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Journal

Urology, 85(3)

ISSN

0090-4295

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Publication Date

2015-03-01

DOI

10.1016/j.urology.2014.11.024

Peer reviewed

HHS Public Access

Author manuscript

Urology. Author manuscript; available in PMC 2016 March 01.

Published in final edited form as:

Urology. 2015 March ; 85(3): 616–620. doi:10.1016/j.urology.2014.11.024.

Effect of Finasteride on Serum Androstenedione and Risk of Prostate Cancer within the Prostate Cancer Prevention Trial: Differential Effect on High and Low Grade Disease

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Abstract

Objectives—To evaluate the effect of finasteride on serum Androst-4-ene-3,17-dione (androstenedione) and its association with prostate cancer risk among subjects who participated in the Prostate Cancer Prevention Trial (PCPT).

Methods—We analyzed serum androstenedione levels in 317 prostate cancer cases and 353 controls, nested in the Prostate Cancer Prevention Trial (PCPT), a randomized, placebo-controlled

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The authors declare no conflict of interest.

trial that found finasteride decreased prostate cancer risk. Androstenedione is the second most important circulating androgen in men beside testosterone and also a substrate for 5α-reductase enzyme.

Results—We observed 22% increase in andostenedione levels compared to baseline values in subjects who were treated with finasteride for 3 years. This significant increase did not vary by case-control status. Adjusted OR and 95% CI for the 3rd tertile of absolute change of androstenedione levels compared to the 1st tertile was 0.42 (95% CI 0.19–0.94) for low-grade (Gleason <7) cases. Similar results were observed when analyzed using percent change. There were no significant associations between serum androstenedione levels and risk of high-grade disease.

Conclusions—The results of this nested case-control study confirm that finasteride blocks the conversion of testosterone to DHT and of androstenedione to 5α-androstanedione-3, 17-dione, which also leads to reduction of DHT formation. This decrease in DHT may help reduce the risk of low-grade prostate cancer in men. Our data on a differential effect of androstenedione also suggest that some high-grade prostate cancers may not require androgen for progression.

Keywords

Prostate Cancer; Finasteride; Androstenedione; Prevention

Androgens play a key role in the maintenance and development of the prostate gland and appear to influence prostate carcinogenesis (1–2). Dihydrotestosterone (DHT), a metabolite of testosterone and the most potent androgen, has been linked to prostate carcinogenesis (2–3). The conversion of testosterone to DHT occurs predominantly and irreversibly through the action of steroid 5α-reductase type II, which is encoded by the *SRD5A2* gene. Besides testosterone, Androst-4-ene-3,17-dione (androstenedione) is another substrate of the type II steroid 5α-reductase enzyme, which converts androstenedione to 5α-androstane-3,17-dione (androstanedione) and subsequently to DHT via the enzyme 17β-hydroxysteroid dehydrogenase type 5 (17β-HSD) (4–5). Androstendione level decreases and sex-hormone binding globulin (SHBG) increases in aging male (6). Although not consistent, previous study has shown association between prostate cancer risk and SHGB (7,8).

A recent study demonstrated that the pathway for DHT formation from androstenedione via androstanedione is more important than via testosterone (9). Another study showed that the main route of DHT synthesis in castration-resistant prostate cancer bypasses testosterone and requires 5-α reduction of androstenedione by *SRD5A1* to 5α-androstanedione and then converted to DHT (10). The ability of the competitive SRD5A inhibitor finasteride to reduce the conversion of testosterone into DHT in the prostate led to the Prostate Cancer Prevention Trial (PCPT) of finasteride versus placebo in 18,880 men (11). Although finasteride in the PCPT was associated with a 24.8% overall reduction in prostate cancer risk, it also was associated with a 25% increased risk of high-grade tumors, which raised questions regarding the ultimate role of finasteride in prostate cancer prevention (11). In this study, we investigated the effect of finasteride on serum androstenedione and its association with prostate cancer risk within the PCPT cohort.

Methods and Materials

Study Design and Study Population

We used data and biospecimens from the PCPT, a large, phase III, double-blind, placebo-controlled trial. The objective of the PCPT trial was to evaluate whether finasteride decrease the period prevalence of prostate cancer during the 7-year intervention period. The study design and population characteristics of the PCPT have been described previously (11). 18,800 men ages 55 years or older were recruited in the PCPT. Men who were included in this trial had a normal digital rectal examination (DRE), a prostate-specific antigen (PSA) level of ≤3 ng/mL, and had no prior history of prostate cancer. Severe benign prostate hyperplasia and other clinically significant diseases were excluded from this trial. Eligible men were randomized to receive finasteride (5 mg/day) or matched placebo. DRE and PSA were performed for all study subjects annually. An abnormal DRE suspicious for cancer or a PSA of ≥4.0 ng/mL were recommended for biopsy. Prostate biopsies prompted by serum PSA level in the finasteride arm was adjusted to ensure similar number of biopsies in both treatment arms. At the end of seven years on study, each study participants were offered end-of-study biopsy who had no previous diagnosis of prostate cancer. All prostate biopsies were done under transrectal ultrasonographic guidance. At least six cores were obtained from each study subject. All biopsies were reviewed by the local study site pathologist and central PCPT pathology laboratory pathologist to confirm the diagnosis of adenocarcinoma. In case of discordant pathology diagnoses, a referee pathologist reviewed the slides of the discordant pathology diagnoses and reached concordance in all cases. Clinical stage assignment was done by the study site pathologist and grading of tumor was done centrally using the Gleason scoring system. Low-grade prostate cancer was defined as Gleason score <7 and high-grade prostate cancer with Gleason score ≥7. In this nested case-control study, we evaluated whether higher levels of serum androstenedione were associated with prostate cancer risk and whether the effects of finasteride on prostate cancer risk differed between men with high and low levels of serum androstenedione. The sample size for this study was a random subset from a larger nested case-control study, where cases were defined as men with biopsy-proven prostate cancer and controls were biopsy-negative, both having available serum samples for androstenedione analysis. In the larger nested case-control study, controls were frequency matched to cases on age in five-year increments, PCPT treatment arm (finasteride vs. placebo) and positive family history (first degree relative with prostate cancer). We oversampled controls to include all non-Whites to increase power for analyses by race/ethnicity. The final sample size for this study subset was 317 cases and 353 controls.

Data Collection

Data on socio-demographic characteristics, including age, race, smoking, and family history of prostate cancer were collected from each study subject after obtaining informed consent. Height and weight was measured at the baseline clinic visit, and weight was measured annually. We calculated body mass index (BMI) as weight (kg) divided by height (m^2) and categorized as <25 (normal), 25 to 30 (overweight) and >30 (obese).

Biospecimen Collection, Processing and Storage

Blood specimens were collected three months before randomization and annually. To process the blood specimens, vacutainers without anticoagulant but with a gel were used to separate serum from clot. Blood specimens were centrifuged 30–60 min at room temperature. Serum were shipped to a central location and stored at −70°C. Detailed procedures for blood collection, processing and storage have been described previously (12).

Serum Androstenedione Measurement

Androstenedione was measured in serum by a well-established and validated radio-immunoassay (RIA) method (13). Appropriate tritiated internal standard was added to each aliquot (0.5 ml) of sample to follow procedural losses, and the steroids were extracted, using ethyl acetate:hexane (3:2). This was followed by separation of androstenedione from other unconjugated steroids by Celite column partition chromatography, using ethylene glycol as the stationary phase; androstenedione eluts with isooctane. After drying the eluate, the residue was reconstituted in assay buffer; an aliquot was taken to determine procedural loss, and duplicate aliquots taken for RIA. The RIA utilized an iodinated radioligand in conjunction with a highly specific antiserum. A 7-point standard was included in each assay. After an overnight incubation (16–18 hr), antibody-bound steroid was separated from unbound steroid by precipitation of the first antibody with a second antibody, and subsequent centrifugation. The antibody-bound steroid was counted in a gamma counter and the counts used to obtain the standard curve and quantify androstenedione in each sample. Quality control samples containing low, medium and high levels of androstenedione were used at the beginning and end of each assay. The interassay coefficients of variation were 8.6% at 0.289 ng/ml, 7.2% at 0.826 ng/ml and 6.9% at 2.41 ng/ml. The assay sensitivity is 30 pg/ml. For men on the finasteride arm, androstenedione concentrations were measured at baseline and at year 3 post-baseline. For men on the placebo arm, to reduce intra-individual variability and to conserve limited pre-randomization samples, 0.5 ml serum samples collected at baseline and at year 3 were pooled.

Statistical Analysis

To compare descriptive characteristics between cases and controls, we used the chi-square test for categorical variables and *t*-test for continuous variables. We used Wilcoxon rank sum test to evaluate the effects of finasteride treatment on circulating androstenedione concentrations by testing the absolute change in concentration from baseline to post-treatment. Serum concentrations of androstenedione were categorized into tertiles based on their distributions among controls to estimate prostate cancer risk.

For additional analyses, we followed approaches that we used in assessing associations between serum estrogen and prostate cancer risk in the PCPT (14). Unconditional logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for overall prostate cancer risk. Polytomous logistic regression models were used for low-grade (Gleason score <7) and high-grade (Gleason score ≥7) prostate cancer compared to controls (14). We analyzed data separately for each treatment arm. In our models, we included age (continuous), current smoking status, and race (white vs non-white) as covariates. We also considered adjusting for concentrations in testosterone, 5a-

androstane-3a,17b-diol glucuronide (3a-dG), a distal metabolite of DHT, estradiol, estrone and sex-hormone binding globulin (SHBG). We assessed whether effects of finasteride on serum concentrations of androstenedione differ among compliant and noncompliant men. Non-compliance was defined as self-report of not using study drug or finasteride concentration is zero in post-treatment year 3 blood. Sensitivity analysis of compliant men did not change results, therefore, we present results that are based on data from all cases and controls regardless of compliance with the study intervention. Analyses that are restricted to compliant cases and controls only are noted in the Tables. All data analyses were performed using SAS 9.2 (SAS Institute, Cary, NC). All P-values were 2-sided with a significance level of 0.05.

Results

Characteristics of the PCPT study population are shown in Table 1. Prostate cancer cases had higher baseline PSA levels than controls. More than 70% of the study participants were either overweight or obese. Controls were supplemented with a higher proportion of non-white men than cases and family history of prostate cancer was similar between cases and controls due to the sampling strategy.

We did not observe significant associations between baseline androstenedione levels and overall prostate cancer risk in the placebo group or finasteride group (Table 2). Odds ratios did not change when evaluated by Gleason grade. In the finasteride group, there was a 23% statistically non-significant decreased risk of prostate cancer risk when the highest tertile of serum andostenedione was compared to the lowest tertile (Table 2). These analyses were adjusted for age, race, current smoking status, testosterone, 3-adg, SHBG, estrone and estradiol.

The effects of finasteride treatment on serum androstenedione concentrations are shown in Table 3. Overall, concentrations of androstenedione were significantly elevated at year 3 of the trial. This effect was similar among cases and controls. There was an approximate 22% increase in serum androstenedione in both cases and controls.

We observed a statistically significant inverse association between prostate cancer risk and increase in levels of androstenedione among men treated with finasteride (Table 4). There was a 56% decreased overall prostate cancer risk (OR=0.44, 95% CI=0.21–0.95) when men in the highest tertile were compared to men in the lowest tertile of the baseline-adjusted change in androstenedione levels. A similar association was observed for the percent change in androstenedione (OR=0.56, 95% CI=0.29–1.08). For low-grade cancer, this association was more pronounced for both the absolute change (OR=0.42, 95% CI=0.19–0.94) and the percent change (OR=0.46, 95% CI=0.22–0.98) in androstenedione. These analyses were adjusted for age, race, current smoking status, testosterone, 3-adg, SHBG, estrone and estradiol. There was no association between increase in androstenedione level and high-grade prostate cancer.

Discussion

There was a significant inverse association between low-grade prostate cancer risk and increases in serum androstenedione levels after treatment with finasteride for 3 years. Interestingly, however, there was no significant association for high-grade disease. Serum androstenedione level significantly increased after treatment with finasteride for 3 years. The results of this nested case-control study suggest that finasteride blocks the conversion of testosterone to DHT as well as conversion of androstenedione to androstanedione, which leads to further reduction of DHT formation and may have been partly responsible for the decreased risk of low-grade prostate cancer in PCPT. Our study has several limitations. First, the study was conducted as a post hoc analyses and measurements of hormones were not timed. Therefore, variations in hormone levels throughout the day could not be controlled during analyses. However, these variations are unlikely to be systematically different between cases and controls.

Previous studies of circulating steroid hormones and prostate cancer risk have shown that high levels of testosterone and adrenal androgens are associated with reduced risk of aggressive prostate cancer but not with nonaggressive disease (15). This study found that androstenedione had similar associations with the risk of prostate cancer as testosterone. They argued that these associations were expected since androstenedione can be converted by 17-beta-hydroxysteroid dehydrogenase to testosterone (15). Also, androstenedione can be converted to DHT by being converted by steroid 5-alpha-reductase to androstanedine and then by 17-beta-hydroxysteroid dehydrogenase to DHT (4–5). In our study, men were treated with finasteride, which is a competitive inhibitor of 5-alpha reductase, therefore, formation of DHT was substantially reduced, which may be responsible for the significant reduction of low-grade prostate cancer. It is possible that low-grade tumors may have a different etiology than high-grade and the effect of finasteride may differ based on tumor characteristics. The underlying mechanism of the differential effects of finsteride on high-grade and low-grade tumors are not clearly understood, one may conclude that low-grade prostate cancer require classical androgenic stimulation whilst we hypothesize that progression to high-grade tumors may at least in some cases not require this stimulus. This hypothesis warrants further investigation with larger sample size with sufficient power as it may have profound consequences for prostate cancer etiology and its treatment.

Acknowledgments

Grant support: Funded in part by grants P01 CA108964(A Hoque, A Kristal, P Goodman, A Hsing, C Tangen, E Platz, J Reichardt, M Neuhouser, R Santella, W Figg, D Price, S Lippman, C Ambrosone, and I Thompson), R03 CA117490 (A Hoque) and CA37429 (I Thompson, C Tangen) from the National Cancer Institute.

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Table 1

Characteristics of cases and controls

	Control (n=353)	Case (n=317)	P-value
	Mean ± SD	Mean ± SD	
Age at Baseline	63.1+/−5.3	63.7+/−5.5	0.150
Baseline PSA	1.1+/−0.7	1.5+/−0.8	<0.001
	N (%)	N (%)	
BMI			0.840
Normal (<25 kg/m^2)	95 (27.2)	91 (28.8)	
Overweight (25–≤30kg/m^2)	179 (51.3)	162 (51.3)	
Obese (30+ kg/m^2)	75 (21.5)	63 (19.9)	
Race			
White	280 (79.3)	289 (91.2)	
Non-White	73 (20.7)	28 (8.8)	
Family History			
No	281 (79.6)	251 (79.2)	
Yes	72 (20.4)	66 (20.8)	
Smoking status			0.320
Never smoker	122 (34.6)	115 (36.3)	
Current smoke	36 (10.2)	22 (6.9)	
Former smoker	195 (55.2)	180 (56.8)	
Treatment arm			
Placebo	208 (58.9)	175 (55.2)	
Finasteride	145 (41.1)	142 (44.8)	

Table 2

Prostate cancer risk by tertiles of baseline and post-treatment androstenedione concentrations, adjusted for all hormones

	All prostate cancer		Gleason score <7		Gleason score ≥7	
	N (case/control)	*OR (95% CI)	N (case/control)	*OR (95% CI)	N case/control)	*OR (95% CI)
Placebo group						
T1 (<0.49 ng/ml)	58/77	ref	43/77	ref	12/77	ref
T2 (0.49 to <0.67 ng/ml)	67/64	1.28 (0.76–2.15)	48/64	1.20 (0.68–2.12)	15/64	1.54 (0.63–3.74)
T3 (>=0.67 ng/ml)	47/66	0.84 (0.45–1.57)	38/66	0.86 (0.44–1.69)	9/66	0.89 (0.29–2.74)
Trend p-value		0.67		0.71		0.92
Finasteride group						
T1 (<0.49 ng/ml)	44/40	ref	28/40	ref	15/40	ref
T2 (0.49 to <0.67 ng/ml)	55/51	0.93 (0.51–1.71)	36/51	0.95 (0.48–1.89)	17/51	0.86 (0.37–2.02)
T3 (>=0.67 ng/ml)	42/52	0.72 (0.36–1.43)	26/52	0.63 (0.28–1.39)	14/52	0.82 (0.32–2.14)
Trend p-value		0.34		0.26		0.68
Finasteride group, post-baseline (compliant)						
T1 (<0.60 ng/ml)	36/41	ref	24/41	ref	9/41	ref
T2 (0.60 to <0.79 ng/ml)	48/40	1.14 (0.58–2.23)	28/40	0.98 (0.46–2.08)	19/40	2.03 (0.76–5.45)
T3 (>=0.79 ng/ml)	29/41	0.77 (0.35–1.68)	20/41	0.77 (0.32–1.87)	9/41	1.15 (0.36–3.66)
Trend p-value		0.54		0.56		0.81

*All odds ratios are adjusted for age, race, current smoking status, testosterone, 3-adg, SHBG, estrone, and estradiol.

Table 3

Change of androstenedione concentrations (ng/ml) between baseline and follow-up in the finasteride group

	N	Baseline	Follow-up	Absolute change	Percent change	*P-value
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
All	286	0.62 ± 0.23	0.70 ± 0.31	0.09 ±0.32	22.2 ± 62.0	<0.0001
Controls	145	0.63 ± 0.22	0.74 ± 0.38	0.11 ±0.36	22.9 ± 65.4	<0.0001
Cases	141	0.61 ± 0.24	0.67 ± 0.22	0.06 ±0.26	21.6 ± 58.6	<0.004

*P-values compare baseline to follow-up and are based on a Wilcoxon rank sum test.

Table 4

Prostate cancer risk by tertiles of absolute change and percent change in androstenedione (ng/ml) concentrations between baseline and follow-up in the finasteride group, compliant men only, adjusted for all hormones

	All prostate cancer		Gleason score <7		Gleason score ≥7	
Variable	**N (case/control**	**OR (95% CI)**	**N (case/ control)**	**OR (95% CI)**	**N (case/ control)**	**OR (95% CI)**
Absolute Change						
T1	47/38	ref	31/38	ref	13/38	ref
T2	35/41	0.63 (0.33–1.22)	24/41	0.61 (0.30–1.27)	11/41	0.83 (0.32–2.17)
T3	31/43	0.56 (0.28–1.10)	17/43	0.42 (0.19–0.94)	13/43	1.02 (0.39–2.64)
p-trend		0.08		0.03		0.97
Baseline-adjusted change						
T1	41/35	ref	26/35	ref	12/35	ref
T2	46/44	0.75 (0.39–1.44)	29/44	0.74 (0.35–1.55)	16/44	0.94 (0.37–2.39)
T3	26/43	0.44 (0.21–0.95)	17/43	0.44 (0.18–1.05)	9/43	0.61 (0.20–1.84)
p-trend		0.04		0.07		0.39
Percent Change						
T1	48/37	ref	32/37	ref	13/37	ref
T2	31/42	0.50 (0.26–0.98)	20/42	0.45 (0.21–0.95)	11/42	0.78 (0.30–2.06)
T3	34/43	0.56 (0.29–1.08)	20/43	0.46 (0.22–0.98)	13/43	0.93 (0.36–2.38)
p-trend		0.08		0.04		0.90

*All odds ratios are adjusted for age, race, current smoking status, testosterone, 3-adg, SHBG, estrone, and estradiol.