Null Results in Brief

Steroid 5-α Reductase Type II *V89L* Substitution Is Not Associated with Risk of Prostate Cancer in a Multiethnic Population Study[1]

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Introduction

Although the genetic causes of prostate cancer are poorly understood, variation in androgen biosynthesis and metabolism genes has been hypothesized to alter prostate cancer risk (1). *Steroid 5-α reductase type II*, which encodes the enzyme responsible for converting testosterone to dihydrotestosterone in the prostate, has been studied as a candidate gene (2–4). A missense single nucleotide polymorphism at codon 89, resulting in a valine to leucine change (*V89L*), was tested in relation to prostate cancer risk in three previous case-control studies. A large nested case-control study within the Physicians' Health Study found a small protective effect of the *LL* genotype that was not statistically significant (2). Similarly, Lunn *et al.* (3) found a 10% reduction in risk associated with the *LL* genotype, but again this result did not achieve statistical significance. However, a recent case-control study suggested a much stronger effect of the *V89L* single nucleotide polymorphism; this study found a 64% decrease in risk associated with the *LL* genotype compared with the *VV* genotype (4).

We report here the results of a large multiethnic case-control study designed to test the association between the *V89L* variant and prostate cancer risk.

Materials and Methods

We completed a case-control study nested in the Hawaii-Los Angeles MEC[3], including 921 incident cases and 1295 male controls from the four major racial/ethnic groups enrolled in the cohort (African-Americans, Japanese-Americans, Latinos, and whites). Details of the MEC have been published previously (5). Incident case ascertainment was completed by computer linkage of the cohort with the Surveillance, Epidemiology and End Results cancer registries in Hawaii and Los Angeles, as well as with the California State Cancer Registry. Both incident prostate cancer cases and a random sample of male controls in the MEC were contacted by phone and asked to provide a blood specimen. The overall participation rate for blood collection was 72% for cases and 69% for controls.

The men who agreed to participate in the blood collection provided written informed consent after study approval by both the University of Hawaii and the University of Southern California Institutional Review Boards.

DNA was purified from lymphocytes of peripheral blood samples for all cases and controls using either a rapid DNA preparation or the Gentra PureGene kit. Genotyping was carried out as described previously (6). All samples were submitted in coded format for genotyping and included 5% masked repeats. PSA levels were determined for all controls in the study.

Logistic regression was used to model the association between risk of prostate cancer and *V89L* genotype. No mode of inheritance was assumed. All analyses were adjusted for age at entry into the MEC and for ethnicity in any analysis that combined the four ethnic groups.

Results

We found no significant association between the *V89L* variant and prostate cancer risk in any individual ethnic group, nor in all groups combined (Table 1). We found a small, nonsignificant protective association between the *LL* genotype and risk of prostate cancer in the Latino and white groups; however, risk was slightly increased among African-American and Japanese-American men (Table 1), indicating no strong or consistent pattern across racial/ethnic groups. The results were unchanged when restricted to cases with advanced disease.

Conclusions

The results presented here agree with two of the three previously published studies suggesting no substantial association between the *V89L* variant and risk of prostate cancer. The findings from the third study may be in disagreement attributable to chance. The participants in our study were not screened for prostate cancer as part of follow-up, and therefore it is possible that some controls could have undetected disease. The low PSA levels in our controls indicate that misclassification of participants because of undetected disease is not likely to explain our lack of significant findings, and our results are unchanged when excluding controls with PSA values of 4 or higher.

Our study had 80% power at the $\alpha = 0.05$ level to detect an OR of 0.64, the risk observed in the previously published "positive" study. A formal meta-analysis of the four studies (including only the white group from our study) revealed a 20% decreased risk for carriers of the *LL* genotype compared with the *VV* genotype (95% CI, 0.59–1.09), but this result was not statistically significant. Although we cannot rule out a small

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[3] The abbreviations used are: MEC, Multiethnic Cohort; PSA, prostate-specific antigen; OR, odds ratio; CI, confidence interval.

Table 1 ORs and 95% CIs for the association between the *V89L* genotype and risk of prostate cancer by racial/ethnic group

Genotype	African-American[a]		Japanese[a]		Latino[a]		White[a]		All groups[b]	
	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)
VV	178/231	1.0	56/85	1.0	112/151	1.0	77/110	1.0	423/577	1.0
VL	134/159	1.05 (0.78–1.43)	71/156	0.68 (0.42–1.10)	111/156	1.03 (0.71–1.50)	71/107	1.05 (0.66–1.66)	387/578	0.95 (0.79–1.15)
LL	25/21	1.52 (0.82–2.83)	35/43	1.27 (0.69–2.36)	36/53	0.91 (0.55–1.53)	15/23	0.91 (0.42–1.98)	111/139	1.15 (0.85–1.54)

[a] ORs adjusted for age at entry into the cohort.
[b] ORs adjusted for age at entry into the cohort and racial/ethnic group.

effect of this missense substitution on prostate cancer risk, the sample size required to detect an OR of 0.80 is quite large (n = 8796). The usefulness of conducting a study powered to detect such a small effect is unclear because this variant would not contribute significantly to the public health burden of prostate cancer in terms of either screening or prevention. Efforts should be focused elsewhere to further our understanding of the role of genetic variation in risk of prostate cancer.

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