

*Null Results in Brief*Steroid 5- α Reductase Type II V89L Substitution Is Not Associated with Risk of Prostate Cancer in a Multiethnic Population Study¹

Celeste L. Pearce,² Nick M. Makridakis, Ronald K. Ross, Malcolm C. Pike, Laurence N. Kolonel, Brian E. Henderson, and Juergen K. V. Reichardt

Departments of Preventive Medicine [C. L. P., R. K. R., M. C. P., B. E. H., J. K. V. R.] and USC/Norris Comprehensive Cancer Center and Hospital [C. L. P., R. K. R., M. C. P., B. E. H., J. K. V. R.] and Biochemistry and Molecular Biology [N. M. M., J. K. V. R.], University of Southern California Keck School of Medicine, The Institute for Genetic Medicine, University of Southern California [N. M. M., J. K. V. R.], Los Angeles, California 90089-9176, and Cancer Research Center, University of Hawaii, Honolulu, Hawaii 96813 [L. N. K.]

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 MEC³, 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 Genra 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

Received 12/7/01; revised 12/7/01; accepted 1/28/02.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

¹ This work was supported by Grants R01 CA68581, R01 CA63464, R01 CA54281, and Cancer Center Core Grant 2 P30 CA14089-26.

² To whom requests for reprints should be addressed, at USC/Norris Comprehensive Cancer Center, Keck School of Medicine, 1441 Eastlake Avenue, Room 4425, Los Angeles, CA 90089-9176.

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.

Acknowledgments

We thank Hanh Nguyen and Nhuc Luong for genotyping assistance.

References

- Ross, R. K., Pike, M. C., Coetzee, G. A., Reichardt, J. K., Yu, M. C., Feigelson, H., Stanczyk, F. Z., Kolonel, L. N., and Henderson, B. E. Androgen metabolism and prostate cancer: establishing a model of genetic susceptibility. *Cancer Res.*, 58: 4497–4504, 1998.
- Febbo, P. G., Kantoff, P. W., Platz, E. A., Casey, D., Batter, S., Giovannucci, E., Hennekens, C. H., and Stampfer, M. J. The V89L polymorphism in the 5- α reductase type 2 gene and risk of prostate cancer. *Cancer Res.*, 59: 5878–5881, 1999.
- Lunn, R., Bell, D., Mohler, J., and Taylor, J. Prostate cancer risk and polymorphism in 17 hydroxylase (CYP17) and steroid reductase (SRD5A2). *Carcinogenesis (Lond.)*, 20: 1727–1731, 1999.
- Nam, R., Toi, A., Vesprini, D., Ho, M., Chu, W., Harvie, S., Sweet, J., Trachtenberg, J., Jewett, M., and Narod, S. V89L polymorphism of type-2,5- α reductase enzyme gene predicts prostate cancer presence and progression. *Urology*, 57: 199–205, 2001.
- Kolonel, L., Henderson, B., Hankin, J., Nomura, A., Wilkens, L., Pike, M., Stram, D., Monroe, K., Earle, M. E., and Nagamine, F. A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics. *Am. J. Epidemiol.*, 151: 346–357, 2000.
- Makridakis, N., Ross, R. K., Pike, M. C., Chang, L., Stanczyk, F. Z., Kolonel, L. N., Shi, C. Y., Yu, M. C., Henderson, B. E., and Reichardt, J. K. V. A prevalent missense substitution that modulates activity of prostatic steroid 5 α -reductase. *Cancer Res.*, 57: 1020–1022, 1997.

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

Celeste L. Pearce, Nick M. Makridakis, Ronald K. Ross, et al.

Cancer Epidemiol Biomarkers Prev 2002;11:417-418.

Updated version Access the most recent version of this article at:
<http://cebp.aacrjournals.org/content/11/4/417>

Cited articles This article cites 6 articles, 3 of which you can access for free at:
<http://cebp.aacrjournals.org/content/11/4/417.full#ref-list-1>

Citing articles This article has been cited by 3 HighWire-hosted articles. Access the articles at:
<http://cebp.aacrjournals.org/content/11/4/417.full#related-urls>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link
<http://cebp.aacrjournals.org/content/11/4/417>.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.