**VDR and SRD5A2 Polymorphisms Combine to Increase Risk for Prostate Cancer in Both Non–Hispanic White and Hispanic White Men**

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Abstract

**Purpose:** Vitamin D and dihydrotestosterone pathways interact to promote the growth of prostatic tissue. The nuclear vitamin D receptor (VDR) moderates the actions of vitamin D. 5α-Reductase type II (SRD5A2) codes for the enzyme that converts testosterone to dihydrotestosterone in the prostate. This study tested the interactions of VDR (CDX2, FokI) and SRD5A2 (V89L, A49T) polymorphisms, and their associations with prostate cancer.

**Experimental Design:** This genetic association study included 932 non–Hispanic White (NHW) men and 414 Hispanic White (HW) men from South Texas. Cases had biopsy-confirmed cancer; controls had normal digital rectal exams and serum prostate-specific antigen levels of ≤2.5 ng/mL.

**Results:** Using logistic regression analyses to test associations with prostate cancer, only the V89L polymorphism (VV genotype compared with LL/LV) in HW men was statistically significant [odds ratios (OR), 0.64; 95% confidence intervals (95% CI), 0.41-0.99]. The interaction terms for FokI and V89L in NHW men and CDX2 and V89L in HW men in the logistic model were significant (P = 0.02 and 0.03, respectively). When stratified by V89L genotype, the FokI polymorphism (TT/TC versus CC) was significantly associated with prostate cancer in NHW men with the V89L VV genotype (FokI OR, 1.53; 95% CI, 1.06-2.23). The CDX2 polymorphism (GG versus AG/AA) was significantly associated with prostate cancer only in HW men with the V89L VV genotype (CDX2 OR, 3.16; 95% CI, 1.39-7.19; interaction term P = 0.02).

**Conclusion:** Our results indicate that the SRD5A2 V89L VV genotype interacts with VDR FokI TT/CT genotypes in NHW men and VDR CDX2 GG genotypes in HW men to increase the risk for prostate cancer.

Prostate cancer is the most commonly diagnosed non–skin cancer and one of the 10 leading causes of death in American men (1). The etiology of prostate cancer is not well known, although both genetic and environmental factors are believed to play a role. A twin study from Scandinavia estimated that 42% of the risk for prostate cancer might be explained by heritable factors (2). A diverse range of foods and nutrients have been found to moderately affect risk for prostate cancer, including soy, isoflavones, milk, saturated fats, and tomato products (3).

A link between prostate cancer and vitamin D has been hypothesized. Lower levels of vitamin D in the serum have been associated with increased prostate cancer risk (4). In vitro studies have found that treating prostate cancer cells with vitamin D inhibits cell proliferation (5). Given these observations, it has been proposed that adequate circulating levels of vitamin D are important to protect against prostate cancer.

The androgen testosterone and its bioactive form, dihydrotestosterone (DHT), are necessary for the normal growth and development of the prostate, and epidemiologic evidence supports their role in the etiology of prostate cancer (6). 5α-Reductase type II is the primary enzyme that converts testosterone to DHT in the prostate (7). Men who lack the gene that codes for 5α-reductase type II have low DHT levels
and small prostates (8). Finasteride, an inhibitor of 5α-reductase type II, reduces the growth of cells from the androgen-dependent LNCaP prostate cancer cell line (9) and is associated with a decrease in tissue DHT levels (10). The Prostate Cancer Prevention Trial showed that men given finasteride had a 24.8% reduction in cancer prevalence over 7 years compared with men given placebo (11). Increased expression of 5α-reductase type II is also associated with recurrent and metastatic prostate cancer implying a role for the enzyme and DHT in prostate cancer progression (12).

The growth and differentiation of normal prostatic tissue is promoted by interactions between the vitamin D and DHT pathways (13). Levels of the bioactive form of vitamin D, calcitriol, are controlled in an autocrine fashion to regulate cell growth and decrease the risk of the cells becoming malignant. DHT seems to act as a regulator of vitamin D activity. When cells from the prostate cancer cell line LNCaP are grown in androgen-depleted medium, vitamin D no longer inhibits cell growth. With the addition of DHT, even at low physiologic levels (1 nmol/L), the antiproliferative effects of vitamin D are restored (14). It was later shown that this effect is mediated by DHT-induced suppression of 24-hydroxylase expression, the enzyme that inactivates calcitriol (15) and its precursor form (16). Additionally, in two androgen receptor–positive prostate cancer cell lines (DHT binds to androgen receptor), androgen receptor signaling was shown to be required for the vitamin D–mediated growth inhibition of the cancer cells (17). This sets up a paradox of androgens being associated with higher risk for cancer development, but at the same time being important for the anticancer activities of vitamin D.

Located on chromosome 12q13-q14, the high-affinity nuclear vitamin D receptor (VDR) gene mediates most of the biological activity of vitamin D (17). If vitamin D can regulate the growth of normal and cancerous prostate cells, then variations in the activity of the VDR may be important in the onset and progression of prostate cancer. Two of the commonly studied VDR polymorphisms, FokI and CDX2, result in functional changes. The FokI (T/C) variant alters the translation start site resulting in two isoforms of the VDR protein with differing activities (18), with the protein product from the FokI T form exhibiting less transcriptional activation than the product from the wild-type C form (19). The presence of the FokI C allele was found to affect immune cell behavior resulting in a more active immune system (20). The CDX2 variant in the promoter region of the VDR modulates promoter activity, and the CDX2 G allele, the most common allele, shows 30% less transcriptional activity compared with the A allele (21). Several studies of the FokI polymorphism and its association with prostate cancer have produced inconsistent results and a meta-analysis of several VDR polymorphisms concluded that FokI was unlikely to have a major role in prostate cancer (22). CDX2 has been less extensively studied but it was found to increase the risk for prostate cancer in men with the heterozygous genotype and high UV-B exposure (23).

The gene that codes for 5α-reductase type II, SRD5A2, located on chromosome 2, has several polymorphisms that have been studied for their relationship with prostate cancer. The most common polymorphism is V89L, which substitutes valine at codon 89 with leucine by a C to G nucleotide transversion. The leucine allele (L) reduces 5α-reductase activity resulting in lower DHT levels (24, 25). The A49T polymorphism results in a threonine substitution for alanine and is associated with increased 5α-reductase activity in vitro causing increased DHT production that may contribute to prostate cancer development or progression (26). The relationship of the V89L and A49T polymorphisms with prostate cancer has not been proven conclusively. A meta-analysis of SRD5A2 polymorphisms concluded that the V89L polymorphism likely has no, or little, relationship to prostate cancer risk and that A49T may have a modest effect, accounting for only a small proportion of prostate cancer (27).

Because of the complex etiology of prostate cancer, the effects of many individual genetic polymorphisms are likely to be small. It is possible that larger effects may only be observed when polymorphisms are considered in combination. A polygenic model incorporating multiple loci might maximize the detection of individuals at high risk for prostate cancer (28).

The current study tested possible interactions of the VDR and SRD5A2 genes as identified by two functional polymorphisms in each gene in determining risk for prostate cancer in a cohort of non–Hispanic White (NHW) and Hispanic White (HW) men from South Texas. The a priori hypotheses of this study were that the FokI T allele and the CDX2 G allele, which both result in decreased vitamin D receptor activity, in combination with the V89L V or A49T T alleles, which result in higher levels of DHT, would lead to increased risk for prostate cancer. Although DHT is important for vitamin D activity and higher DHT levels might be hypothesized to reduce risk by increasing vitamin D levels, we believe that the less efficient vitamin D receptor as indicated by the presence of the FokI T and CDX2 G alleles will not use the higher vitamin D levels to counter the increased risk posed by higher DHT levels.

Materials and Methods

Study population. Study participants came from the population-based prospective San Antonio Biomarkers of Risk (SABOR) for prostate cancer cohort study at the University of Texas Health Sciences Center at San Antonio, San Antonio, TX (29). SABOR began enrolling men in May 2001 to examine differences in risk for prostate cancer by race/ethnicity. Three racial/ethnic groups reflecting the diversity of the Southern Texas population were enrolled: NHW, HW, and African Americans. Only NHW and HW men were used in this study due to limited numbers of African American men (less than 65 prostate cancer cases). Race is self-identified and Hispanic ethnicity was assigned using the Hazuda model for the identification of Mexican Americans and other Hispanic ethnicities (30). The Hispanic population of South Texas is ~95% Mexican American. All participants consented to the genetic studies in accordance with the rules and regulations of the Institutional Review Board of University of Texas Health Sciences Center at San Antonio.

Cases in this analysis were men with histologically confirmed prostate cancer in the SABOR cohort, as well as men diagnosed with confirmed prostate cancer from the same clinics and health fairs from which the SABOR cohort was recruited. Gleason scores (range 2-10) were determined from chart reviews. High-grade cancers were defined as cases with Gleason scores of ≥7. Prostatectomy scoring was used preferentially over biopsy scores when available.

Controls, selected from the SABOR cohort, were eligible for this analysis if they had prostate-specific antigen values of <2.5 ng/mL at all visits (up to five annual visits) and a normal digital rectal exam at all visits. Age, defined as age at diagnosis for the cases and age at last visit for the controls, was truncated at ≥45 years old for both cases and
controls. The study population consisted of 1,346 men for a total of 585 cases and 761 controls. HW men accounted for 44% of the study sample.

Polymorphism selection and genotyping. Two VDR polymorphisms and two SRD5A2 polymorphisms were genotyped: CDX2 (rs17883968; G/A) in the VDR promoter region and FokI (rs10735810; C/T) in VDR exon 2, and V89L (rs523349) and A49T (rs9282858) in exon 1 of the SRD5A2 gene.

DNA for genotyping was extracted from blood samples using a QiAamp blood kit (Qiagen). Genotyping for CDX2, V89L, and A49T was done with TaqMan allelic discrimination assays using the ABI 7900 HT Sequence Detection System (Applied Biosystems). Originally, a TaqMan assay could not be successfully designed for FokI. This polymorphism was genotyped using endonuclease restriction enzyme digestion. Subsequently, a FokI kit was developed and purchased. To do a quality control check on the original FokI genotyping, 324 men (19% of the sample) were re-genotyped using the TaqMan kit. There was only one discrepancy between the two methodologies for an error rate of 0.3%. Applied to our larger sample of 1,685 men, this means that there were potentially 5 men who were discordant. We feel that this is an acceptable error rate and that the original methodology is validated. All genotyping was done in a molecular genetics laboratory at the University of Texas Health Science Center at San Antonio.

Men homozygous for each risk allele in the individual polymorphisms were compared with heterozygotes and homozygotes for the complimentary allele combined. Men homozygous for the VDR CDX2 risk allele (G) were compared with men with AG or AA genotypes. For the SRD5A2 V89L polymorphism, the VV genotype was compared with LL and LV genotypes in all analyses. Due to a limited number of men homozygous for the risk alleles in the VDR FokI and SRD5A2 A49T polymorphisms, the risk genotype was combined with the heterozygous genotype and compared with men homozygous for the complimentary allele. Thus, for FokI, the comparison was between TT/CT and CC genotypes, and for A49T, it was between the TT/AT and AA genotypes if any TT genotypes were found.

Statistical analyses. All analyses were stratified according to ethnicity. Associations between genotypes and prostate cancer were assessed by $\chi^2$ test (Pearson $\chi^2$ with 1 or 2 df) and logistic regression analyses. All logistic regression models included age as a continuous variable. Interactions between VDR and SRD5A2 polymorphisms were tested in the logistic regression analyses by adding an interaction term to the model. Nominal logistic regression was used to test the relationship of the Gleason score groups (low grade, 2-6; and high grade, 7-10) to controls as the referent group. For hypothesis testing, $z = 0.05$ was used whereas 95% confidence intervals (95% CI) were computed for all relative risk estimates (odds ratios, OR). For NHW men, the study sample size had 80% power for one discrepancy between the two methodologies for an error rate of 3%. Applied to our larger sample of 1,685 men, this means that there were potentially 5 men who were discordant. We feel that this is an acceptable error rate and that the original methodology is validated. All genotyping was done in a molecular genetics laboratory at the University of Texas Health Science Center at San Antonio.

Results

The study sample consisted of 932 NHW men (444 cases and 488 controls) and 414 HW men (141 cases and 273 controls; Table 1). Controls were somewhat younger than cases in both ethnic groups. Gleason score distribution was not different between ethnic groups.

Genotype distributions for the individual polymorphisms within each ethnic group did not differ by case-control status (Table 2). Genotype distributions for controls differed by ethnicity, however, for the VDR FokI and the SRD5A2 V89L polymorphisms. Approximately 13% of NHW controls had the FokI TT genotype compared with 21% of HW controls ($P = 0.009$). For the V89L polymorphism, 52% and 44% of

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<th>Table 1. Participant characteristics</th>
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<tr>
<td>n</td>
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<tr>
<td>Age (y)</td>
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<td>45-59</td>
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<td>60-69</td>
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<td>70+</td>
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<td>Median</td>
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</table>

$^*P < 0.0001$ for differences between cases and controls in both ethnic groups ($t$ test).

$^1P < 0.23$ for differences between NHW and HW men (Wilcoxon rank sum test).

NHW and HW controls, respectively, had the VV genotype ($P = 0.001$). The genotype distributions in controls for these polymorphisms do not differ significantly from previously published results (31, 32). Additionally, CDX2 genotype distributions in NHW controls are similar to what was found earlier (33). There are no published data on CDX2 for HW men.

All polymorphisms were in Hardy-Weinberg equilibrium within each ethnic group. ORs and 95% CIs for the hypothesized risk genotypes are presented in Table 2. The SRD5A2 A49T AT genotype was compared with the AA genotype as there were no homozygous TT genotypes in the sample. Only the V89L polymorphism in HW men was marginally significant (VV OR, 0.64; 95% CI, 0.41-0.99; $P = 0.05$). No significant results were seen with the A49T polymorphism and, given the small number of men with the T allele, no interaction analyses were done with this polymorphism.

Evidence of effect modification of the VDR FokI polymorphism by SRD5A2 V89L was found (logistic regression interaction term, $P = 0.02$). When the effect of the FokI polymorphism was analyzed by V89L genotype, the previously nonsignificant FokI effect was significant in NHW men (Table 3). In men with the V89L VV genotype, men with the FokI TT or CT genotypes were at a 50% increased risk for prostate cancer (OR, 1.53; 95% CI, 1.06-2.23; $P = 0.03$). There was no evidence of interaction between FokI and V89L in HW men.

There was evidence of effect modification of the VDR CDX2 polymorphism by V89L in HW men (logistic regression interaction term, $P = 0.03$). Men with the higher-risk V89L VV genotype combined with another higher-risk genotype, the CDX2 GG genotype, to increase risk for prostate cancer. HW men with the CDX2 GG and V89L VV genotypes have more than three times the risk for prostate cancer (CDX2 GG OR, 3.16; 95% CI, 1.39-7.19; $P = 0.01$; Table 4). There was no evidence of interaction in NHW men.

The individual polymorphisms were investigated for their associations with higher Gleason score (the measure of cancer grade). Gleason score is an important predictor of disease.
progression (34). Decrease in differentiation as measured by the Gleason grade is related to lack of tissue function and the Gleason score correlates with overall disease-free survival: the higher the score, the more likely that disease will recur (35). There was no evidence of associations with Gleason grade in HW men or in NHW men (results not shown).

### Discussion

This study is one of the few to examine genetic risks for prostate cancer in a group of Hispanic men. Using a population of NHW and HW (largely Mexican American) men from South Texas, we found evidence of interaction between three

### Table 3. Distribution of VDR FokI genotypes stratified by SRD5A2 V89L LL/LV and VV genotype groups with age-adjusted logistic regression ORs and 95% CI for associations of FokI TT/CT genotypes with prostate cancer in NHW and HW men

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>V89L Genotype</th>
<th>FokI Genotype</th>
<th>No. (%)</th>
<th>P*</th>
<th>FokI OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHW</td>
<td>VV</td>
<td>TT/CT</td>
<td>276 (62)</td>
<td>290 (59)</td>
<td>0.39</td>
<td>1.12 (0.86-1.46)</td>
</tr>
<tr>
<td></td>
<td>VV</td>
<td>CC</td>
<td>168 (38)</td>
<td>198 (41)</td>
<td></td>
<td>1.0</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.03</td>
<td>1.53 (1.06-2.13)</td>
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<td></td>
<td></td>
<td></td>
<td>0.33</td>
<td>0.79 (0.54-1.16)</td>
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<td>1.0</td>
<td>1.0</td>
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<td></td>
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<td></td>
<td></td>
<td>0.77</td>
<td>1.00 (0.63-1.57)</td>
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<td></td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>VV</td>
<td>TT/CT</td>
<td>96 (68)</td>
<td>182 (67)</td>
<td>0.03</td>
<td>1.43 (0.66-3.13)</td>
</tr>
<tr>
<td></td>
<td>VV</td>
<td>CC</td>
<td>45 (32)</td>
<td>91 (33)</td>
<td></td>
<td>1.0</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.34</td>
<td>0.86 (0.49-1.54)</td>
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<td></td>
<td>1.0</td>
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</table>

*Pearson $\chi^2$ test with 1 df.

1 Interaction term in full logistic regression model for FokI-V89L ($P = 0.02$).

2 Interaction term in full logistic regression model for FokI-V89L ($P = 0.32$).
Table 4. Distribution of VDR CDX2 genotypes stratified by SRD5A2 V89L LL/LV and VV genotype groups with age-adjusted logistic regression ORs and 95% CIs for associations of CDX2 GG genotype with prostate cancer in NHW and HW men

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>V89L Genotype</th>
<th>CDX2 Genotype</th>
<th>No. (%)</th>
<th>P*</th>
<th>CDX2 OR (95% CI)</th>
<th>P</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHW†</td>
<td>All</td>
<td>GG</td>
<td>282 (64)</td>
<td>323 (66)</td>
<td>0.39</td>
<td>0.87 (0.67-1.14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AG/AA</td>
<td>162 (36)</td>
<td>165 (34)</td>
<td>1.0</td>
<td>0.57 (0.35-0.92)</td>
</tr>
<tr>
<td></td>
<td>VV</td>
<td>GG</td>
<td>140 (61)</td>
<td>164 (65)</td>
<td>0.31</td>
<td>0.82 (0.57-1.20)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AG/AA</td>
<td>90 (39)</td>
<td>87 (35)</td>
<td>1.0</td>
<td>0.57 (0.35-0.92)</td>
</tr>
<tr>
<td></td>
<td>LV/LL</td>
<td>GG</td>
<td>142 (66)</td>
<td>159 (67)</td>
<td>0.87</td>
<td>0.93 (0.63-1.39)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AG/AA</td>
<td>72 (34)</td>
<td>78 (33)</td>
<td>1.0</td>
<td>0.93 (0.63-1.39)</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>GG</td>
<td>98 (69)</td>
<td>174 (64)</td>
<td>0.24</td>
<td>1.57 (0.99-2.50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AG/AA</td>
<td>43 (31)</td>
<td>99 (36)</td>
<td>1.0</td>
<td>0.93 (0.63-1.39)</td>
</tr>
<tr>
<td></td>
<td>VV</td>
<td>GG</td>
<td>42 (81)</td>
<td>74 (62)</td>
<td>0.02</td>
<td>3.16 (1.39-7.19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AG/AA</td>
<td>10 (19)</td>
<td>45 (38)</td>
<td>1.0</td>
<td>0.93 (0.63-1.39)</td>
</tr>
<tr>
<td></td>
<td>LV/LL</td>
<td>GG</td>
<td>56 (63)</td>
<td>100 (65)</td>
<td>0.75</td>
<td>1.13 (0.63-2.02)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AG/AA</td>
<td>33 (37)</td>
<td>54 (35)</td>
<td>1.0</td>
<td>0.93 (0.63-1.39)</td>
</tr>
</tbody>
</table>

*Pearson χ² with 1 df.
†Interaction term in full logistic regression model for CDX2-V89L (P = 0.63).
‡Interaction term in full logistic regression model for CDX2-V89L (P = 0.03).

functional polymorphisms from two genes in the vitamin D and androgen pathways to affect risk for prostate cancer. In NHW men, there was an interaction between the VDR FokI and SRD5A2 V89L polymorphisms to increase risk in men with the FokI TT or CT genotypes and the V89L VV genotype. On the other hand, in HW men, the interaction for increased risk was between the VDR CDX2 GG and V89L VV genotypes.

This study examined two genes potentially involved with prostate cancer risk in combination. A polygenic approach may be a more appropriate method to study genetic associations with complex diseases such as cancer (28). The association of FokI with colon cancer was seen only when analyzed in women with less than 23 CAG repeats in the androgen receptor (36). The association with prostate cancer aggressiveness of a polymorphism in a gene that codes for an enzyme involved with the degradation of DHT, 3β-hydroxysteroid dehydrogenase type II, is strengthened when analyzed by SRD5A2 V89L genotype (37).

This study found a heterogeneity of effects according to ethnicity. Neither FokI nor V89L alone were associated with prostate cancer in NHW men, but taken together, the odds for disease were increased by 50% in men with the FokI TT/CT and V89L VV genotypes. No such association was found in HW men. HW men had more than three times the odds of prostate cancer if they had the CDX2 GG and the V89L VV genotype.

Previous studies have also observed the heterogeneity of effects by ethnicity with the FokI polymorphism. For example, a significant trend for increasing waist-to-hip ratio with FokI genotype was found in Hispanic women but not in NHW women (31).

Differences in linkage disequilibrium to unmeasured genes and/or gene-gene interactions may contribute to the differences found by ethnicity. It is possible that these differences may depend on the different combinations of these genes, or other unmeasured genes, either linked or unlinked to the FokI, CDX2, and V89L polymorphisms. The findings of this study suggest that associations and interactions of the VDR and SRD5A2 polymorphisms may be specific to ethnicity, arguing that research results should be stratified by race or ethnicity.

The association of the SRD5A2 V89L polymorphism with prostate cancer ran counter to our hypothesized effect. We hypothesized that the VV genotype would be associated with increased risk for prostate cancer compared with the LL genotype because the L allele is associated with a moderate reduction in 5α-reductase type II activity resulting in lower DHT levels (24). A meta-analysis of SRD5A2 polymorphisms, however, concluded that the V89L polymorphism likely has no, or little, relationship to prostate cancer risk (27). Most of the studies in the meta-analysis were done in NHW or African American men. Information on Hispanic men is sparse. A 2005 study in Southern California found that Hispanics with the LL genotype were at significantly increased risk from prostate cancer compared with men with the VV genotype (OR, 7.3; 95% CI, 1.5-35.5), although this finding is based on only 84 cases and 44 controls, of which only 2 controls had the LL genotype (38). In the current study, HW men with the SRD5A2 V89L VV genotype had a reduced risk compared with the VL/LL genotypes (OR, 0.64; 95% CI, 0.41-0.99; P = 0.05). There was no association with risk in NHW men. The result in HW men was marginal, however, and may reflect a more limited sample size in HW men. These findings need to be studied in a larger cohort.

In contrast to associations with prostate cancer risk, several studies found that the LL genotype was associated with increased risk for measures of disease severity or progression (37). For example, the LL genotype was associated with more aggressive disease (39), a poorer prognosis as measured by prostate-specific antigen failure (40), and by the presence of metastases at the time of diagnosis (41). Thus, it seems that reduced DHT is associated with increased risk for disease progression (42).

HW men in this study have a higher proportion of the LL genotype (15%) than NHW men (7%). Thus, it seems that HW men are more likely to have a less efficient SRD5A2 gene and therefore less DHT available. This could partly explain the
paradox that, overall, HW men have lower prostate cancer rates but are more likely to have higher clinical stage at diagnosis (43), poorer survival (44), and more nonlocalized disease (45) compared with NHW men. A recent study looked at the distribution of V89L polymorphisms in low-risk Inuit natives in Greenland compared with high-risk Swedish men. The proportion of the higher activity VV V89L genotype was significantly lower in Inuits compared with Swedish men (46). The authors hypothesized that this contributes to the lower risk of prostate cancer seen in the Inuits.

The cases in the SABOR study are largely prevalent rather than incident cases. Most men who were diagnosed during the up to five annual SABOR exams had probably already developed the disease that only became clinically evident during the increased surveillance as part of their participation in the study. Therefore, it is difficult to discern between markers that are associated with initiation or with progression of the disease. Long-term follow-up is needed to determine which cancer cases will progress. Although Gleason score is an imperfect measure of cancer progression, it can be useful to determine between the high-risk (usually Gleason score 7 and above) versus lower-risk cases. Even though no overall association with Gleason score was observed, the high-risk HW cases were more likely to have the V89L LL genotype (23%) than the low-risk cases (9%); there was no difference in NHW men (6% and 7%, respectively).

The presence of population stratification (genetic subgroups), particularly in HW men, could lead to inaccurate estimates of the genetic effects if the subgroups are not equally distributed between cases and controls. A recent study comparing admixture and substructure in Mexicans and Puerto Ricans, the two largest Hispanic/Latino subgroups in the United States, found population substructure in both groups (47). However, in their study of asthma, they found that this substructure only confounded their results in Puerto Ricans and not in Mexicans. The effect of population stratification may be important only if the substructure includes populations that have differential risk for the disease of interest and differential distributions of the gene of interest (48). Mexican Americans, who comprise >90% of the SABOR sample, are primarily made up of European and Native American ancestors. Native Americans are at lower risk for prostate cancer compared with NHW men (49). Only one of the polymorphisms in the current study has been examined in a native population, the Inuits in Greenland, where the proportion of the higher-activity V89L YV genotype was significantly lower in Inuits compared with Europeans (46). Depending on the percentage of native admixture in the SABOR Hispanic population and if there are different distributions between cases and controls, there could be an inaccurate estimate of the risk effect for the V89L polymorphism or the other polymorphisms in this study. Although a source of systematic bias has not been identified, a panel of ancestry-informative markers on the SABOR population is being run to study this issue.

This study found evidence that the SRD5A2 V89L polymorphism interacts with the functional VDR FokI and CDK2 polymorphisms to affect risk for prostate cancer in NHW and HW men, respectively. This illustrates the importance of examining multiple genes to understand the genetic risks for prostate cancer and the differences seen according to ethnicity. Additionally, a complex analysis may be necessary to understand a complex disease. Because genomewide linkage studies found strong locus heterogeneity of prostate cancer susceptibility genes (50), prostate cancer is not likely caused by a few genes but by multiple genes from different pathways. Therefore, a more complex analysis looking at interactions between genes rather than a single gene analysis may be necessary to understand complex diseases like prostate cancer.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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References


Hispanic White and Hispanic White Men

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VDR and SRD5A2 Polymorphisms Combine to Increase Risk for Prostate Cancer in Both Non-Hispanic White and Hispanic White Men

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