corporation, Cary, NC).

Additional details of the DNA extraction method, genotyping assay, study description, sample collection, measurements of serum androgens and SHBG concentrations, and statistical methods are described in the Supporting Information.

Results

Table 1 gives the demographic and lifestyle characteristics of the PCPT study population. Cases and controls were similar in age and family history of prostate cancer due to matching; they were also similar with respect to BMI, protein consumption, and mean concentrations of serum androgens and SHBG as well as physical activity, smoking status, and alcohol intake (data not shown). Controls had lower baseline PSA levels than cases and were more likely to be diabetic.

Associations between genetic polymorphisms in genes involved in androgen biosynthesis and metabolism pathways with prostate cancer risk that were statistically significant for either the placebo or finasteride arms are shown in Table 2. In the placebo arm, there was a statistically significant positive association of the homozygous minor variant of *SRD5A2* rs2300700 [OR, 1.34; 95% CI, 1.01-1.77, $P_{\text{trend}}=0.04$] with risk of overall prostate cancer. When stratified by disease grade [low- vs. high-grade (Gleason score 2-6 vs. 7-10)], there were significant associations of SNPs in *SRD5A1* (rs3736316, rs3822430, rs1560149, rs248797, rs472402) and *SRD5A2* (rs2300700) with risk of high-grade prostate cancer. The homozygous variants of two SNPs were statistically significantly associated with a >1.5 to

2-fold increased risk of high-grade disease (*SRD5A1* rs472402, $P_{\text{trend}}=0.03$; *SRD5A2* rs2300700, $P_{\text{trend}}=0.01$)). The homozygous variant allele of three SNPs reduced the risk of high-grade disease by about half (*SRD5A1* rs3736316, $P_{\text{trend}}=0.02$; rs3822430, $P_{\text{trend}}=0.02$; and rs248797, $P_{\text{trend}}=0.03$). In the finasteride treatment arm, the heterozygous variant of *SRD5A1* rs1560149 was associated with a decreased risk of high-grade prostate cancer [OR, 0.59; 95% CI, 0.41-0.84, $P_{\text{trend}}=0.07$]. Treatment arms were combined when there was no statistically significant SNP/treatment interaction (Supporting Table S1); the homozygous variant allele of *SRD5A2* rs2300700 remained significantly associated with an increased risk of high-grade disease ($P_{\text{trend}}=0.01$, Supporting Table S2).

Table 3 gives the association between SNPs in androgen metabolism genes and mean serum androgen and SHBG concentrations of all participants in the PCPT. Genetic variations of 11 SNPs in *SRD5A1*, *SRD5A2*, *CYP11B1*, and *CYP3A4* were found to modify serum androgen and SHBG levels. Collectively, only two SNPs (*SRD5A1* rs824811, all $P_{\text{trend}}=0.03$ and *CYP11B1* rs10012, all $P_{\text{trend}}=0.02$) consistently and significantly altered all three serum androgen and SHBG concentrations. Serum androstenedione concentrations were not significantly affected by any of the SNPs in the androgen metabolism genes (data not shown).

Table 4 examined the joint effects of serum androgen and SHBG concentrations and genetic variants in the androgen metabolism pathway and their association with prostate cancer risk. In the placebo treatment group, prostate cancer risk was increased >1.5 to 2-fold in individuals who possess the variant allele for *CYP19* rs700519 and serum 3 α -dG [OR, 2.13; 95% CI, 1.18-3.84, $P_{\text{trend}}=0.01$] or SHBG concentrations [OR, 1.93; 95% CI, 1.02-3.67, $P_{\text{trend}}=0.04$] at or above the median; or *SRD5A2* rs2300700 and serum SHBG concentrations below the median ($P_{\text{trend}}=0.03$). Prostate cancer risk was decreased by almost half in men who are carriers of the homozygous variant allele of *SRD5A1* rs3822430 with serum 3 α -dG concentrations at or above the median ($P_{\text{trend}}=0.02$); or *CYP3A4* rs800672 with serum testosterone ($P_{\text{trend}}=0.03$) or SHBG ($P_{\text{trend}}=0.04$) concentrations at or above the median. Results for the finasteride treatment arm and stratification by serum androstenedione concentrations are presented in Supporting Tables S3-S4.

Discussion

Our study assessed the association of genetic variants in androgen-related pathways with prostate cancer risk. In the placebo group, when stratified by disease grade, there were significant associations of SNPs in *SRD5A1* (rs3736316, rs3822430, rs1560149, rs248797, rs472402) and *SRD5A2* (rs2300700) with risk of high-grade prostate cancer. Specifically, the homozygous variants of *SRD5A1* rs472402 and *SRD5A2* rs2300700 were statistically significantly associated with a >1.5 to 2-fold increased risk of high-grade disease; while the homozygous variant allele of three SNPs (*SRD5A1* rs3736316, rs3822430, rs248797) reduced the risk of high-grade disease by about half.

The PCPT found that finasteride reduced the risk of prostate cancer by 25%, even though high-grade prostate cancer was more common in the finasteride group.¹⁴ Findings from the current study provide further insight into the genetic etiology of the increased risk of high-

grade cancer among men treated with finasteride. Indeed, in the finasteride treatment group, the heterozygous variant of *SRD5A1* rs1560149 was associated with decreased risk with high-grade compared to wild type. This suggests that finasteride treatment may decrease the odds of high-grade disease in men who are heterozygote carriers of *SRD5A1* rs1560149 from 1.83 (OR, placebo arm) to 0.58 (OR, finasteride arm). All other SNPs identified in the placebo arm were not significant in the finasteride treatment group. Polymorphisms in *SRD5A2* have been studied as potential genetic markers of prostate cancer risk and results have not always been consistent in the literature (reviewed in ¹⁷). The common nonsynonymous SNP *SRD5A2* rs9282858 had no significant associations with prostate cancer risk in our study consistent with recent meta-analysis studies.¹⁸⁻²⁰ Studies on the positive association of *SRD5A1* polymorphisms and prostate cancer risk are fewer^{11, 21, 22} with our study being the first to identify the association of several novel *SRD5A1* SNPs that have not been previously reported.

We determined factors involved in modifying serum androgen and SHBG concentrations. Here, we found several non-genetic factors (obesity, smoking, diabetes, physical activity, protein consumption) influencing androgen and SHBG concentrations that have been previously reported to be associated with prostate cancer risk (Supporting Table S5).²³ More importantly, we identified genetic factors that impact androgen metabolism as reflected by significant changes in circulating androgen and SHBG concentrations. Genetic variations of 11 SNPs in *SRD5A1*, *SRD5A2*, *CYP11B1*, and *CYP3A4* were found to modify serum androgen and SHBG levels. Collectively, this is the first study to show that only two SNPs (*SRD5A1* rs824811 and *CYP11B1* rs10012) consistently and statistically significantly altered all androgen and SHBG concentrations. Five *SRD5A2* SNPs (rs6732223, rs2300700, rs9332975, rs4952197, rs6760199) modified serum 3 α -dG concentrations while no associations were found for testosterone or SHBG levels in our study. Previous studies have shown *SRD5A2* polymorphisms (rs12470143, rs2208532, rs523349, rs676033, rs2300700) altering levels of circulating steroid glucuronide metabolites of DHT in prostate cancer patients.^{11, 24, 25} Our study is the first to report rs6732223 in prostate cancer, a SNP that is located 7 kb downstream of *SRD5A2*, and increased enzyme activity has been suggested for the minor allele in cortisol metabolism.²⁶ Our results are consistent with previous findings on the impact of select *SRD5A2* SNPs affecting circulating androgen metabolites rather than upstream substrates.¹¹ To the best of our knowledge, this is the first report of the association of rs824811, located in an intron of *SRD5A1*, with modifying androgen concentrations for prostate cancer and its functional activity remains to be determined. The minor alleles of four additional SNPs (*CYP11B1* rs10012, *CYP3A4* rs2242480, rs4646437 and rs4986910) were significantly associated with higher serum T or SHBG concentrations. *CYP11B1* is involved in the activation of many procarcinogens and hydroxylation of testosterone; thus, variations in *CYP11B1* may lead to higher susceptibility to prostate cancer.²⁷ Nonsynonymous SNPs rs10012 and rs1056827 have been evaluated for association with prostate cancer risk²⁸⁻³⁰ and functional studies indicate that allelic combinations can alter the catalytic activity of *CYP11B1* in estrogen hydroxylation^{31, 32}. Two common nonsynonymous *CYP11B1* SNPs rs1056836 and rs1800440 were not associated with either serum androgen concentrations or prostate cancer risk (data not shown). *CYP3A4* SNP rs4646437 (lies within intron 7) undergoes positive selection in Caucasians and male carriers

of the variant allele have been associated with reduced CYP3A4 protein expression and enzyme activity.³³ The minor allele of *CYP3A4* rs4986910 (*CYP3A4**3, located in exon 12) has low allele frequency and was shown to be associated with reduced enzyme function.³⁴ A study by Siemes et al. did not find any association of SNPs in *CYP3A4*, *CYP3A5*, or *CYP3A43* with androgen concentrations.³⁵ Further studies to verify these results are warranted.

Several association studies have investigated polymorphisms in genes involved in androgen-related pathways as candidates for prostate cancer risk.³⁶⁻³⁹ A few evaluated the association of these SNPs with serum hormone levels in prostate cancer.^{24, 40-42} While inherited variants that modify circulating hormone concentrations may differ from those affecting disease risk, our study found SNPs that are statistically significantly associated with both serum androgen or SHBG levels and prostate cancer risk. In the placebo arm, higher 3 α -dG concentrations were associated with increased disease risk for the heterozygous variant alleles of *SRD5A3* rs7682870 and *CYP19* rs700519. This is the first study to implicate *SRD5A3* in prostate cancer risk and its functional activity is unknown. Our results showed that genetic variability in factors controlling androgen concentrations likely confer differential risk of developing prostate cancer and that subgroups of men may be more susceptible to the disease.

There are strengths and limitations to our study. The PCPT was a large placebo-controlled randomized trial that used prostate biopsies to verify absence or presence of cancer; thus, the control group all had confirmed negative prostate biopsies, largely eliminating the possibility that controls may have had undiagnosed or undetected disease. Additional strengths included the use of a central pathology laboratory for uniform adjudication of all cases (including adjudication of Gleason grade), highly sensitive and specific assays for quantitating serum androgen and SHBG concentrations, and the large sample size of our patient population. Our study was limited in that serum androgen/SHBG concentrations were measured at one time point and may also not be representative of tissue levels. This analysis included only white participants; however, this minimized concerns of selection bias or population stratification. Given the hypothesis-driven nature of SNP selection, we did not systematically correct for multiple testing in our analyses, as might be done for agnostic genetic studies.

In conclusion, this study demonstrates that genetic polymorphism of genes in androgen biosynthesis and metabolism pathways may influence prostate cancer risk. We identified variants involved in modifying serum androgen and SHBG concentrations that may explain the inter-individual variation observed in concentration differences. Our study demonstrates the significance of androgen metabolism in prostate cancer and suggests that in addition to the agnostic approach of genome wide association studies, candidate gene and pathway approach with biological rationale are important strategies to clarify the role of genetic susceptibility and androgen in prostate cancer. Future replication studies are warranted to confirm the novel SNPs identified and to investigate the functional consequences of causal variants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Androgen pathway and genes involved in androgen biosynthesis and metabolism. Serum concentrations of androgens measured in the study are boxed.

Abbreviations: DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; 3 α -diol, 3 α -androstenediol; 3 β -diol, 3 β -androstenediol; 3 α -dG, 3 α -androstenediol glucuronide

Table 1
Demographics and lifestyle characteristics at baseline, among cases and controls in the Prostate Cancer Prevention Trial, white men only

Characteristic	Controls (n=1380)	Cases (n=1506)	P-value
	Mean (SD)	Mean (SD)	
Age (y)	63.96 (5.64)	63.74 (5.62)	0.29
Prostate specific antigen (ng/mL)	1.20 (0.76)	1.54 (0.74)	<0.0001
Protein consumption (g)	95.37 (38.02)	93.36 (37.60)	0.18
3 α -dG (ng/mL)	6.56 (4.02)	6.86 (5.28)	0.09
Testosterone (ng/dL)	376.78 (131.19)	379.60 (131.21)	0.57
SHBG (nmol/L)	39.03 (15.23)	39.04 (15.92)	0.99
	N (%)	N (%)	
Treatment Arm			0.11 *
Finasteride	532 (38.55)	625 (41.50)	
Placebo	848 (61.45)	881 (58.50)	
Family history of prostate cancer	313 (22.68)	322 (21.38)	0.40 *
Diabetes	75 (5.43)	60 (3.98)	0.07
Body mass index (kg/m ²)			0.18
Normal (<25)	345 (25.26)	425 (28.47)	
Overweight (25 to <30)	745 (54.54)	770 (51.57)	
Obese ($\geq$ 30)	276 (20.20)	298 (19.96)	

* Frequency-matched, so p-values are not interpretable.

Abbreviations: 3 α -dG = 3 α androstane-20-one glucuronide; SHBG = Sex hormone-binding globulin

Table 2
Prostate cancer risk by genotypes of androgen metabolizing genes in the Prostate Cancer Prevention Trial *

Gene	SNP	Genotype	All prostate cancer			Low-grade prostate cancer			High-grade prostate cancer			
			Controls	Cases	OR (95% CI)	P-trend	Cases	OR (95% CI)	P-trend	Cases	OR (95% CI)	P-trend
Placebo arm												
SRD5A1	rs3736316	GG	329	351	1	0.15	261	1	0.43	79	1	0.02
		AG	396	425	1 (0.82-1.23)		328	1.04 (0.84-1.3)		76	0.8 (0.57-1.13)	
		AA	96	72	0.7 (0.5-0.99)		60	0.78 (0.55-1.13)		10	0.43 (0.22-0.87)	
rs3822430		AA	318	339	1	0.22	253	1	0.54	76	1	0.02
		AG	390	422	1.01 (0.83-1.25)		325	1.04 (0.84-1.3)		75	0.81 (0.57-1.15)	
		AA	118	97	0.77 (0.57-1.05)		80	0.85 (0.61-1.18)		14	0.50 (0.27-0.91)	
rs1560149		GG	520	534	1	0.63	430	1	0.19	84	1	0.07
		CG	270	304	1.1 (0.9-1.35)		210	0.94 (0.76-1.18)		80	1.82 (1.3-2.56)	
		CC	49	33	0.66 (0.41-1.04)		28	0.69 (0.43-1.12)		5	0.63 (0.24-1.63)	
rs248797		CC	225	218	1	0.93	162	1	0.62	53	1	0.03
		CT	408	451	1.14 (0.9-1.43)		341	1.15 (0.9-1.48)		88	0.92 (0.63-1.35)	
		TT	207	197	0.98 (0.75-1.28)		160	1.07 (0.8-1.43)		27	0.56 (0.34-0.92)	
rs472402		CC	231	228	1	0.81	184	1	0.36	33	1	0.03
		CG	407	446	1.11 (0.88-1.39)		338	1.04 (0.82-1.32)		87	1.50 (0.98-2.32)	
		GG	201	190	0.96 (0.73-1.26)		138	0.86 (0.65-1.15)		49	1.70 (1.05-2.75)	
rs39847		TT	410	459	1	0.27	343	1	0.47	98	1	0.13
		CT	355	338	0.85 (0.7-1.04)		266	0.9 (0.73-1.11)		59	0.69 (0.49-0.98)	
		CC	68	72	0.95 (0.66-1.35)		54	0.95 (0.65-1.4)		14	0.86 (0.46-1.59)	
SRD5A2	rs2300700	GG	253	234	1	0.04	180	1	0.09	36	1	0.01
		AG	418	437	1.13 (0.9-1.41)		333	1.11 (0.87-1.41)		92	1.57 (1.04-2.38)	
		AA	148	183	1.34 (1.01-1.77)		137	1.30 (0.96-1.76)		41	1.94 (1.19-3.18)	
rs6760199		CC	450	454	1	0.52	353	1	0.31	85	1	0.73

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Gene	SNP	Genotype	All prostate cancer			Low-grade prostate cancer			High-grade prostate cancer			
			Controls	Cases	OR (95% CI)	P-trend	Cases	OR (95% CI)	P-trend	Cases	OR (95% CI)	P-trend
Finasteride arm	SRD5A1 rs1560149	AC	316	361	1.13 (0.93-1.38)		272	1.09 (0.88-1.35)		72	1.21 (0.86-1.72)	
		AA	78	54	0.69 (0.47-0.99)		39	0.64 (0.42-0.96)		13	0.89 (0.47-1.66)	
		GG	303	389	1	0.20	226	1	0.72	148	1	0.07
		CG	201	193	0.75 (0.59-0.96)		127	0.86 (0.65-1.14)		58	0.59 (0.41-0.84)	
		CC	24	35	1.13 (0.66-1.95)		22	1.21 (0.66-2.22)		13	1.13 (0.56-2.28)	

* Analyses are adjusted for age and family history, and include white men only. Low grade = Gleason < 7; high grade = Gleason 7

Table 3
Association between SNPs in androgen metabolism genes and serum androgen/SHBG concentrations *

3α-dG (ng/mL)											Testosterone (ng/dL)			SHBG (nmol/L)		
Gene	SNP	Genotype	N	Mean	P-trend	Mean	P-trend	Mean	P-trend	Mean	P-trend					
SRD5A1	rs824811	TT	1494	6.6	0.03	383.9	0.01	39.6	0.002							
		CT	1062	6.8		368.2		38.0								
		CC	141	7.1		374.3		37.8								
	rs1560149	GG	1746	6.8	0.04	378.5	0.88	38.6	0.07							
		CG	968	6.6		375.8		39.6								
		CC	141	6.3		387.9		39.3								
SRD5A2	rs6732223	CC	704	6.2	<0.001	377.9	0.80	38.9	1.00							
		CT	1400	6.8		379.3		39.3								
		TT	608	7.2		375.8		38.5								
	rs2300700	GG	800	6.3	<0.0001	378.8	0.50	39.0	0.75							
		AG	1413	6.7		380.5		39.2								
		AA	593	7.4		373.3		38.9								
	rs4952197	GG	1563	7.0	<0.0001	378.3	0.66	39.4	0.49							
		AG	1080	6.4		377.4		38.4								
		AA	206	6.0		386.3		39.5								
	rs6760199	CC	1518	7.0	<0.0001	376.5	0.46	39.2	0.80							
		AC	1122	6.6		378.4		38.6								
		AA	222	5.9		383.6		39.6								
	rs9332975	AA	2294	6.6	<0.001	378.5	0.99	39.0	0.65							
		AG	543	7.0		378.7		39.2								
		GG	29	10.1		377.6		42.2								
	CYP17	rs10012	CC	1153	6.6	<0.01	370.3	0.02	37.6	0.002						
			CG	804	6.8		381.4		39.9							

Gene	SNP	Genotype	N	3 α -dG (ng/mL)			Testosterone (ng/dL)			SHBG (nmol/L)		
				Mean	P-trend	Mean	Mean	P-trend	Mean	P-trend	Mean	P-trend
CYP3A4	rs2242480	GG	169	7.6		391.1			40.5			
		CC	2384	6.7	0.47	375.8	38.8	0.05	38.8	0.19		
		CT	443	6.9		389.0	40.0		40.0			
		TT	24	7.4		392.8	38.1		38.1			
	rs4646437	CC	2318	6.7	0.51	375.8	38.8	0.03	38.8	0.09		
		CT	504	6.9		390.5	40.1		40.1			
		TT	29	6.0		386.2	39.7		39.7			
	rs4986910	AA	2661	6.7	0.56	378.1	39.0	0.03	39.0	0.01		
		AG	32	7.4		427.3	45.0		45.0			

Abbreviations: 3 α -dG = 3 α androstanediol glucuronide; SHBG = Sex hormone-binding globulin

* Means are raw means, and p-values are calculated using linear regression adjusted for age, family history, and case/control status. Analysis includes white men only.

Table 4
Prostate cancer risk by genotypes of androgen metabolizing genes and serum hormone levels in the placebo arm of the PCPT *

Gene	SNP	Genotype	Controls	Cases	OR (95% CI)	P-trend	Controls	Cases	OR (95% CI)	P-trend
SRD5A1	rs3822430	AA AG GG	3α-dG < 5.7 ng/mL				3α-dG ≥ 5.7 ng/mL			
			177	168	ref	139	171	ref		
			191	203	1.12 (0.84-1.50)	0.61	195	216	0.90 (0.67-1.21)	0.02
			56	56	1.06 (0.69-1.62)		62	41	0.54 (0.34-0.85)	
SRD5A3	rs7682870	AA AC CC	268	256	ref		256	266	ref	
			142	159	0.85 (0.64-1.14)	0.62	165	121	1.42 (1.06-1.89)	0.09
			20	16	1.19 (0.61-2.36)		15	16	0.97 (0.47-2.00)	
CYP19	rs700519	CC CT TT	407	408	ref		397	389	ref	
			25	26	0.96 (0.55-1.69)	0.89	37	17	2.13 (1.18-3.84)	0.01
			0	0	NA		0	0	NA	
SRD5A1	rs472402	CC CG GG	Testosterone < 362 ng/dL				Testosterone ≥ 362 ng/dL			
			125	94	ref	105	134	ref		
			199	218	1.45 (1.05-2.02)	0.23	201	224	0.87 (0.63-1.20)	0.14
			105	99	1.25 (0.86-1.84)		96	91	0.75 (0.51-1.10)	
	rs1560149	GG CG CC	274	251	ref		242	280	ref	
			137	147	1.17 (0.87-1.56)	0.53	129	156	1.04 (0.78-1.39)	0.20
			19	16	0.92 (0.46-1.84)		30	17	0.49 (0.26-0.91)	
	rs3822430	AA AG GG	167	178	ref		149	161	ref	
			193	193	0.94 (0.70-1.26)	0.06	192	225	1.08 (0.81-1.46)	0.98
			65	43	0.62 (0.40-0.96)		53	54	0.95 (0.61-1.47)	
CYP3A43	rs800672	CC CT TT	122	111	ref		104	137	ref	
			209	203	1.07 (0.78-1.48)	0.66	191	217	0.87 (0.63-1.19)	0.03
			93	93	1.09 (0.74-1.60)		103	89	0.65 (0.45-0.96)	
SHBG < 36.6 nmol/L										
SHBG ≥ 36.6 nmol/L										

Gene	SNP	Genotype	Controls	Cases	OR (95% CI)	P-trend	Controls	Cases	OR (95% CI)	P-trend
<i>SRD5A2</i>	rs2300700	GG	104	129	ref		127	123	ref	
		AG	230	179	1.59 (1.15-2.19)	0.03	206	235	0.86 (0.63-1.17)	0.41
		AA	91	76	1.48 (1.00-2.21)		92	71	1.25 (0.84-1.87)	
<i>CYP11B1</i>	rs1800440	AA	258	291	ref		291	292	ref	
		AG	119	136	1.01 (0.75-1.36)	0.12	134	121	0.90 (0.67-1.21)	0.93
		GG	19	5	0.23 (0.09-0.63)		10	16	1.60 (0.71-3.58)	
<i>CYP3A43</i>	rs800672	CC	113	116	ref		113	132	ref	
		CT	195	207	1.04 (0.75-1.44)	0.60	205	213	0.89 (0.65-1.23)	0.04
		TT	84	96	1.11 (0.75-1.64)		112	86	0.66 (0.45-0.96)	
<i>CYP19</i>	rs700519	CC	372	395	ref		424	408	ref	
		CT	28	34	1.14 (0.68-1.93)	0.61	15	28	1.93 (1.02-3.67)	0.04
		TT	0	0	NA		0	0	NA	

Abbreviations: 3α-dG = 3α androstane-3,17-diol glucuronide; SHBG = Sex hormone-binding globulin

* Analyses are adjusted for age and family history of prostate cancer, and include white men only.