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Serum Androgens and Prostate Cancer Risk: Results From the Placebo Arm of the Prostate Cancer Prevention Trial

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Abstract

Background—Compelling and long-standing data suggest that androgens play an important role in the development of both normal prostate epithelium and prostate cancer. Although testosterone administration can induce prostate cancer (PCA) in laboratory animals, serum-based epidemiologic studies examining serum androgens in humans have not consistently supported a role for androgens in prostate carcinogenesis. We examined whether pre-diagnostic serum androgens were associated with PCA risk in the placebo arm of the Prostate Cancer Prevention Trial (PCPT).

Methods—In this nested case-control study, cases (n=1,025) were primarily local stage, biopsy-detected cancers, and controls (n=1,037) were biopsy-confirmed to be PCA-free. Pre-diagnostic

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serum androgens (total testosterone, 3α-androstanediol glucuronide (3α-diol G), free testosterone), estrogen:testosterone ratio and sex hormone binding globulin (SHBG) concentrations were measured in pooled (baseline and year 3) blood samples.

Results—We found no significant associations between serum androgens, estrogen:testosterone ratios or SHBG and risk of total, low (Gleason < 7) or high-grade (Gleason 7-10) PCA.

Conclusion—Much remains to be learned about the role of androgens in prostate carcinogenesis. Further research is needed to evaluate the role of androgens, timing of exposure, genetic modulators of androgen metabolism, or environmental exposures that may affect androgen influence on prostate carcinogenesis.

Keywords

prostate cancer; androgens; Prostate Cancer Prevention Trial

Introduction

Data from animal and clinical studies support a role for androgens in prostate cancer (PCA) growth, proliferation, and progression.(1-3) However, results from serum-based epidemiologic studies in humans have been inconsistent.(4) Earlier prospective studies suggested that higher serum concentrations of testosterone and 3α-androstanediol glucuronide (3α-diol G) were associated with an increased risk of PCA(5-7); however, in 2008 a large pooled analysis of prospective studies found no association between serum androgens and PCA risk.(8) More recent studies have confirmed the lack of association between androgens with PCA risk(9-11), although others found a positive association for serum testosterone and PCA risk only among men with lowest concentrations of testosterone(12), and an inverse association of estradiol:testosterone ratio and aggressive PCA(13).

Within the prostate, testosterone is converted to the most active androgen dihydrotestosterone (DHT) by the enzyme steroid 5α-reductase type II then metabolized to 3α- or 3β-diol G for clearance.(14, 15) Thus, 3α-diol G is a frequently used marker for steroid 5α-reductase type II activity and DHT levels.(16) The conversion of testosterone to DHT is inhibited by steroid 5α-reductase inhibitors: finasteride and dutasteride.(17) Previously we reported that men treated with 5 mg of finasteride daily had a 74% reduction in 3α-diol G and 10% increase in serum testosterone.(18) Although these findings were consistent with the action of finasteride, these large changes in androgen concentrations were not associated with subsequent PCA risk.(18) Furthermore, neither pre- nor post-treatment concentrations of androgens among men in the finasteride arm were associated with subsequent PCA risk.(18)

Here we examine whether serum concentrations of total testosterone, free testosterone, estrogen:testosterone ratios, 3α-diol G, and sex hormone binding globulin (SHBG), a carrier protein for androgens are associated with subsequent risk of PCA among men in the placebo arm of the Prostate Cancer Prevention Trial (PCPT), where screening was standardized and PCA status was confirmed by biopsy.

Materials and Methods

The PCPT was a randomized, double-blinded, placebo-controlled trial testing whether the 5α-reductase type II inhibitor finasteride could reduce the 7-year period prevalence of PCA. Details of the PCPT and participant characteristics have been described previously.(19) During the trial, men underwent annual digital rectal exam (DRE) and prostate-specific antigen (PSA) screening; men with abnormal DRE or PSA (>4.0 ng/ml) were recommended for biopsy. Men not diagnosed with PCA during their 7-year participation were recommended to undergo an end-of-study prostate biopsy. Biopsies were reviewed for adenocarcinoma both at local clinical sites and by Central Pathology review, with concordance achieved in all cases. Clinical stage was assigned locally and tumors were graded centrally using the Gleason scoring system.

Case and Control Selection

This study was part of a large nested case-control study from the placebo arm designed to examine multiple hypotheses about PCA biology and risk.(20) Briefly, cases (n=1,041) had biopsy-confirmed PCA and baseline blood available for analysis. Controls (n =1,037) were chosen from the 3,323 men who had a negative end-of-study biopsy and baseline blood available for analysis. All non-whites were included as controls, and remaining controls were frequency-matched to cases on distributions of age (±5 years) and history of PCA in a first-degree relative.

Data Collection and Laboratory Methods

Information on age, race, education, physical activity, alcohol intake, history of smoking, history of diabetes, family history of PCA in first-degree relatives, was collected at baseline using self-administered questionnaires. Participant height and weight were measured at baseline; body mass index (BMI) was calculated as weight (kg)/height (m^2).

Non-fasting blood was collected at baseline and annually thereafter until PCA diagnosis or the end of the study. Venous blood was drawn into tubes without anticoagulant, refrigerated, and shipped to a central repository where it was centrifuged, aliquoted, and stored at −70°C until analysis; 0.5-mL serum samples were collected at baseline and year 3 and pooled before analysis to better characterize androgen levels and reduce intraindividual variability. Alternate years were selected if men were missing a year 3 sample or were diagnosed before year 3 (n=237), and a single, baseline sample was used if a post-baseline, pre-diagnostic sample was unavailable. We further excluded men missing ≥1 covariates (n=21), leaving 1,032 cases and 1,025 controls for analysis.

Total testosterone, estrone, estradiol, 3α-diol G, and SHBG were quantified in serum by highly specific immunoassays at the Reproductive Endocrine Research Laboratory, Keck School of Medicine University of Southern California (F.Z.S.), as described previously.(18) Briefly, total testosterone and SHBG were measured by a direct solid-phase competitive chemilumiscent enzyme immunoassay and a direct solid-phase 2-site chemiluminescent immunometric assay, respectively. 3α-diol G and estrogens were measured by radioimmunoassay. Free testosterone was calculated as described previously(18) using total

testosterone and SHBG concentrations, assuming an average concentration for albumin. Pooled serum from healthy volunteers was included as quality controls in each analytic batch and coefficients of variation for 3α-diol G, testosterone, and SHBG were 14.0%, 10.5%, and 12.2%, respectively. Assays were not successful for a small number of samples, thus sample sizes differ slightly for each analyte.

Statistical Analysis

Descriptive statistics were used to characterize the study sample. To generate distributions of hormones in cases and controls, adjusted least-square means of hormone concentrations were estimated using linear regression, stratified by race and adjusted for age and BMI.

Unadjusted concentrations of androgens and estrogen:testosterone ratios were categorized into quartiles based on distributions among controls. To explore whether associations between androgen concentrations and PCA risk were nonlinear we examined PCA detection rates over the range of hormone concentrations using locally weighted scatterplot smoothing (LOWESS). There was no suggestion of non-linearity apparent; thus, we report only the analyses for hormones defined as quartiles. Individual associations of estrogen and estradiol with PCA risk in the same study sample have been reported previously(21).

Unconditional logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for overall prostate cancer risk, and multinomial logistic regression models were used for low-grade (Gleason 2-6, n=780) and high-grade (Gleason 7-10, n=217) PCA compared to controls. To capture a more phenotypically-uniform group of highly aggressive cancers, high-grade PCA was also defined as Gleason 8–10 (n=47) although results did not differ substantively and are presented only for Gleason 7-10. Models were adjusted for age (continuous), race (Caucasian, other) and family history of PCA in first-degree relatives (yes, no), as well as for BMI (continuous). Further control for SHBG, serum cholesterol (continuous), physical activity (sedentary, light, moderate, active) and history of diabetes did not affect results and were not included in final models. Tests for linear trend across quartiles were performed by using an ordinal variable corresponding to rank from the lowest category to the highest.

To evaluate whether associations differed by body mass index (<25, 25-29.9, 30+) or race (white vs. non-white), we also examined associations stratified by these variables. All statistical tests were two-sided, with statistical significance set at p=0.05, and were carried out using SAS statistical software (version 9.2, SAS Corporation, Cary, NC).

Results

Table 1 gives means and distributions of hormones and demographic, anthropometric, and health-related variables. Due to the sampling scheme, cases and controls were similar in age and family history of PCA, and there were more non-white controls. Cases had a higher baseline PSA than controls, and were less likely to be diabetic or overweight/obese (Table 1); however, education, smoking status, alcohol consumption, physical activity and mean concentrations of serum androgens and SHBG were similar among cases and controls. The

median follow-up time was similar for cases and controls (7.0 years (Interquartile range: 6.97-7.09) and 6.9 years (IQR: 5.03-7.05), respectively).

Associations between serum androgens and SHBG and PCA are given in Table 2. There were no statistically significant associations of serum testosterone, 3α-diol G, estrogen:testosterone ratios and SHBG concentrations with risk of PCA overall. When stratified by disease grade [low- vs. high-grade (Gleason score 2-6 vs. 7-10)], there was a suggestion of a positive association for estradiol:testosterone ratio ≥ 0.07 with risk of high-grade PCA compared to controls; however, there was no clear monotonic trend. There were no other associations for serum testosterone, 3α-diol G, estrone:testosterone ratio or SHBG with risk of low- or high-grade PCA. Associations of serum androgens, estrogen:testosterone ratios and SHBG with overall, low- and high-grade PCA did not differ when stratified by BMI or race (data not shown).

Discussion

In this study of primarily local-stage PCA, in which the presence or absence of cancer was determined by biopsy, a unique attribute of the PCPT, there were no statistically significant associations of serum testosterone (total or free), 3α-diol G, estrogen:testosterone ratios or SHBG concentrations with risk of total, low- or high-grade PCA.

The lack of significant associations between serum androgens and PCA is consistent with results from most prospective studies. A pooled analysis of 3,886 and 6,438 controls from 18 prospective studies, not including the PCPT, did not find a clear association between serum androgens and PCA risk(8). Since this initial pooled analysis, additional large prospective studies have reported null associations for serum testosterone and PCA.(9, 10, 22) Associations of SHBG with PCA have been less consistent. The initial pooled analysis reported a modest inverse association of SHBG and total PCA risk (RR for highest vs. lowest quintile=0.86, 95%CI=0.75, 0.98; P_{trend}=0.01)(8), though no large prospective studies since, including this one, have found an association(9, 10, 22). We found a suggestion of a positive association for estradiol:testerone ratio with risk of high-grade PCA, which is consistent with at least one prior study(23); however, other studies have reported inverse(7, 13, 24) and null associations(11, 25).

In a prior study from the PCPT, we reported that among men treated with finasteride, serum androgens were not associated with PCA risk.(18) Finasteride inhibits the intraprostatic conversion of testosterone to DHT, decreasing serum concentrations of 3α-diol G, a marker for steroid 5α reductase activity(15) Although finasteride treatment reduced serum 3α-diol G by 74% and increased serum testosterone by 10%, neither post-treatment concentrations, nor change in concentrations were associated with subsequent PCA risk.(18) In the placebo arm of the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) Trial, which also determined presence/absence of PCA for all men by biopsy, testosterone was associated with a positive risk of PCA among men with low (≤288.4 ng/dl) testosterone, but there was no association among men with normal (> 288.4 ng/dl) testosterone concentrations.(12) In post-hoc analyses among men with concentrations ≤288.4 ng/dl in the current study, we found no association of serum testosterone with risk of total, low- or high-grade PCA (OR

for log-transformed testosterone with total PCA=1.31 (95%CI: 0.58-2.96); low-grade PCA=1.11 (0.46, 2.71); high-grade PCA=1.95 (0.47, 8.05)).

Although results from serum-based observational studies have been largely null, data from genetic studies have suggested that certain genes in the androgen metabolism pathways, such as the androgen receptor, *CYP17*, or *UGT* may play a role in PCA development.(26, 27) Future large studies should examine the joint effects of serum androgens and genetic variants in the androgen metabolism pathway to determine whether subgroups of men have a higher risk of PCA.

A unique strength of this study is the use of androgen and SHBG concentrations from pooled blood samples, which reduces measurement error due to intraindividual variability in androgen concentrations and may better reflect average hormonal status in older men compared to a single blood sample. Other strengths of PCPT include the standardized screening with DRE and PSA, and the end-of-study biopsy recommended to all cancer-free men at study completion, which minimized detection bias and the likelihood of undiagnosed PCA in controls. Several limitations should also be acknowledged. First, differences in associations of hormone concentrations with PCA risk by time from measurement to diagnosis cannot be evaluated in this study because many men were diagnosed via the end-of-study biopsy; thus, the time from androgen measurement to diagnosis of PCA is somewhat ‘artificial’. Second, although high-quality hormone assays were used, mean testosterone concentrations were slightly lower than those reported in other studies, which may be related to the use of pooled samples, assay-related non-differential measurement error, or characteristics of the overall PCPT population.

In addition, although the use of pooled blood samples from multiple time points may better reflect hormonal status in older men, the etiological relevance to subsequent PCA development is unclear. It is possible that cumulative hormonal exposure over a lifetime, exposure at an earlier age, such as in utero or adolescence, or changes in androgens over time are important for prostate carcinogenesis.(8) Furthermore, circulating androgen concentrations may not adequately reflect intraprostatic androgen concentrations(28) or androgenic actions, as evidenced by our prior finding from PCPT that even with over 70% reduction in serum 3α diol G, a marker of intraprostatic androgen levels, there is little reduction of risk of prostate cancer in the PCPT.(18) Additional etiologic research is needed to better understand the issues of timing and duration of hormone exposures with respect to the development of PCA. Finally, none of these data provide information regarding the impact of androgen supplementation in aging men on PCA risk.

In summary, in this large sample of primarily early-stage, biopsy-detected cancers from the placebo arm of the PCPT, we found that pre-diagnostic serum androgen and SHBG concentrations were not associated with PCA risk. Although there is strong biologic rationale for the role of androgens in PCA growth, proliferation, and progression, much remains to be learned about this relationship. Further research should explore issues of timing and duration of hormone exposures and the effects of exogenous androgen supplementation on PCA risk, and whether genetic predictors of androgen metabolism or

lifestyle and other health exposures that may affect androgen influence on prostate carcinogenesis.

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Table 1

Demographic and health-related characteristics at baseline and pre-diagnostic androgen concentrations among cases and controls in the placebo arm of the Prostate Cancer Prevention Trial 1993-2003

Characteristic	Cases n=1,032		Controls n=1,025		
	Mean	SD	Mean	SD	P value[b]
Age (Years)	63.6	5.5	63.5	5.5	Matched
Waist-to-hip Ratio (WHR)	0.96	0.05	0.96	0.05	0.383
Prostate specific antigen (PSA; ng/ml)	1.5	0.8	1.2	0.7	<0.0001

	Mean[a]	95% CI	Mean[a]	95% CI	
Total testosterone (ng/dL)	384	376-392	382	374-390	0.72
3a-diol G (ng/mL)	6.7	6.5-7.0	6.6	6.3-6.8	0.34
Free testosterone (pg/mL)	8.6	8.5-8.8	8.6	8.4-8.7	0.52
Sex hormone-binding globulin (SHBG; nmol/L)	39.2	38.3-40.0	39.5	38.6-40.4	0.71
Estrone:Testosterone ratio	0.13	0.13-0.13	0.13	0.13-0.13	0.62
Estradiol:Testosterone ratio	0.10	0.09-0.10	0.10	0.09-0.10	0.81

	n	%	n	%	
Race					Over-sampled
White (Non-Hispanic)	958	92.8	860	83.9	
Black (Non-Hispanic)	46	4.5	74	7.2	
Hispanic	22	2.1	68	6.6	
Other	6	0.6	23	2.2	
Education					0.12[c]
<=12 yr	175	17.0	187	18.2	
13-15 yr	277	26.9	303	29.6	
16+ yr	579	56.2	535	52.2	
Smoking status					0.38
Current	381	36.9	350	34.1	
Former	70	6.8	78	7.6	
Never	581	56.3	597	58.2	
Alcohol Consumption					0.90[c]
Non-drinker	239	23.2	236	23.0	
<30 g/day	702	68.0	703	68.6	
>=30 g/day	91	8.8	86	8.4	
Body mass index (BMI; kg/m^2)					0.01[c]
<25	301	29.2	243	23.7	
25 to <30	531	51.5	560	54.6	
≥30	200	19.4	222	21.7	
Waist to Hip ratio (WHR)					0.40[c]
<0.94	282	30.7	312	33.4	

	n	%	n	%	
0.94 to <0.98	328	35.7	312	33.4	
≥0.98	310	33.7	311	33.3	
Family History					Matched
No	818	79.3	814	79.4	
Yes	214	20.7	211	20.6	
Diabetes					0.002
No	990	95.9	950	92.8	
Yes	42	4.1	74	7.2	
Physical Activity					0.77[c]
Sedentary	168	16.3	169	16.5	
Light	423	41.1	432	42.3	
Moderate	350	34.0	306	29.9	
Active	88	8.6	115	11.3	
T-stage					
T1a, b	224	22 .3			
T1c	536	53.3			
T2a	135	13.4			
T2b, c	99	9.9			
T3	11	1.1			
N-stage					
0	295	98.3			
1	5	1.7			
Gleason Grade					
2-6	776	78.5			
7-10	212	21.5			

[a] least-square means and p-values adjusted for age and BMI

[b] *P* value from Chi-square test (categorical variables) or *t* test (continuous variables)

[c] *P* value calculated in a trend test

Table 2

Odds ratios (ORs) and 95% confidence intervals (CIs)[a] for total, low-grade, and high-grade prostate cancer in relation to serum concentrations of androgen in the PCPT

	Total Cancer		Low Grade <Gleason <7)		High Grade (Gleason 7+)	
	N case/control	**OR (95% CI)**	**N case/control**	**OR (95% CI)**	**N case/control**	**OR (95% CI)**
Total Testosterone (ng/dL)						
<292	249/256	ref	179/256	ref	58/256	ref
292 to <362	247/255	1.01 (0.79-1.30)	179/255	1.01 (0.77-1.33)	55/255	1.00 (0.67-1.52)
362 to <456	283/256	1.14 (0.89-1.46)	218/256	1.20 (0.92-1.58)	53/256	0.98 (0.64-1.49)
≥456	252/257	1.01 (0.78-1.30)	200/257	1.09 (0.82-1.44)	45/257	0.86 (0.55-1.33)
p-trend		0.74		0.35		0.50
3α-diol G (ng/mL)						
<4.0	257/255	ref	190/255	ref	51/255	ref
4.0 to <5.6	261/256	1.03 (0.81-1.32)	203/256	1.09 (0.84-1.43)	48/256	0.93 (0.60-1.44)
5.6 to <8.0	254/255	1.00 (0.78-1.29)	197/255	1.05 (0.80-1.38)	47/255	0.93 (0.60-1.43)
≥8.0	260/259	1.02 (0.79-1.31)	186/259	0.99 (0.75-1.30)	66/259	1.26 (0.84-1.90)
p-trend		0.95		0.87		0.25
Free Testosterone (pg/mL)						
<6.9	245/256	ref	174/256	ref	56/256	ref
6.9 to <8.3	241/257	0.98 (0.76-1.25)	175/257	0.99 (0.75-1.30)	56/257	1.04 (0.69-1.57)
8.3 to <10.0	289/255	1.19 (0.93-1.53)	222/255	1.25 (0.96-1.64)	55/255	1.08 (0.71-1.64)
≥10.0	257/257	1.07 (0.83-1.38)	205/257	1.16 (0.88-1.53)	45/257	0.93 (0.60-1.45)
p-trend		0.33		0.12		0.83
Estrone:Testosterone Ratio						
<0.09	266/253	ref	211/253	ref	45/253	ref
0.09 to <0.12	265/253	1.01 (0.79-1.29)	198/253	0.97 (0.74-1.26)	56/253	1.20 (0.78-1.85)
0.12 to <0.15	212/253	0.82 (0.64-1.07)	165/253	0.83 (0.63-1.09)	36/253	0.75 (0.46-1.21)
≥0.15	277/253	1.11 (0.86-1.43)	197/253	1.03 (0.78-1.36)	68/253	1.38 (0.89-2.13)
p-trend		0.76		0.90		0.38
Estradiol:Testosterone Ratio						
<0.07	235/255	ref	195/255	ref	35/255	ref

	Total Cancer		Low Grade <Gleason <7)		High Grade (Gleason 7+)	
	N case/control	**OR (95% CI)**	**N case/control**	**OR (95% CI)**	**N case/control**	**OR (95% CI)**
0.07 to <0.09	297/257	1.28 (1.00-1.64)	218/257	1.14 (0.88-1.49)	62/257	1.71 (1.09-2.69)
0.09 to <0.11	248/255	1.09 (0.85-1.41)	180/255	0.97 (0.74-1.27)	60/255	1.64 (1.04-2.60)
≥0.11	248/256	1.13 (0.87-1.48)	182/256	1.04 (0.78-1.39)	52/256	1.32 (0.81-2.16)
p-trend		0.66		0.91		0.38
SHBG (nmol/L)						
<29	245/256	ref	187/256	ref	49/256	ref
29 to <37	277/249	1.17 (0.91-1.50)	203/249	1.13 (0.87-1.49)	58/249	1.21 (0.79-1.84)
37 to <46	236/263	0.93 (0.72-1.20)	178/263	0.92 (0.70-1.21)	52/263	1.03 (0.67-1.59)
≥46	273/256	1.07 (0.83-1.39)	208/256	1.08 (0.81-1.43)	52/256	1.04 (0.66-1.63)
p-trend		0.95		0.98		0.94

Abbreviations: SHBG = Sex hormone-binding globulin; 3αdiol G = 3α androstanediol glucuronide

All odds ratios adjusted for age, race, BMI, and family history of prostate cancer