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Joint effects of inflammation and androgen metabolism on prostate cancer severity

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Abstract

Multiple pathways of prostate carcinogenesis have been proposed, including those involving androgen metabolism and inflammation. These pathways are not independent, and may act together in prostate cancer etiology: androgens promote both inflammatory processes and serve as mitogens in prostate tumor growth. To explore the possible joint effects of these pathways in prostate cancer severity, we studied 1,090 Caucasian prostate cancer cases to evaluate whether tumor severity is influenced by a history of benign prostatic hyperplasia (BPH) interacting with genotypes involved in inflammation or androgen metabolism including *MSR1, RNASEL, AR, CYP3A4, CYP3A43, CYP3A5* and *SRD5A2*. We observed a statistically significant interaction between a number of genotypes and BPH. After considering the potential for false positive associations, the only remaining significant associations involved *CYP3A43* P340A genotypes and history of BPH on both Gleason grade (interaction *p*-value = 0.026) and tumor stage (interaction *p*-value = 0.017). These results suggest that androgen metabolism may act in concert with inflammatory phenotypes such as BPH in determining prostate cancer severity.

Keywords

prostate cancer; gene interactions; hormone metabolism; inflammation

The relationship between prostate cancer and physiological states with inflammatory components, including chronic prostatitis, proliferative inflammatory atrophy (PIA) and benign prostatic hypertrophy (BPH), is not well understood. BPH has been widely studied, but it is not understood whether BPH is a prostate cancer precursor lesion, or whether BPH simply shares similar risk factors and histological proximity with prostate cancer.[1] In epidemiologic studies, measurement error and bias probably have limited the ability to tease apart the relationship between BPH and prostate cancer risk.[2]

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Despite the limitations of epidemiological data in establishing the relationship of prostate cancer with states that have an inflammatory component, including BPH, there is growing evidence that chronic inflammation plays an important role in prostate carcinogenesis. PIA are highly proliferating cells that sometimes lead to high-grade prostatic intraepithelial neoplasia (PIN), and have been linked with prostate cancer risk.[1,3,4] Atrophy in and around BPH nodules in the transition zone of the prostate may be PIA.[3] As a result, some have proposed that BPH may be a form of PIA that occurs in the transitional zone.[3] Prostate inflammation can arise from a number of sources[3] including infection, hormonal exposures and injury that lead to exposure to reactive oxygen species and DNA damage. In addition, a number of genes have been identified that are associated with prostate cancer risk or severity and are also involved in immune/inflammatory processes. These include *MSR1, RNASEL*, toll-like receptors, *MUC1* and a number of genes that encode the interleukins and their receptors.[3,5]

Steroid hormones and the genes that regulate them may also influence prostate carcinogenesis by at least 2 mechanisms. First, androgens are known to influence the immune and inflammatory responses.[6,7] In the prostate, androgen withdrawal induces expression of genes involved in the immune/inflammatory response including members of the interleukin and interferon families.[8–10] Chronic administration of exogenous androgens (sometimes in the presence of exogenous estrogens) induces or suppresses a number of genes in the interferon and interleukin families,[8,9] some of which genes have androgen response promoter elements. There is also evidence for crosstalk between the androgen and interferon signaling pathways that involve both the androgen receptor (AR) and *RNASEL* that may contribute to cell survival and suppression of apoptosis in prostate carcinogenesis.[10] An inverse relationship is thought to exist between declining androgen levels and age in older men.[11] Therefore, it has been hypothesized that early inflammatory events stimulated by steroid hormone exposures may be required for prostate carcinogenesis.[12] Second, androgens regulate the growth and differentiation of the prostate as well as of BPH and prostate tumors.[13] It is well established that androgens serve as signaling growth factors in prostate tissue, through binding with AR to cause cellular proliferation to promote prostate carcinogenesis.[14,15]

While there is ample evidence for a role of inflammation as well as androgen metabolism in prostate carcinogenesis, interactions between these pathways in prostate cancer etiology is not well understood. We propose a model based on the schema of Palapattu et al.[16] and Ho et al.[12] that hypothesizes immune/inflammatory events causing chronic inflammation and PIA, PIN and/or BPH are associated with predisposition to prostate cancer, and that these events are regulated by genes that control androgen exposure as well as the immune/inflammatory response (Fig. 1). To address this hypothesis, we undertook a study of 1,090 Caucasian prostate cancer cases to evaluate whether interactions between BPH and genes involved in either inflammatory/immune and androgen metabolism pathways are associated with prostate cancer severity.

Methods

Study participants and data collection

A sample of 1,090 Caucasian incident prostate cancer cases was identified through Urologic Oncology Clinics at multiple hospitals of the University of Pennsylvania Health System (UPHS) and the adjacent Philadelphia Veteran's Administration Hospital between 1995 and 2006. Case status was confirmed by medical records review using a standardized abstraction form. Cases were excluded from our study if they reported having exposure to finasteride (Proscar) at the time of their prostate cancer diagnosis. Patients who were nonincident cases (*i.e.*, those diagnosed more than 12 months prior to the date of study ascertainment), or had a prior diagnosis of cancer at any site except nonmelanoma skin cancer, were also excluded.

Risk factor, medical history, prostate cancer screening history and prostate cancer diagnostic information was obtained using a standardized questionnaire and review of medical records. Information collected included personal history of BPH and vasectomy, previous cancer diagnoses and demographic information and prostate cancer screening history. Our definition of BPH was based around clinically evident or symptomatic BPH based on evidence from patient or clinician reports as confirmed in medical records. Therefore, this research reflects the association of clinically apparent BPH rather than a broader definition of BPH that may also include screened-detected BPH, although the latter may be under-ascertained in our sample. All study participants provided written informed consent for participation in this research under a protocol approved by the Committee for Studies Involving Human Subjects at the University of Pennsylvania and the Philadelphia Veteran's Administration Hospital.

Biosample collection and genotype analysis

Genomic DNA for the present study was self-collected by each study participant using sterile cheek swabs (Cyto-Pak Cytosoft Brush, Medical Packaging Corporation, Camarillo, CA), and processed using either a protocol modified from Richards et al. (43) as described previously (44) or using a modified protocol on the Qiagen 9604B robot with the QIAamp 96 DNA Buccal Swab Biorobot Kit (Valencia, CA). Genotypes were determined for putatively functional variants in a series of candidate androgen metabolism genes.

We chose candidate prostate cancer genotypes hypothesized to be involved in prostate carcinogenesis that may predict disease severity in 2 pathways: androgen metabolism and hereditary prostate cancer genes thought to be involved in inflammation. In each of these genes, we selected a variant that was most likely to be causally relevant based on prior associations or functional data. To ensure sufficient power for our interaction analyses, we only considered SNPs with a frequency of 5% or greater in every stratum defined by tumor characteristics (Gleason grade or tumor stage) and history of BPH. The variants selected for analysis were *ARCAG* repeat, *SRD5A2 A49T* (rs9282858), *CYP3A4**1B (rs2740574), *CYP3A5*3* (rs776746) and *CYP3A43*3* (P340A;rs680055),[17] *MSR1* TTAdel and *RNASEL* Arg462Gln (rs486907). Genotypes were determined as previously described.[17–19] For AR genotype determination, we used forward primer sequence 5′-TCC AGA ATC TGT TCC AGA GCG TG-3′ and reverse sequence 5′-GCT GTG AAG GTT GCT GTT CCT CAT-3′. Using the GC-Rich Kit (Roche), the 25 μl PCR reaction mixture included 6.5 μl double-distilled H_2O, 5 μl reaction buffer, 5 μl resolution solution, 0.5 μl enzyme mix, 2.5 μM of each primer (2×) and 2 μl template DNA. The temperature profile for the PCR reaction was 1 cycle of 95°C for 3 min; 10 cycles of 95° C for 30 sec, 57°C for 30 sec, 62°C for 45 sec; 30 cycles of 95°C for 30 sec, 57°C for 30 sec, 62°C for 45 sec plus 5 sec per cycle; 1 cycle of 72°C for 7 min; and a final hold at 10°C. Sequencing was completed using the reverse PCR primer.

Statistical methods

For genotype associations, we considered univariate and joint effects of each candidate gene with ever/never history of BPH. For all genes, we combined putative risk alleles based on functional information into binary genotype classes. For genotypes at each locus, we combined hypothesized risk alleles based on functional information into binary genotype classes coded 0 to represent the baseline risk genotype, and 1 to represent the “variant” genotype. Genotype associations were undertaken using unconditional logistic regression adjusted for age and educational attainment. Other confounders were explored, but only age and education changed the genotype point estimate by 10% or more, or were associated with a significance level of $p < 0.10$. We further evaluated whether there were differences in the association of genotypes by tumor characteristics, including organ-confined tumors (*i.e.*, stages T1 and T2) and tumors diagnosed with extracapsular extension or metastasis (*i.e.*, stages T3 and T4) as well as Gleason grade (*i.e.*, Gleason sum < 7 and Gleason sum > 7).

A 2-sided *p*-value of 0.05 or less was considered statistically significant. However, because we have performed multiple hypothesis tests, we also considered the potential for false-positive findings. Accordingly, we applied the false-positive report probability approach[20] that allows the investigator to interpret the results of hypothesis testing to ensure against making false-positive inferences. Our primary hypotheses involved tests for interaction among genotypes and BPH. We considered 14 *a priori* hypotheses involving interaction and 58 main effects corresponding to a total of 72 hypothesis tests. All analyses were performed in STATA (version 9.0, STATA Corporation, College Station, TX).

Results

Table I presents characteristics of the 1,090 Caucasian prostate cancer cases and genotype frequencies. The mean age of diagnosis for the sample as a whole was 60.9 years (SD = 7.3 years). Overall, 23% of men in our study sample had a history of BPH. This proportion was similar across stage and grade groups. Genotype frequencies at all loci were consistent with previously reported distributions in Caucasian men.[17,19]

Table II presents the results of the main effects, stratum-specific effects and interactions of genotypes and BPH on Gleason grade and tumor stage. The left-most column of results in Table II presents the main effect of genotype disregarding BPH status. The top row of results in Table II presents the main effect of BPH disregarding genotype. We observed no significant association between history of BPH and tumor severity for either Gleason grade or tumor stage. We also identified no statistically significant main effects of any genotype with tumor grade or stage.

The joint effect of genotype and BPH is presented as 3 odds ratios, all referent to the control stratum, which was defined as the group of individuals who did not carry the risk genotype and did not have prior BPH (denoted "(Ref)" in Table II): first, the effect of genotype among those with no prior BPH; second, the effect of BPH among those without the putative risk genotype; and finally the multiplicative interaction of BPH and genotype on the log odds scale. We observed a number of statistically significant interactions involving *CYP3A43*, *RNASEL* and *SRD5A2* (Table II).

First, we observed a statistically significant interaction between *CYP3A43* genotypes and history of BPH with both tumor stage ($p_{\text{interaction}} = 0.017$) and Gleason grade ($p_{\text{interaction}} = 0.026$). Individuals who carry any 340A genotype at *CYP3A43* had a higher probability of having an unfavorable Gleason grade tumor if they also had no prior BPH (OR = 1.82, 95% CI: 1.15–2.87). In contrast, those homozygous for the 340P allele are protected from having an unfavorable Gleason grade if they had a prior history of BPH (OR = 0.66, 95% CI: 0.44–0.99). A nonstatistically significant increased probability of having a higher grade tumor was also observed in men with both prior BPH and who were homozygous for the 340P allele. We also observed a significantly increased probability of having a high stage tumor among men who had both prior BPH and carried any Ala allele at *CYP3A43* (OR = 3.50, 95% CI: 1.21–10.17). The direction of the other odds ratios involved in this interaction was similar to that seen for Gleason grade.

Second, we observed a statistically significant interaction of *RNASEL* R462Q genotypes with BPH ($p_{\text{interaction}} = 0.042$). Men who are homozygous for the 462R allele and who have a prior BPH are less likely to have a high-grade tumor than men who had no prior BPH and this same genotype (OR = 0.48, 95% CI: 0.24–0.95).

Third, we observed a statistically significant interaction of *SRD5A2* A49T ($p_{\text{interaction}} = 0.018$) genotypes with BPH on Gleason grade. Men who have any 49T allele and who have a prior

BPH are more likely to have a high-grade tumor than men who had no prior BPH and did not carry a 49T allele (OR = 11.35, 95% CI: 1.24–104.33).

To evaluate whether the statistically significant associations reported in Table II represent false-positive findings, we calculated the false-positive report probability[20] for associations in which statistically significant interactions were observed by assuming prior probabilities of association to be 0.05, 0.1 and 0.2. For 2 main effect odds ratios that we reported as statistically significantly different from an odds ratio of 1.0, the false-positive report probability was less than 0.2 even for a low prior probability of association. The 2 associations that appeared to be the least likely to be false positive effects based on these criteria both involved *CYP3A43* and BPH. In the first situation, an OR = 1.82 (95% CI: 1.15–2.87) was observed for the relationship of these factors with Gleason grade (Table II). In the second situation, an OR = 3.5 (95% CI: 1.21–10.17) was observed for the relationship of these factors with tumor stage. A false-positive report probability of 0.2 or less was observed when the prior probability of these associations was assumed to be 0.05 or more. That is, these estimated odds ratios can be considered likely to be true-positive associations only when the prior probability for this association is assumed to be 0.05 or more. This prior probability may be reasonable given the biologic plausibility that the androgenic activity of *CYP3A43* could be involved in mediating the biologic effect of prostate inflammation. For the remaining statistically significant interactions and the associated stratum-specific OR's, FPRP probabilities were not lower than 0.3 and the best of these FPRP probabilities were only seen for very high prior probabilities of >0.1. Therefore, we cannot exclude the possibility that these associations represent false positive reports, and we conclude that only those that involve *CYP3A43* (Table II) represent noteworthy findings.

Discussion

Prostate carcinogenesis has been hypothesized to involve both inflammation and androgen exposure. To date, neither epidemiological studies nor molecular approaches have resolved whether BPH is a direct precursor of prostate cancer or whether it is not a precursor but shares similar risk factors and histological proximity to prostate cancer.[1] In part, the difficulty in resolving the BPH-prostate cancer relationship may be confounded by the use of prostate cancer screening, where the presence of BPH may directly influence prostate cancer detection and diagnosis.

PIA, sometimes leading to high grade PIN, has been linked with prostate cancer risk.[1,3] BPH can be considered a form of PIA.[3] cDNA microarray analysis of BPH and prostate cancer revealed that patients with the severe form of BPH and patients with prostate cancer exhibit similar genetic alterations involving primarily growth regulating and signaling genes, stroma-associated genes and immunological genes.[21] Thus, it is likely that chronic inflammation, including PIA/BPH, plays a role in prostate carcinogenesis. Furthermore, androgens are involved both in the generation of chronic inflammation and as growth factors that promote the proliferation and growth of prostate tumors. Therefore, it is reasonable to hypothesize that prostate tumors initiated under conditions of chronic inflammation are fed by androgen exposures to lead to clinically more severe tumor phenotypes (Fig. 1).

The data presented here support this hypothesis. We observed interactions of BPH with a number of candidate genes, including *RNASEL*, *CYP3A43* and *SRD5A2*. After considering the potential that these interactions and stratum-specific odds ratios represented false positive findings, only the associations involving *CYP3A43* remained noteworthy. *CYP3A43* may catalyze the oxidative metabolism of testosterone into less active metabolites including 2β-, 6β- and 15β-hydroxytestosterone.[22] The function of the *CYP3A43* P340A variant is not known, but it has been previously reported in 2 independent studies[17,23] to be associated with

increased prostate cancer risk. In the present study, we report that the increased risk of high Gleason grade or high stage prostate cancer appears in men homozygous for the 340P allele who have had prior BPH, as well as in those that have both the 340A allele and no history of BPH. Men with any 340A allele and prior BPH are protected from high-grade tumors. These results suggest that the *CYP3A4* P340A variant may modulate the effect of BPH on prostate cancer severity. While our stated hypothesis is that androgen metabolism may drive prostate cancer etiology, there is also a relationship between inflammation and estrogen metabolism.[24] Since CYP3A43 may act in the metabolism of both androgens and estrogens, the present results do not clarify whether the effect of CYP3A43 is through androgen metabolism pathways, through the related estrogen metabolism pathways, or both. Additional studies are required to further inform the specific hormonal effects that explain our observations.

There are a number of limitations to the analyses presented here. We have attempted to assess first-order interactions between a selected set of candidate genotypes and BPH. The power to address these interactions is limited, so we have not considered some rare variants in the present analyses. In addition, the variants studied here may not be causative of the effects we report, particularly if they are in linkage disequilibrium with other variants in these genes. We assessed BPH by using self report and medical records that were available from patients in our study. No systematic assessment of BPH was used on all patients in our study. Therefore, it is possible that we have misclassified the true prevalence of BPH in the men studied here. This misclassification would tend to bias the association of BPH with prostate cancer toward the null hypothesis. However, because men with symptoms of BPH may be more likely to be screened for prostate cancer, it is not clear how this misclassification may affect the association with disease severity as reported here. Furthermore, it is difficult to assess the direction or magnitude of bias that may be acting to influence genotype-BPH interactions in disease severity. A related concern of our approach is that the anatomical location of BPH or prostate tumors was not available. Therefore, our analyses are unable to asses whether the inflammation that is relevant to prostate carcinogenesis may be localized to the transitional zone or other areas of the prostate, and may not reflect a prostate-wide phenomenon. Finally, we specified a large number of *a priori* hypothesis tests, and it was therefore important to determine if we detected false-positive associations. We have computed the false-positive report probability of Wacholder et al.[20] to aid in interpreting our findings. In situations which we have observed statistically significant associations (Table II), the false-positive report probability results led us to conclude that some of the associations identified here were not noteworthy. Thus, we have been conservative in our interpretation of our results, despite statistically significant *p*-values for some associations. Although we have limited our analyses to evaluate first-order interactions between genotypes and BPH, the sample sizes for the joint effects of these factors sometimes were very small. Therefore, we may not have the power to detect some important effects in groups for which the joint genotype-BPH interaction effects were small. Despite these limitations, the present results suggest that further exploration of the relationship between chronic inflammation and genes involved in inflammation or androgen-mediated growth may be of interest.

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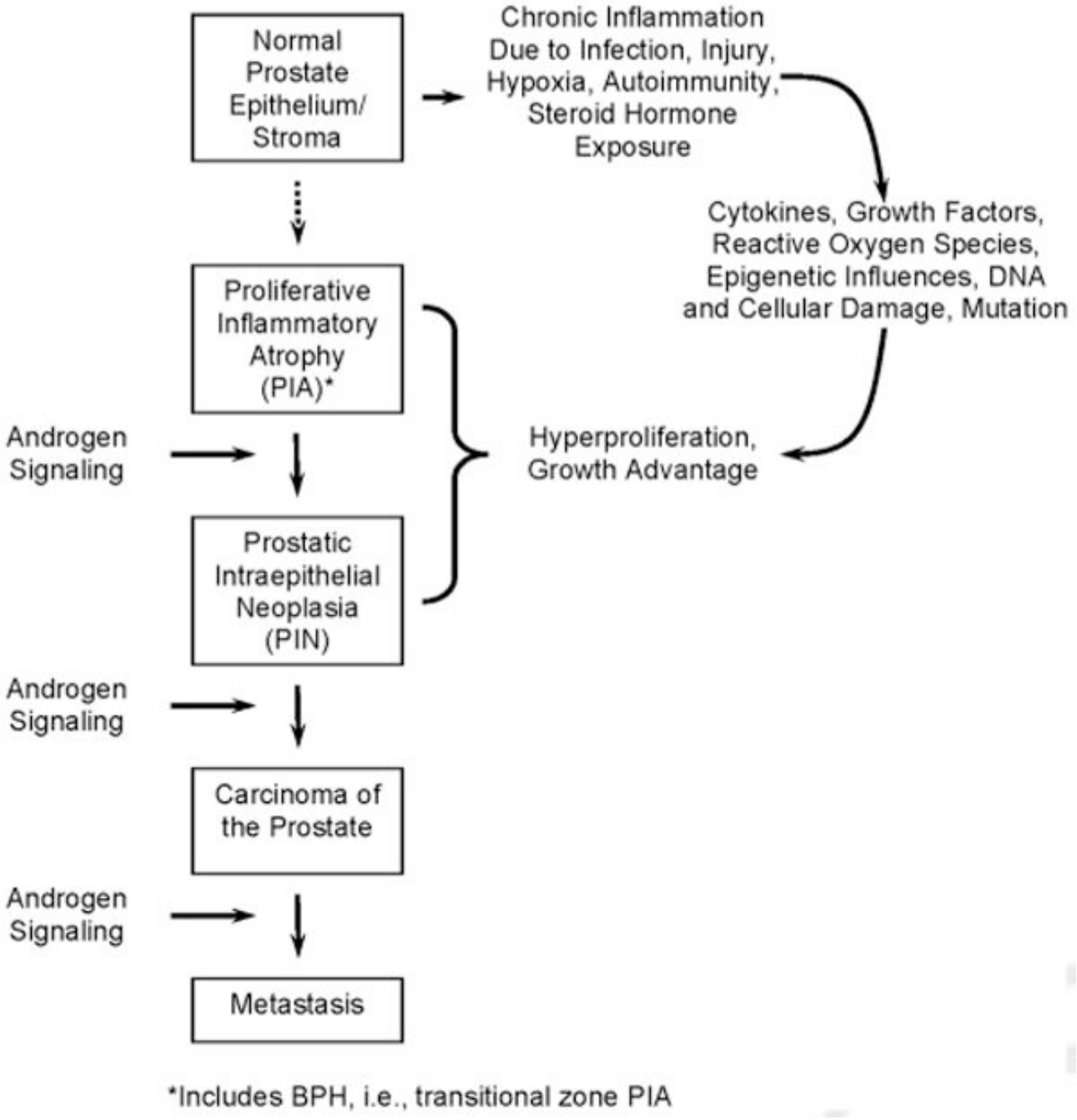

Figure 1.
Model of inflammatory and androgenic influences on prostate cancer etiology and outcome.

Table I

Descriptive Characteristics of the Prostate Cancer Case Sample

Variable		Total (*N* = 1,090)	Gleason < 7 (*N* = 619)	Gleason ≥ 7 (*N* = 417)	TNM stage 1–2 (*N* = 802)	TNM stage 3–4 (*N* = 260)
Mean age at diagnosis in years (SD)		60.9 (7.3)	60.4 (7.5)	61.0 (6.8)	61.2 (7.2)	59.1 (6.7)
BPH	Never	720 (77%)	336 (66%)	291 (76%)	440 (72%)	170 (78%)
	Ever	221 (23%)	130 (28%)	90 (24%)	171 (28%)	48 (22%)
AR-CAG	≥20 Repeats	404 (69%)	212 (66%)	163 (72%)	260 (69%)	101 (69%)
	<20 Repeats	184 (31%)	108 (34%)	62 (28%)	118 (31%)	46 (31%)
CYP3A4	Any *1B	59 (7%)	30 (7%)	23 (6%)	41 (7%)	12 (6%)
	*1A/*1A	788 (93%)	408 (93%)	338 (94%)	535 (93%)	194 (94%)
CYP3A5	*3/*3	681 (85%)	350 (85%)	299 (87%)	466 (86%)	176 (24%)
	Any *1	121 (15%)	61 (15%)	46 (13%)	78 (14%)	24 (12%)
CYP3A43	340PP	514 (76%)	273 (77%)	226 (82%)	365 (80%)	126 (79%)
	Any 340A	159 (24%)	83 (23%)	50 (18%)	92 (20%)	34 (21%)
MSR1	No TTA/del	43 (10%)	18 (8%)	23 (12%)	26 (9%)	15 (13%)
	Any TTA/del	387 (90%)	198 (82%)	175 (88%)	274 (91%)	97 (87%)
RNASEL	462RR	203 (42%)	107 (45%)	85 (43%)	146 (43%)	45 (36%)
	Any 462Q	283 (58%)	129 (55%)	146 (63%)	196 (57%)	78 (63%)
SRD5A2	49AA	697 (94%)	351 (94%)	301 (94%)	479 (94%)	159 (92%)
	Any 49T	46 (6%)	23 (6%)	20 (6%)	28 (6%)	13 (8%)

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Table II

Odds Ratios[1] and 95% Confidence Intervals for Main Effects and Interactions of Candidate Genotypes and History of BPH on Tumor Severity

	Gleason grade (<7 *vs.* ≥7)				TNM stage (<TNM 1,2 *vs.* >TNM 3,4)			
	Genotype main effect	**No prior BPH**	**Prior BPH**	**Interaction *p*-value**	**Genotype main effect**	**No prior BPH**	**Prior BPH**	**Interaction *p*-value**
effect	—	(1)	0.82 (0.59–1.13)	—	—	(1)	0.85 (0.59–1.25)	—
Variant class								
≤ 20 Repeats	(1)	(Ref)	0.77 (0.47–1.26)	0.994	(1)	(Ref)	0.96 (0.55–1.68)	0.556
>20 Repeats	0.79 (0.54–1.16)	0.79 (0.51–1.21)	0.78 (0.36–1.68)		1.03 (0.67–1.57)	0.96 (0.59–1.57)	1.25 (0.56–2.78)	
Any *1B	(1)	(Ref)	0.37 (0.09–1.55)	0.282	(1)	(Ref)	1.11 (0.23–5.26)	0.778
*1A/*1A	1.14 (0.64–2.01)	0.93 (0.48–1.80)	0.88 (0.62–1.23)		1.25 (0.64–2.45)	1.34 (0.62–2.93)	0.82 (0.55–1.23)	
*3/*3	(1)	(Ref)	0.90 (0.63–1.29)	0.483	(1)	(Ref)	0.83 (0.55–1.26)	0.687
Any *1	0.81 (0.53–1.25)	0.89 (0.54–1.47)	0.62 (0.24–1.57)		0.79 (0.48–1.32)	0.74 (0.41–1.35)	1.06 (0.36–3.10)	
340PP	(1)	(Ref)	2.08 (0.80–5.44)	0.026	(1)	(Ref)	3.50 (1.21–10.17)	0.017
Any 340A	1.41 (0.94–2.12)	1.82 (1.15–2.87)	0.66 (0.44–0.99)		0.96 (0.61–1.52)	1.27 (.75–2.15)	0.78 (0.48–1.26)	
No TTA/del	(1)	(Ref)	0.25 (0.06–1.06)	0.116	(1)	(Ref)	0.78 (0.35–1.76)	0.800
Any TTA/del	0.69 (0.36–1.33)	0.49 (0.22–1.10)	0.89 (0.56–1.42)		0.59 (0.30–1.17)	0.56 (0.25–1.25)	1.23 (0.68–2.23)	
462RR	(1)	(Ref)	0.48 (0.24–0.95)	0.042	(1)	(Ref)	0.77 (0.18–3.23)	0.336
Any 462Q	1.39 (0.95–2.02)	1.09 (0.70–1.68)	1.23 (0.72–2.11)		1.26 (0.82–1.95)	1.11 (0.67–1.84)	0.96 (0.56–1.64)	
49AA	(1)	(Ref)	0.77 (0.54–1.10)	0.018	(1)	(Ref)	0.90 (0.59–1.37)	0.169
Any 49T	1.01 (0.53–1.90)	0.62 (0.30–1.30)	11.35 (1.24–104.33)		1.26 (0.62–2.58)	0.97 (0.42–2.24)	2.89 (0.57–14.73)	

os adjusted for age and educational attainment.