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Research Article

Cancer Epidemiology, Biomarkers & Prevention

Association between Genetic Variants in the 8q24 Cancer Risk Regions and Circulating Levels of Androgens and Sex Hormone–Binding Globulin

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Abstract

Background: Genome-wide association studies have identified multiple independent regions on chromosome 8q24 that are associated with cancers of the prostate, breast, colon, and bladder.

Methods: To investigate their biological basis, we examined the possible association between 164 single nucleotide polymorphisms (SNPs) in the 8q24 risk regions spanning 128,101,433-128,828,043 bp, and serum androgen (testosterone, androstenedione, 3αdiol G, and bioavailable testosterone), and sex hormone–binding globulin levels in 563 healthy, non-Hispanic, Caucasian men (55-74 years old) from a prospective cohort study (the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial). Age-adjusted linear regression models were used to determine the association between the SNPs in an additive genetic model and log-transformed biomarker levels.

Results: Three adjacent SNPs centromeric to prostate cancer risk-region 2 (rs12334903, rs1456310, and rs980171) were associated with testosterone ($P < 1.1 \times 10^{-3}$) and bioavailable testosterone ($P < 6.3 \times 10^{-4}$). Suggestive associations were seen for a cluster of nine SNPs in prostate cancer risk region 1 and androstenedione ($P < 0.05$).

Conclusions: These preliminary findings require confirmation in larger studies but raise the intriguing hypothesis that genetic variations in the 8q24 cancer risk regions might correlate with androgen levels.

Impact: These results might provide some clues for the strong link between 8q24 and prostate cancer risk.

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Introduction

Genome-wide association studies have identified multiple independent regions on chromosome 8q24 that are associated with cancers of the prostate (1-7), breast (8), colon (9-11), and bladder (12). All of these risk regions lie outside of coding regions, with the exception of a pseudogene (*POU5F1P1*) in prostate cancer risk region 3 (13), and have no known function. The most proximal gene to these risk regions is the well known oncogene *MYC* at ~30 kb telomeric to the bladder cancer region. However, there is currently no evidence to suggest that 8q24 cancer risk markers are in linkage disequilibrium (LD) with common genetic variants in *MYC* or its promoters, nor is there definitive evidence for an association between 8q24 risk variants and *MYC* expression (14-16).

To investigate the biological basis for the link between 8q24 risk regions and cancer risk, we examined the correlation between common genetic variants in 8q24 and serum levels of androgen and sex hormone–binding globulin (SHBG) in 563 healthy non-Hispanic Caucasian males within the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Included in the analysis were 164 single nucleotide polymorphisms (SNPs) encompassing the six identified 8q24 risk regions (spanning chromosome 8: 128,101,433-128,828,043 bp) from the National Cancer Institute Cancer Genetic Markers of Susceptibility (CGEMS) Project and serum androgens [testosterone, 5α-androstane-3α,17β-diol glucuronide (3αdiol G), and androstenedione], and SHBG.

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Table 1. Selected characteristics of 563 study participants

Characteristic	Participants, *N* = 563 *n* (%)
Age at enrollment (y)	
55-59	96 (16.8)
60-64	192 (33.7)
65-69	180 (31.6)
70-74	95 (16.7)
Education level	
Less than high school	46 (8.1)
Completed high school	99 (17.4)
Some college or vocational training	191 (33.5)
Completed college and above	227 (39.8)
Family history of prostate cancer	
No	524 (92.1)
Yes	31 (5.4)
Cigarette smoking status	
Never	215 (37.7)
Former	293 (51.4)
Current	55 (9.6)
Body mass index	
Normal (18.5-24.9)	145 (25.6)
Overweight (25-29.9)	288 (50.8)
Obese (≥30)	127 (22.4)

Serum marker	Mean	SD	Range
Total testosterone (nmol/L)	17.7	8.6	0.6-60.0
Bioavailable testosterone (nmol/L)	4.9	1.9	0.2-14.5
4-Androstene-3,17-dione (androstenedione; ng/dL)	126.1	44.3	29.6-301.6
5α-Androstane-3α, 17β-diol glucuronide (3αdiol G; ng/dL)	828.6	585.6	67.6-5,346.7
SHBG (nmol/L)	48.7	22.9	13.1-152.3

Materials and Methods

Study subjects

The PLCO Cancer Screening Trial is a randomized trial designed to determine if screening for prostate, lung, colorectal, and ovarian cancers leads to mortality reduction for these cancers. Details of the study have been described previously (17, 18). Briefly, the trial includes 155,000 men and women (ages 55 to 74 with no reported history of prostate, lung, colon, or ovarian cancer) enrolled between 1992 and 2001 and randomized to either the screening or control arm of the trial. Men randomized to the screening arm provided basic risk factor information through the baseline questionnaire and were offered prostate-specific antigen tests and digital rectal exams at baseline and annually thereafter for 3 years, followed by 2 years of screening with prostate-specific antigen alone. These men also donated serial blood samples at each of six screening rounds and were followed by an annual survey for self-reported cancer diagnosis. The study protocol was approved by the institutional review board at each study center and the National Cancer Institute. Participants also provided informed consent.

In the current study, we included 563 healthy non-Hispanic Caucasian men with both genotyping (4) and baseline serum androgen (19) data. These men were originally selected as controls for two nested case-control studies of prostate cancer as described previously (4, 19). Briefly, the selection criteria for the controls for these two studies were (*a*) had been screened for prostate cancer (prostate-specific antigen and/or digital rectal exam) at least once before October 1, 2003; (*b*) had no prior history of prostate cancer before randomization; (*c*) completed the baseline risk factor questionnaire and returned at least one annual study update questionnaire; (*d*) were non-Hispanic Caucasian; (*e*) signed an informed consent; (*f*) provided a blood sample; and (*g*) were selected by incidence-density sampling to be matched to the cases by age of entry in 5-year intervals, time since initial screen (1-year time windows), and year of blood draw at study entry. In total, 1,087 controls were selected for the genotyping study (4) and 889 healthy men were selected for the serum androgen study (19). For this study, only men with both genotyping and serum androgen data were eligible (563 men).

Serum androgen and SHBG

Serum androgen and SHBG assays have been described previously (19). Briefly, all assays were done at the IARC on serum drawn at baseline. Total testosterone was measured by direct RIA (Immunotech), androstenedione and 3αdiol G by direct double-antibody RIA (Diagnostic Systems Laboratories), and SHBG by sandwich immunoradiometric assay (CIS-Bio); overall coefficients of variation from duplicate samples were 14%, 11%, 14%, and 18% for testosterone, 3αdiol G, androstenedione, and SHBG, respectively (19). Total testosterone (nmol/L) and SHBG (nmol/L) were used to calculate bioavailable testosterone using the following equation as described previously (20):

$$\text{Bioavailable testosterone} = e^{(-0.266+[0.955\times\ln(\text{total testosterone})]-[0.228\times\ln(\text{SHBG})])}$$

Genotyping

Genotyping was done under contract by Illumina Corporation as part of the CGEMS Project and was coordinated by the National Cancer Institute Core Genotyping Facility as described previously (4). The assay consisted of a fixed panel of 561,494 tag SNPs, of which 181 SNPs were located in and around the 8q24 cancer risk regions (128,101,433-128,828,043 bp; NCBI Build 36.3). We excluded 19 SNPs with minor allele frequencies

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of <5% and/or SNPs that were not in Hardy-Weinberg equilibrium ($P < 0.001$), leaving 164 SNPs for analysis. These 164 SNPs encompass the following regions (from centromere to telomere): prostate cancer region 2 (128,101,433-128,279,002 bp; 38 SNPs), breast/prostate cancer region (128,280,411-128,472,696; 53 SNPs), prostate cancer region 3 (128,473,069-128,535,996; 18 SNPs), prostate cancer region 1 (128,541,502-128,614,565; 22 SNPs), bladder cancer region (128,617,860-128,816,653; 31 SNPs), and *MYC* (128,819,722-128,828,043; 2 SNPs). Quality control evaluations were described in detail in the original CGEMS Project analysis (4).

Statistical analysis

We used Stata (version 9.0, Stata Corp.) to run all analyses unless stated otherwise. Linear regression analysis was used for determining effect sizes and significance of associations between natural log-transformed androgen or SHBG levels and all 164 SNPs. Polytomous regression analysis was also used to determine the associations of the SNPs with androgens or SHBG categorized in quartiles and quintiles. All genotypes were coded as 0, 1, and 2 according to the copy number of the less common allele and were modeled linearly. All regression models were adjusted for age at entry in 5-year intervals (55-59, 60-64, 65-69, and 70-74); race was not included in the analysis because all study participants were non-Hispanic Caucasian men. *P* values for SNP effect were based on two-sided Wald test statistics. To adjust for multiple comparisons, we used a parametric bootstrap procedure (21), with 20,000 replicates generated under the null, for the evaluation of global significance levels accounting for all SNPs tested within each subregion or for all 164 SNPs tested within the entire 8q24 region. For a select number of SNPs identified by linear regression analysis to be most significantly correlated with androgen levels,

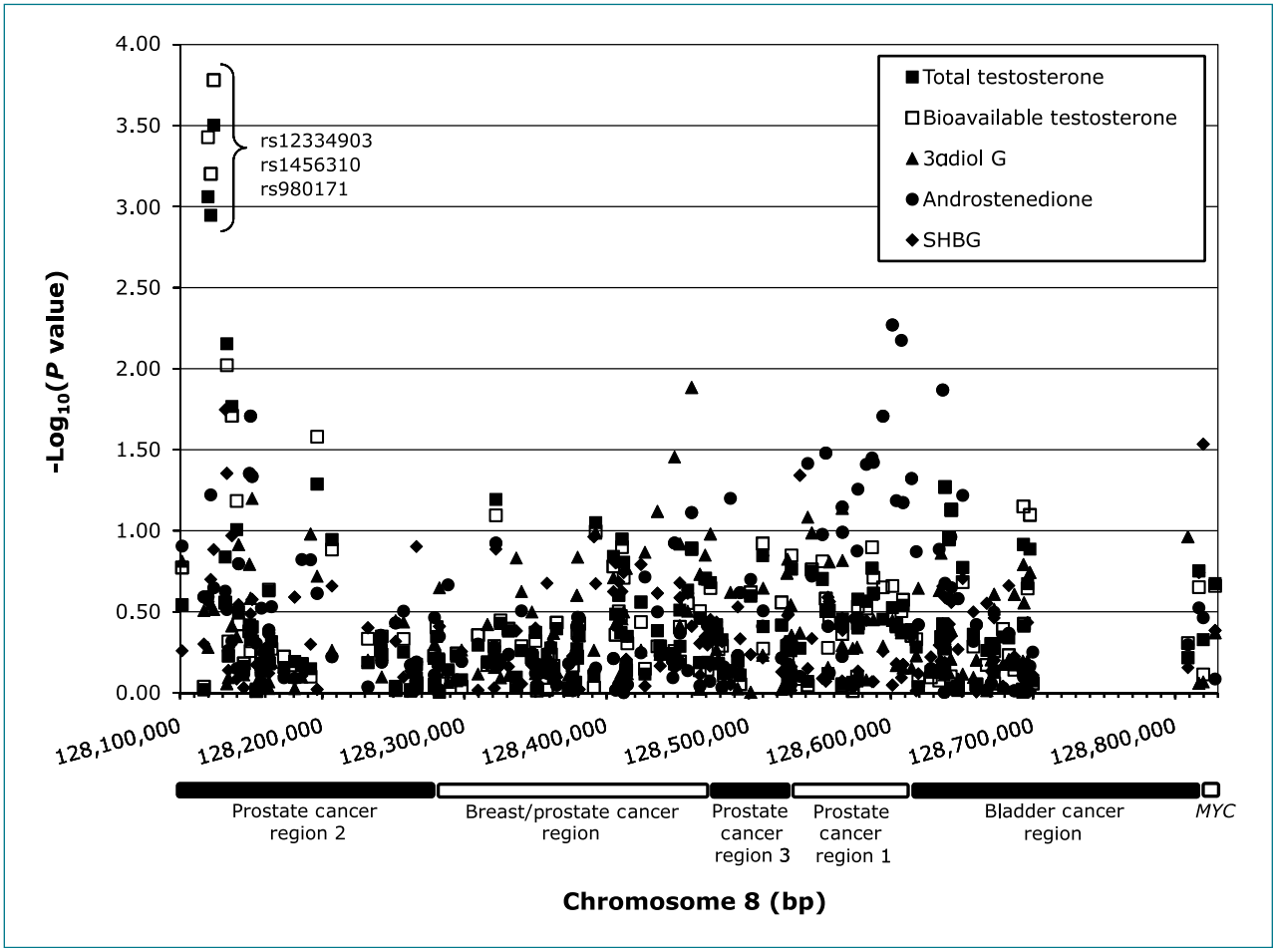

Figure 1. Summary graph of the significance of the associations between all 164 SNPs in the six 8q24 cancer risk regions and all androgen and SHBG measures. Significance of the association [*Y*-axis; $-\log_{10}$ (*P* value)] of each SNP (*X*-axis) with total testosterone (■), bioavailable testosterone (□), 3αdiol G (▲), androstenedione (●), and SHBG (◆) are presented; filled symbols represent measured markers and open symbols represent calculated markers. Results based on age-adjusted linear regression analysis of associations between log-transformed androgen and SHBG measurements and SNPs in an additive genetic model. Bars below the *X*-axis denote approximate boundaries of the cancer risk regions.

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Table 2. Associations between the three most significant SNPs in 8q24 cancer risk regions and serum testosterone measures in 563 male subjects

Serum androgen	SNP (major/minor alleles)	Location (bp)	MAF*	β†	SE†	*P*†	*P*‡	*P*§
Total testosterone	rs12334903 (C)	128,119,695	0.40	−0.10	0.03	8.69×10^{-4}	0.023	0.100
	rs1456310 (A)	128,121,615	0.43	−0.10	0.03	1.13×10^{-3}	0.030	0.127
	rs980171 (G)	128,123,704	0.39	−0.11	0.03	3.14×10^{-4}	9.60×10^{-3}	0.039
Bioavailable testosterone	rs12334903 (C)	128,119,695	0.40	−0.09	0.03	3.73×10^{-4}	0.012	0.049
	rs1456310 (A)	128,121,615	0.43	−0.08	0.02	6.28×10^{-4}	0.019	0.076
	rs980171 (G)	128,123,704	0.39	−0.09	0.03	1.66×10^{-4}	4.95×10^{-3}	0.023

*MAF, minor allele frequency.

†Based on age-adjusted linear regression analysis of log-transformed androgen and SHBG measurements using SNPs in an additive genetic model.

‡Adjusted for multiple comparisons using a parametric bootstrap procedure with 20,000 replicates generated under the null for the evaluation of significance levels accounting for all 38 SNPs tested within prostate cancer region 2.

§Adjusted for multiple comparisons using a parametric bootstrap procedure with 20,000 replicates generated under the null for the evaluation of significance levels accounting for all 164 SNPs tested in the 8q24 region.

we used the Kruskall-Wallis nonparametric one-way ANOVA to determine if median androgen levels differ by genotype. Pair-wise LD was estimated between SNPs in each of the 8q24 regions based on D' and r^2 statistics calculated in Haploview (22).

Results

Selected demographic and serologic characteristics of the 563 study participants are shown on Table 1. Over 65% of the men were between the ages of 60 and 70 and the majority (>70%) had at least some college education. In addition, over half of the men were former smokers and 5.4% had a family history of prostate cancer. Furthermore, over half of the men were overweight and ~22% were obese. Means and ranges of serum androgens and SHBG levels for participants of this study were similar to those reported previously in the PLCO study (19).

Figure 1 shows the summary graph of $-\log_{10}$ of P values from linear regression analysis of the associations between all 164 SNPs typed within a 727 kb region of chromosome 8q24 and four serum androgen measures and SHBG plotted against the chromosomal locations of each SNP. Of the 164 SNPs analyzed, 24 were associated with serum androgens or SHBG at $P < 0.05$, with 6 reaching $P < 0.01$; a total of 30 tests were significant at $P < 0.05$, with 10 reaching $P < 0.01$. Similar results were found when analyzing androgens and SHBG in quartiles and quintiles or comparing the highest with the lowest levels (data not shown). Additional adjustment for hour of blood draw to account for variations in circadian variation serum androgen levels (23, 24) did not change the results (data not shown).

The strongest associations seen were for three adjacent SNPs at the centromeric ends of prostate cancer risk region 2 (rs12334903, rs1456310, and rs980171) with total and bioavailable testosterone ($P \leq 1.13 \times 10^{-3}$ and 6.28×10^{-4}, respectively; Table 2 and Supplementary Table S1). These three SNPs are in relatively strong LD with each other ($D' > 0.88$, $r^2 > 0.69$), have similar minor allele frequencies (39-43%), and have similar effects on testosterone (each copy of the risk allele is associated with an 8% to 10% decrease in mean testosterone levels). All three SNPs remained significantly associated with testosterone after adjustment for multiple comparisons of 38 SNPs tested within region 2 ($P < 0.03$); after adjustment for all 164 SNPs tested, rs980171 remained associated with total and bioavailable testosterone ($P = 0.039$ and 0.023, respectively) and rs12334903 with bioavailable testosterone ($P = 0.049$). The Kruskal-Wallis nonparametric ANOVA also shows that median total and bioavailable testosterone levels differed significantly among groups defined by the genotypes of the three SNPs (nominal $P < 1.48 \times 10^{-3}$ and 7.5×10^{-4}, respectively; Fig. 2). Also of note is the association of a cluster of nine SNPs (128,541,502-128,607,399 bp) in prostate cancer region 1 with androstenedione (nominal $P < 0.05$; Supplementary Table S1), with five of the nine SNPs (rs1447295, rs4242382, rs4242384, rs7017300, and rs11988857) in relatively strong LD ($D' > 0.89$, $r^2 > 0.71$); these SNPs did not remain significant after adjustment for multiple testing of 22 SNPs in region 1 ($P < 0.34$).

Discussion

In this study of 563 healthy men, we found several SNPs in the 8q24 cancer risk regions associated with circulating levels of androgens. Specifically, SNPs centromeric to prostate cancer region 2 were associated with testosterone measures, whereas those in prostate cancer region 1 were suggestively associated with androstenedione. Because many of the SNPs within each region

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are in strong LD with each other, the effect of the SNPs within each region on serum androgens might reflect their link with the same causal variant. These findings suggest a potential relationship between the 8q24 cancer risk regions and serum androgens, which in turn, might provide some biological clues into the strong link between 8q24 variants and cancer risk. Future studies with larger sample sizes are needed to confirm these findings.

It is noteworthy that the 8q24 SNPs identified as being associated with androgens in this study were also associated with or were in LD with SNPs that were associated with prostate cancer risk (2-6, 25-27), suggesting that serum testosterone might be related to the link between 8q24 variants and prostate cancer. Although the exact mechanism is unclear, data from a recent study showed that the 8q24 cancer risk regions harbor several androgen-responsive transcriptional enhancers, one of which contained a SNP, rs11986220, in prostate cancer region 1 that facilitated stronger androgen responsiveness *in vitro* (28). This particular SNP was not genotyped in our study but is in moderate to strong LD with several SNPs identified in the study as being associated with androstenedione ($D' = 1$ and $r^2 > 0.54$ based on the International HapMap Project data; ref. 29). The interactive effects of 8q24 variants and serum androgens on prostate cancer risk warrants further investigation, in particular, in studies with large sample sizes.

Our study has several strengths. First, we had high-quality genotyping data, as suggested by high concordance and high completion rates, thereby minimizing misclassification of genotyping (4). Second, we had high-quality serum assays of biomarkers, with low intra-assay and interassay variation (coefficients of variation <18%; ref. 19), which minimizes misclassification of

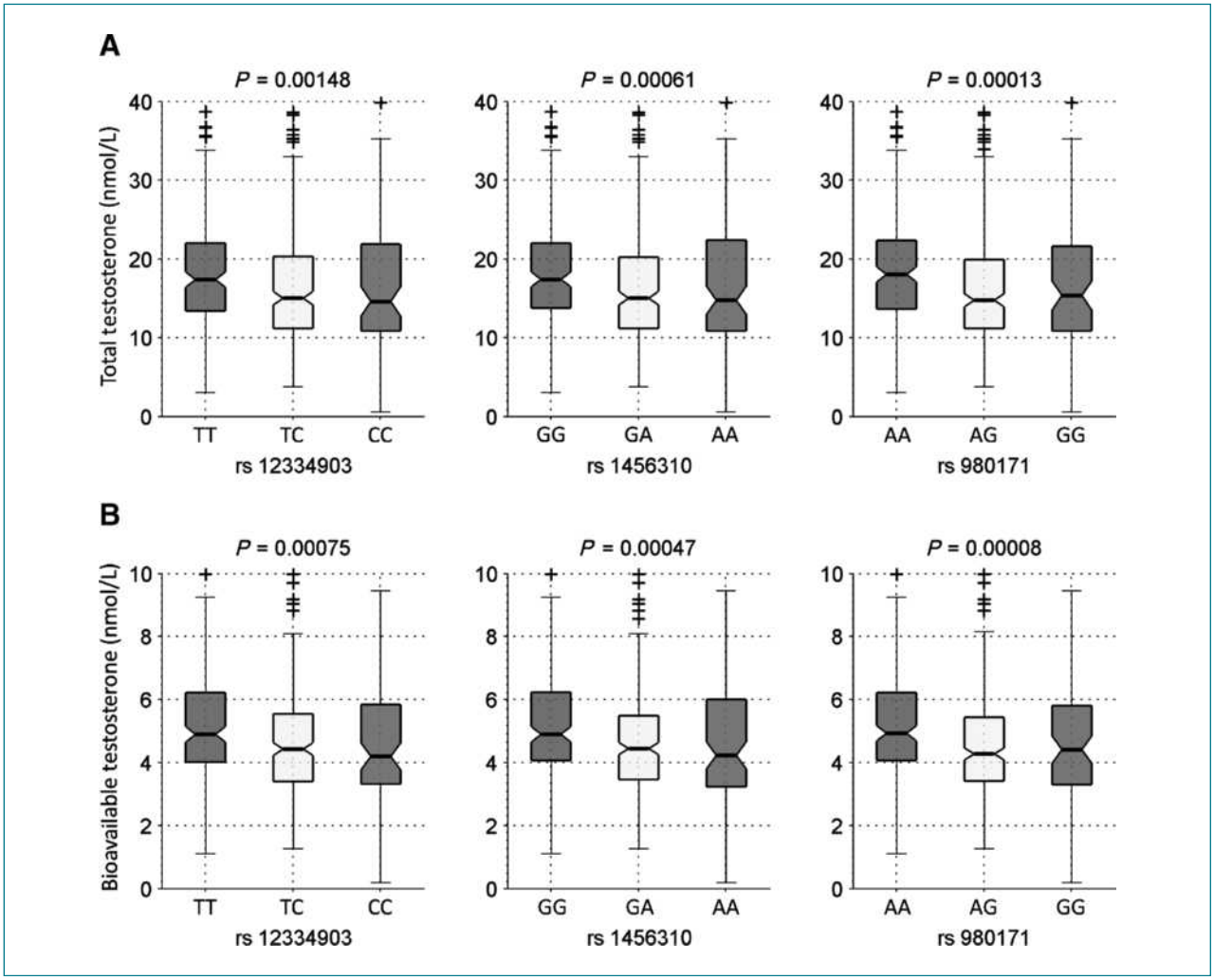

Figure 2. Notched box plots of median total testosterone (A) and bioavailable testosterone (B) levels by genotypes of rs12334903, rs1456310, and rs980171, respectively, displaying the median value, interquartile range, 10th and 90th percentiles, and outliers (+). Notches show 95% confidence intervals for the median. Nominal *P* values at the top of each panel are based on the Kruskal-Wallis nonparametric one-way ANOVA that tests the equality of median testosterone levels among groups defined by the genotypes of each SNP.

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the outcome. And third, the effect of disease status (prostate cancer) was minimized by including only participants of the screening arm of the PLCO trial that had not been diagnosed with prostate cancer at the time of subject selection.

The limitations of the study should also be noted. Our findings are only borderline significant after adjustment for the tests on 164 SNPs with five biomarker measures. However, the 164 SNPs tested were over five distinct and independent regions, as defined by LD structure, and we conservatively accounted for these in our assessment of the statistical analyses. Given the relatively small sample size of our study and the existing strong evidence on the relevance of the 8q24 region to various cancers, our findings require confirmation in studies with larger sample sizes to clarify the relationship between 8q24 and androgens. Future studies are also needed to determine the relationship between 8q24 and androgens in other ethnic groups.

In summary, our study showed that variations in the 8q24 cancer risk regions might be associated with serum androgen levels, which suggests the intriguing hypothesis that serum androgens might be related to the reported association between the 8q24 risk regions and cancer, especially that of the prostate. Future studies with larger sample sizes and in other ethnic populations are needed to confirm these findings and to enable generalization to other populations. In addition, future investigations into the mechanisms underlying the link between the 8q24 cancer risk variants, androgen levels, and prostate carcinogenesis are warranted.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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