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ORIGINAL ARTICLE

WILEY **The Prostate**

Circulating and intraprostatic sex steroid hormonal profiles in relation to male pattern baldness and chest hair density among men diagnosed with localized prostate cancers

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Background: Prospective cohort studies of circulating sex steroid hormones and prostate cancer risk have not provided a consistent association, despite evidence from animal and clinical studies. However, studies using male pattern baldness as a proxy of early-life or cumulative androgen exposure have reported significant associations with aggressive and fatal prostate cancer risk. Given that androgens underlie the development of patterned hair loss and chest hair, we assessed whether these two dermatological characteristics were associated with circulating and intraprostatic concentrations of sex steroid hormones among men diagnosed with localized prostate cancer.

Methods: We included 248 prostate cancer patients from the NCI Prostate Tissue Study, who answered surveys and provided a pre-treatment blood sample as well as fresh frozen adjacent normal prostate tissue. Male pattern baldness and chest hair density were assessed by trained nurses before surgery. General linear models estimated geometric means and 95% confidence intervals (95%CIs) of each hormone variable by dermatological phenotype with adjustment for potential confounding

variables. Subgroup analyses were performed by Gleason score (<7 vs ≥7) and race (European American vs. African American).

Results: We found strong positive associations of balding status with serum testosterone, dihydrotestosterone (DHT), estradiol, and sex hormone-binding globulin (SHBG), and a weak association with elevated intraprostatic testosterone. Conversely, neither circulating nor intraprostatic sex hormones were statistically significantly associated with chest hair density. Age-adjusted correlation between binary balding status and three-level chest hair density was weak ($r = 0.05$). There was little evidence to suggest that Gleason score or race modified these associations.

Conclusions: This study provides evidence that balding status assessed at a mean age of 60 years may serve as a clinical marker for circulating sex hormone concentrations. The weak-to-null associations between balding status and intraprostatic sex hormones reaffirm differences in organ-specific sex hormone metabolism, implying that other sex steroid hormone-related factors (eg, androgen receptor) play important roles in organ-specific androgenic actions, and that other overlapping pathways may be involved in associations between the two complex conditions.

1 | INTRODUCTION

Androgens have long been hypothesized to underlie the development of prostate cancer. However, the association between serum sex steroid hormones and prostate cancer risk remains inconsistent. A meta-analysis of 18 prospective studies reported null associations using study-specific circulating concentrations,[1] albeit limited by the use of blood at a single time-point after midlife that may have missed the etiologically relevant time window, and a potentially diluted effect through inclusion of a variable proportion of indolent prostate cancer cases in the era of prostate-specific antigen (PSA) testing. Later epidemiologic studies also did not support the association between circulating sex steroid hormones and prostate cancer risk,[2–4] although some subgroup analyses reported a positive association of aggressive prostate cancer with total testosterone/sex hormone-binding globulin (SHBG) ratio,[5,6] and an inverse association with the highest quintile of total estradiol/total testosterone ratio.[7]

Despite the paucity of evidence for an association between circulating sex steroid hormones and prostate cancer risk, androgenic alopecia (also commonly known as male pattern baldness) used as a proxy for early-life or cumulative exposure to sex steroid hormones has been reported to be associated with aggressive and fatal prostate cancer.[8–10] Male pattern baldness is the most common hair loss in men and affects approximately 50% of Caucasian men by age 50. Bald scalp overexpresses androgen receptor (AR)[11–14] and has higher levels of dihydrotestosterone (DHT),[15] compared with the non-bald region. This enhanced androgenic action induces miniaturization of scalp hair follicles and causes progressive hair loss.[16] On the other hand, men

born with 5α-reductase type II (5αR2, which intracellularly converts testosterone to DHT) deficiency,[17] or castrated before puberty show complete retention of scalp hair.[18] The former observation has led to the use of finasteride (a 5αR2 inhibitor) in balding treatment, which slows scalp hair loss and promotes new scalp hair growth.[19]

Although no study has assessed the direct relationship between chest hair density and prostate cancer risk, associations between chest hair density and circulating sex steroid hormones have been reported. The development of chest hair parallels the surge of androgens in men during puberty.[20] Denser chest hair has been correlated with higher levels of circulating 3α-androstanediol glucuronide (3α-diol-G; a metabolite of DHT in peripheral tissue)[21] and lower SHBG concentrations.[22] Given the role of androgenic action in these dermatological phenotypes, we investigated clinically assessed balding status and chest hair density in relation to circulating and intraprostatic concentrations of sex steroid hormones in the NCI Prostate Tissue Study in an attempt to understand the potential biological mechanisms underlying associations between the dermatological phenotypes and prostate cancer risk.

2 | MATERIALS AND METHODS

2.1 | Study population

A detailed description of the Prostate Tissue Study has been reported elsewhere.[23] In brief, 422 patients were enrolled from five hospitals during January 2000 to April 2004. Eligible study subjects were men aged 18 years or older, scheduled for prostatectomy or

cystoprostatectomy, newly diagnosed with localized prostate cancer, and had not taken any medication that may influence sex steroid hormone concentrations (eg, dehydroepiandrosterone [DHEA], finasteride, and neoadjuvant hormone therapy) during the 24 h preceding surgery.

Each patient provided 30 mL of fasting blood before surgery, which was aliquoted within 4 h at room temperature and subsequently frozen at −70°C. During surgery and immediately after the prostate gland was resected, the pathologist sliced a maximum of three pieces of macroscopically normal tissue from each of the peripheral and non-peripheral zones of the prostate, each piece weighing 200-400 mg. Each macroscopically normal tissue had the ends trimmed and fixed in formalin for Haemotoxylin and Eosin stain. A genitourinary pathologist (I.A.S.) subsequently evaluated the morphology and histology of these margins to rule out slices containing cancer. The remaining tissue was placed in a pre-labeled cryovial, flash frozen in liquid nitrogen and stored at −70°C.

Each patient underwent a physical examination before surgery by trained hospital nurses for anthropometric and dermatological information and a follow-up telephone interview approximately six weeks after surgery for information on demographics, medical history, family history of cancer, and lifestyle. Medical and pathology reports were also extracted.

2.2 | Sex steroid hormone quantitation

Sex steroid hormones were quantified at the University of Southern California under the direction of F.Z.S. A detailed description of sample handling and laboratory process have been previously reported.[23] In brief, serum concentrations of total testosterone (testosterone), DHT, 4-Androstene-3, 17-dione (androstenedione), estrone, and total estradiol (estradiol) were measured by in-house radioimmunoassays (RIA), 3α-diol-G was measured by a commercial RIA kit (Diagnostics Systems Laboratories, Webster TX, presently Beckman-Coulter, Minneapolis, MD), and SHBG was measured by a solid-phase, two-site chemiluminescent immunometric assay on the Immulite analyzer (Diagnostic Products Corporation, Los Angeles, CA, presently Siemens Healthcare Diagnostics, Deerfield, IL) during 2007. RIAs were used after organic solvent extraction to remove conjugated steroids and Celite column partition chromatography to separate potential interfering unconjugated steroids. In addition, highly specific antisera were used in the RIAs to provide added specificity. Concentrations of serum free testosterone and free estradiol were calculated using validated algorithms.[24,25] Coefficients of variation (CV)—calculated on the logarithmic scale using a mixed model which included 2-7 replicates from each of seven different individuals—were all less than 15% (mean = 10%).

Intraprostatic sex steroid hormones, including androstenedione, testosterone, DHT, 3α-diol-G, estrone, and estradiol, were extracted from each homogenized prostate tissue sample weighing 100-400 mg during 2008-2009. These hormones then underwent the same preparation procedures and RIAs as in the serum hormone quantitation, and were expressed as picograms per gram of wet tissue weight. In-house assays for tissue hormones had small technical variability with CVs below 20% (mean = 13.8%) for all, except for androstenedione (21%). CVs were calculated on the logarithmic scale using a mixed model including an average of six technical replicates from each of five different individuals. For intraprostatic sex steroid hormone analysis, we used all eligible pieces of adjacent normal tissue regardless of sampling locations to calculate subject-level mean concentrations, as our pilot study of 30 prostate cancer patients showed that this provided generally superior CV and intra-class correlation coefficient (ICC) values, compared with using the mean concentrations of solely peripheral or solely non-peripheral tissue.[23] Both serum and tissue sex steroids RIAs used tritiated internal standards, and the concentrations were corrected for procedural losses ranging from 15% to 30%.

2.3 | Exposure measurement

Trained hospital nurses assessed scalp hair pattern using a Norwood-Hamilton Scale[26] and grouped participants into three categories: 1) no/little baldness (I/II); 2) vertex baldness (III-vertex, IV/V/Va/VI, and VII); and 3) frontal baldness (IIa/III/IIIa/IVa) (Supplementary Figure S1). A previous validation study asked dermatologists and residents to rate balding patterns using Norwood-Hamilton scale against photographs of male heads, reporting modest ICCs (0.63-0.68) for original classes and recommending reduced classes to achieve higher ICCs.[27] Therefore, the three-level balding variable was further collapsed into two categories: no/little versus any baldness to minimize potential misclassification. Chest hair density was originally measured on the Ferriman-Gallwey five-level scale (ie, none, sparse, moderate, dense, and very dense).[28] A previous validation study reported good inter-observer agreement (kappa = 0.80) for the original scale among Turkish women.[29] This variable was subsequently collapsed into three categories in the analysis: none-to-sparse (lowest two levels), moderate, and dense (highest two levels).

2.4 | Analytic sample

Of 422 enrolled patients, we included 248 prostate cancer patients for this analysis, after excluding 148 without sex hormones assayed in tissue, 14 without a diagnosis of prostate cancer, one without serum hormones and 11 without any measured dermatological information.

2.5 | Statistical analysis

Pearson χ^2 tests assessed independence of categorical patient characteristics from balding status and chest hair density. Partial Spearmen's correlation coefficients were estimated for pairs of circulating and intraprostatic sex hormones, adjusting for continuous age at surgery and body mass index (BMI, kg/m^2). General linear models estimated geometric means and 95% confidence intervals (95%CIs) of hormones by balding status, chest hair density and Gleason

score (from prostatectomy or biopsy) with adjustment for pre-defined potential confounding variables including age at surgery, study site, race, BMI, education, smoking status, and regular alcohol use. As hormone variables were skewed, natural log transformation was applied to non-missing values, and patients with missing values were dropped from regression models for individual hormone variables. Missing values of potential confounding variables were included in regression models as a separate category. Subgroup analyses were performed by Gleason score (<7 vs ≥7) and race (European American vs African American).

We also conducted two sensitivity analyses: 1) for intraprostatic sex steroid hormones, we used the mean concentrations of two randomly selected tissue pieces to evaluate the robustness of the main results in general linear models, given the potential variation in measurement errors from the use of a variable number of eligible tissue pieces per subject (median = 4); and 2) we alternatively modeled balding status or three-level chest hair density as the outcome and tertiles of each hormone variable as the exposure using binary and ordinal logistic regression, respectively. To assess trends across tertiles, we assigned the median value of each tertile and modeled this as a continuous variable in logistic regressions.

Two-sided P values <0.05 were considered statistically significant. SAS v9.3 (SAS Institute, Inc., Cary, NC) was used for statistical analyses.

3 | RESULTS

Of the 248 patients in this analysis, 144 (58%) presented some degree of baldness and 52 (22%) some degree of dense chest hair (Table 1). Age-adjusted correlation between binary balding status and three-level chest hair density was weak ($r = 0.05$). Patient characteristics distributed evenly by balding status, while patients with dense chest hair were more likely to be European Americans, have a college degree or higher, and have high-grade prostate cancer. After adjustment for age, differences in these characteristics by chest hair density became minimal (data not tabulated). Supplemental Table S1 shows the distribution of crude concentrations of sex hormones and SHBG. Partial Spearmen's correlation coefficients adjusted for age and BMI demonstrated very strong correlations for pairs of testosterone and DHT ($r = 0.74$), testosterone and SHBG ($r = 0.68$), testosterone and estradiol ($r = 0.53$), DHT and SHBG ($r = 0.61$), and estrone and estradiol ($r = 0.66$) in serum, as well as estrone and estradiol ($r = 0.64$) in tissue (data not tabulated).

Geometric means of hormone variables by balding status are shown in Table 2. Bald patients were more likely to have higher serum testosterone, DHT, estrone, estradiol, and SHBG, as well as higher intraprostatic testosterone concentrations with full adjustment for potential confounding variables. Stratified analyses by Gleason score showed that such associations were mainly observed in Gleason score ≥7 prostate cancers, although the multiplicative interaction between balding status and Gleason score for each hormone variable was not statistically significant (Supplemental Table S2). Meanwhile, stratified analyses by race demonstrated that only bald European Americans had statistically significantly higher

testosterone, DHT, and SHBG in serum, and estrone, estradiol, and androstenedione/estrone ratio in tissue (Supplemental Table S3). However, associations were in the same direction among African Americans, and multiplicative interactions were null between balding status and race for individual hormone variables. Given androgenic sensitivity differs by scalp region,[15] we also presented geometric means by three-level scalp balding category in Supplemental Table S4, despite limited counts for frontal balding only ($n = 20$). Distributions of hormone variables were similar between frontal balding only and vertex plus frontal balding, although the latter group appeared to have higher androstenedione in serum ($P = 0.013$).

Sensitivity analyses in which tertiles of each hormone variable were modeled as the exposure, as opposed to the outcome, provided mostly consistent results, except that the association for intraprostatic testosterone concentrations became null and an inverse association for intraprostatic androstenedione/estrone ratio was observed (adjusted $P_{trend} = 0.042$, Supplemental Table S5). Increased SHBG appeared to drive the association for testosterone in serum; when we modeled testosterone and SHBG simultaneously, the positive association for testosterone was attenuated to the null ($OR_{third\ tertile\ vs\ first\ tertile} = 1.62$, 95%CI = 0.67-3.91), whereas the positive association for SHBG remained significant ($OR_{third\ tertile\ vs\ first\ tertile} = 3.00$, 95% CI = 1.19-7.53) (data not tabulated). Results were consistent when we simultaneously modeled testosterone and SHBG as continuous variables ($P_{testosterone} = 0.83$ and $P_{SHBG} = 0.01$). Tentative evidence was found that increased testosterone drove the association for estradiol in serum, as simultaneous adjustment for continuous testosterone and estradiol attenuated the association for estradiol to the null ($P_{estradiol} = 0.197$ and $P_{testosterone} = 0.05$), but simultaneous adjustment for tertiles of these hormones attenuated the associations to the null for both estradiol ($OR_{third\ tertile\ vs\ first\ tertile} = 2.16$, 95% CI = 0.90-5.20) and testosterone ($OR_{third\ tertile\ vs\ first\ tertile} = 2.03$, 95% CI = 0.90-4.57) (data not tabulated).

Geometric means of hormone variables by chest hair density provided no evidence of an association (Table 3). There was little evidence for effect modification by Gleason score (Supplemental Table S6) or race (Supplemental Table S7). Compared with the main results for chest hair density, modeling tertiles of each hormone variables as the exposure resulted in similarly null associations (Supplemental Table S5).

Sensitivity analyses for intraprostatic sex steroid hormones that used two pieces of randomly selected adjacent normal tissue per subject did not materially alter the results, compared with the main models that used all eligible tissues (data not tabulated).

4 | DISCUSSION

In this study, serum and intraprostatic sex steroid hormones were quantified in relation to male pattern baldness and chest hair density in men diagnosed with localized prostate cancer. We found evidence for strong positive associations of circulating testosterone, DHT, estradiol,

TABLE 1 Patient characteristics by balding status and chest hair density (N = 248)

Characteristics	Balding status (n = 248)			Chest hair density (n = 239)[a]			
	No (n = 104)	Any (n = 144)	P-value[b]	None/sparse (n = 110)	Moderate (n = 77)	Dense (n = 52)	P-value[b]
Age at surgery (years)							
N	104	143		109	77	52	
Mean (SD)	58.4 (8.1)	60.4 (6.4)	0.055[c]	60.0 (7.3)	59.4 (7.6)	59.0 (6.4)	0.803[c]
≤55	37 (35.6%)	32 (22.2%)	0.088[d]	27 (24.5%)	23 (29.9%)	16 (30.8%)	0.945[d]
56-60	23 (22.1%)	44 (30.6%)		32 (29.1%)	20 (26.0%)	14 (26.9%)	
61-65	25 (24.0%)	32 (22.2%)		26 (23.6%)	16 (20.8%)	13 (25.0%)	
>65	19 (18.3%)	35 (24.3%)		24 (21.8%)	18 (23.4%)	9 (17.3%)	
Race			0.291				<0.001
European American	61 (58.7%)	73 (50.7%)		40 (36.4%)	50 (64.9%)	36 (69.2%)	
African American	38 (36.5%)	68 (47.2%)		66 (60.0%)	26 (33.8%)	13 (25.0%)	
Other	3 (2.9%)	3 (2.1%)		4 (3.6%)	1 (1.3%)	1 (1.9%)	
Education			0.935				<0.001
Less than high school	8 (7.7%)	12 (8.3%)		16 (14.5%)	3 (3.9%)	0 (0%)	
High school/Technical school	25 (24.0%)	33 (22.9%)		26 (23.6%)	23 (29.9%)	9 (17.3%)	
College or higher	58 (55.8%)	73 (50.7%)		50 (45.5%)	35 (45.5%)	38 (73.1%)	
Gleason score			0.822				0.009
<7	56 (53.8%)	81 (56.3%)		57 (51.8%)	53 (68.8%)	20 (38.5%)	
=7	38 (36.5%)	55 (38.2%)		42 (38.2%)	23 (29.9%)	28 (53.8%)	
>7	6 (5.8%)	6 (4.2%)		6 (5.5%)	1 (1.3%)	4 (7.7%)	
Body mass index (BMI, kg/m^2)							
N	102	143		109	77	51	
Mean (SD)	26.9 (3.3)	28.1 (10.4)	0.358[c]	26.7 (3.9)	29.1 (13.7)	27.3 (2.9)	0.139[c]
<25.0	29 (27.9%)	37 (25.7%)	0.593[d]	36 (32.7%)	18 (23.4%)	11 (21.2%)	0.115[d]
25.0-29.9	58 (55.8%)	76 (52.8%)		57 (51.8%)	38 (49.4%)	33 (63.5%)	
≥30.0	17 (16.3%)	31 (21.5%)		17 (15.5%)	21 (27.3%)	8 (15.4%)	
Smoking status			0.295				0.162
Never	38 (36.5%)	48 (33.3%)		36 (32.7%)	25 (32.5%)	23 (44.2%)	
Former	38 (36.5%)	55 (38.2%)		39 (35.5%)	32 (41.6%)	16 (30.8%)	
Current	12 (11.5%)	8 (5.6%)		12 (10.9%)	2 (2.6%)	5 (9.6%)	
Regular alcohol use			0.087				0.347
Never	31 (29.8%)	45 (31.3%)		35 (31.8%)	23 (29.9%)	14 (26.9%)	
Former	11 (10.6%)	25 (17.4%)		19 (17.3%)	9 (11.7%)	5 (9.6%)	
Current	49 (47.1%)	47 (32.6%)		38 (34.5%)	29 (37.7%)	27 (51.9%)	

Column percentage does not add up to 100% due to missing data.

[a]Nine prostate cancer patients were excluded for tabulation of chest hair density due to missing data.

[b]P-values were computed by Wilcoxon Rank-sum test for continuous variables and Chi-square/Fisher's exact test for categorical variables using non-missing values.

[c]P-values were calculated for the continuous covariate.

[d]P-values were calculated for the categorical covariate.

and SHBG with male pattern baldness. However, we found limited evidence for associations between intraprostatic sex hormones and baldness, although the direction of these associations was consistent with what was observed in the serum analyses. Neither circulating nor intraprostatic sex hormones were statistically significantly associated with chest hair density. There was little evidence to suggest that

Gleason score or race modified these relationships, although the statistical power for interaction tests may be limited by the modest sample size.

Both the prostate gland and human hair follicles are responsive to sex steroid hormones. Testosterone produced by Leydig cells of the testes is the predominant circulating androgen in men and is

TABLE 2 Geometric means of sex steroid hormones and SHBG by balding status at mean age of 60 years (N = 248)

| Sex hormones | N | Minimally adjusted[a] | | P-value[c] | Fully adjusted[b] | | P-value[c] |
		No (n = 104)	Any (n = 144)		No (n = 104)	Any (n = 144)	
Serum (ng/dl)							
T	248	420.1 (387.9, 455.0)	481.5 (450.1, 515.1)	0.012	416.4 (384.1, 451.3)	484.6 (452.8, 518.6)	0.006
DHT	248	46.4 (43.0, 50.0)	53.7 (50.4, 57.2)	0.004	45.9 (42.7, 49.4)	54.1 (50.9, 57.5)	0.001
3α-diol-G	248	507.2 (458.3, 561.2)	492.3 (451.9, 536.3)	0.663	500.3 (451.4, 554.4)	497.2 (456.0, 542.1)	0.930
A	248	67.9 (62.7, 73.4)	70.1 (65.6, 75.0)	0.539	66.9 (61.7, 72.5)	70.9 (66.2, 75.9)	0.294
E1	248	5.0 (4.7, 5.4)	5.6 (5.3, 5.9)	0.030	5.0 (4.7, 5.4)	5.6 (5.3, 5.9)	0.027
E2	248	2.9 (2.7, 3.1)	3.3 (3.1, 3.5)	0.004	2.9 (2.7, 3.1)	3.2 (3.1, 3.4)	0.010
T/E2 ratio	248	147.7 (135.8, 160.6)	147.1 (137.0, 157.9)	0.948	144.9 (134.0, 156.7)	149.1 (139.6, 159.3)	0.592
A/E1 ratio	248	13.5 (12.4, 14.6)	12.6 (11.8, 13.6)	0.242	13.3 (12.3, 14.4)	12.8 (11.9, 13.7)	0.458
SHBG (nmol/L)	248	29.8 (27.7, 32.0)	35.4 (33.3, 37.6)	0.001	29.7 (27.7, 31.9)	35.4 (33.4, 37.6)	<0.001
Free T	248	10.7 (9.9, 11.4)	11.4 (10.8, 12.1)	0.140	10.6 (9.8, 11.4)	11.5 (10.8, 12.2)	0.092
Free E2	248	0.08 (0.08, 0.09)	0.09 (0.08, 0.09)	0.064	0.08 (0.08, 0.09)	0.09 (0.08, 0.09)	0.138
Adjacent normal prostate tissue (pg/g W)							
T	245	205.1 (187.7, 224.1)	230.5 (214.1, 248.0)	0.051	204.3 (186.8, 223.4)	230.9 (214.4, 248.6)	0.045
DHT	248	6433.6 (6080.3, 6807.4)	6663.9 (6353.2, 6989.8)	0.357	6456.1 (6104.7, 6827.7)	6647.1 (6341.3, 6967.7)	0.446
3α-diol-G	244	2599.8 (2402.7, 2813.1)	2704.4 (2527.2, 2894.1)	0.463	2568.4 (2372.7, 2780.2)	2731.1 (2552.3, 2922.5)	0.261
A	229	593.3 (537.8, 654.5)	579.4 (534.1, 628.6)	0.719	585.1 (529.9, 646.1)	581.5 (535.9, 630.8)	0.924
E1	232	67.0 (61.2, 73.2)	75.6 (70.2, 81.4)	0.044	67.5 (61.8, 73.6)	75.2 (70.0, 80.8)	0.065
E2	232	44.2 (40.1, 48.8)	51.3 (47.3, 55.7)	0.024	44.8 (40.6, 49.4)	50.7 (46.7, 55.0)	0.062
T/E2 ratio	232	4.6 (4.2, 5.0)	4.4 (4.0, 4.7)	0.500	4.5 (4.1, 4.9)	4.4 (4.1, 4.8)	0.831
A/E1 ratio	220	9.0 (8.0, 10.1)	7.7 (7.0, 8.5)	0.050	8.9 (7.9, 9.9)	7.8 (7.1, 8.5)	0.086

A, androstenedione; DHT, dihydrotestosterone; E1, estrone; E2, estradiol; SHBG, sex hormone-binding globulin; T, testosterone; 3α-diol-G, 3α-androstanediol glucuronide.
[a]Adjusted for age at surgery (year, continuous), race (European American, African American, other, unknown), study site (five sites, not listed here).
[b]Additionally adjusted for BMI (<25.0, 25.0-29.9, ≥30.0 kg/m^2), education (less than high school, high school/technical school, college or higher, unknown), smoking status (never, former, current, unknown), and regular alcohol use (never, former, current, unknown).
[c]P-values were calculated for a global test of differences in geometric means.

irreversibly converted to the most potent androgen, DHT, by 5αR in many peripheral tissues, such as the prostate and skin. DHT and, to a lesser extent, testosterone intracellularly bind to AR stimulating downstream androgenic action including hair stimulation and inhibition, as well as prostate growth and carcinogenesis. There are three isoenzymes of 5αR (types I, II, and III). The function of 5αR3 in the prostate remains unclear but previous studies reported its role in converting testosterone to DHT in castration resistant prostate cancers.[30,31] Meanwhile, 5αR1 and 5αR2 are consistently related to testosterone metabolism, and are expressed at different body sites and organ compartments.[32] Prostatic epithelium and stroma express higher concentrations of 5αR2,[33] as highlighted by an efficient reduction in intraprostatic DHT through finasteride treatment[27] and by its comparable efficacy to dutasteride (a dual inhibitor for 5αR1 and 5αR2) treatment for benign prostatic hyperplasia.[34] Meanwhile, sebaceous glands predominantly express 5αR1, and scalp hair follicles produce higher levels of 5αR2.[35–37] Both isoenzymes play critical roles in balding development as supported by the superior efficacy of dutasteride versus finasteride in treating baldness.[38,39] Lastly, 5αR1 is

the predominant form expressed in chest skin.[40] However, chest hair follicles have been suggested to be less androgen-dependent,[41] and this is in line with the null association of chest hair density with sex steroid hormones in this analysis, albeit two prior observational studies have reported otherwise.[21,22]

Direct comparison of results from epidemiological studies on circulating sex hormones in relation to male pattern baldness is challenging given differences in age, race, laboratory assays (eg, RIA, mass spectrometry, electrochemiluminescence immunoassay), health status (with/without malignancy/other metabolic diseases), and balding categories. Several small studies (n = 6) have assessed this relationship among apparently healthy younger (<45 years old) men and found conflicting associations; some reported that bald men were more likely to have increased testosterone,[15,42] increased testosterone/SHBG ratio,[42,43] increased DHT[15] and decreased SHBG levels,[42–44] whereas others have reported either null or opposing findings.[45,46] On the other hand, a cross-sectional study among older (>65 years) healthy Greek men specifically compared vertex balding to those without (ie, no/minimal plus frontal balding

TABLE 3 Geometric means of sex steroid hormones and SHBG by chest hair density at mean age of 60 years (N = 239)

Sex hormones	N	Minimally adjusted[a]				Fully adjusted[b]			
		None/Sparse (n = 110)	Moderate (n = 77)	Dense (n = 52)	P-value[c]	None/Sparse (n = 110)	Moderate (n = 77)	Dense (n = 52)	P-value[c]
Serum (ng/dL)									
T	239	472.8 (436.1, 512.6)	443.9 (404.1, 487.6)	434.3 (386.4, 488.3)	0.454	466.3 (429.4, 506.3)	456.4 (414.5, 502.4)	429.3 (380.9, 483.9)	0.558
DHT	239	52.3 (48.4, 56.5)	48.5 (44.3, 53.0)	50.7 (45.3, 56.7)	0.458	51.1 (47.3, 55.1)	50.5 (46.2, 55.1)	50.3 (45.1, 56.1)	0.971
3α-diol-G	239	470.3 (425.7, 519.5)	538.4 (479.7, 604.3)	518.6 (449.1, 598.8)	0.221	474.7 (429.0, 525.4)	535.6 (475.8, 602.8)	512.3 (442.2, 593.5)	0.338
A	239	69.7 (64.3, 75.5)	69.4 (63.2, 76.1)	68.6 (61.0, 77.0)	0.976	69.6 (64.0, 75.7)	69.6 (63.1, 76.7)	68.4 (60.6, 77.2)	0.968
E1	239	5.0 (4.7, 5.4)	5.4 (5.0, 5.9)	5.8 (5.3, 6.4)	0.074	5.2 (4.8, 5.5)	5.3 (4.9, 5.7)	5.7 (5.2, 6.3)	0.248
E2	239	3.0 (2.8, 3.2)	3.1 (2.9, 3.4)	3.3 (3.0, 3.7)	0.208	3.0 (2.8, 3.3)	3.0 (2.8, 3.3)	3.3 (2.9, 3.6)	0.536
T/E2 ratio	239	160.1 (147.2, 174.2)	141.8 (128.6, 156.3)	130.7 (115.8, 147.7)	0.027	152.9 (141.3, 165.5)	150.5 (137.2, 165.0)	131.9 (117.5, 147.9)	0.111
A/E1 ratio	239	13.8 (12.7, 15.0)	12.8 (11.6, 14.0)	11.8 (10.5, 13.4)	0.121	13.5 (12.4, 14.7)	13.1 (11.9, 14.4)	11.9 (10.6, 13.5)	0.282
SHBG, nmol/L	239	34.9 (32.4, 37.6)	32.1 (29.4, 34.9)	30.3 (27.2, 33.7)	0.098	34.1 (31.7, 36.7)	32.6 (29.9, 35.5)	31.1 (27.9, 34.6)	0.405
Free T	239	11.3 (10.5, 12.1)	10.9 (10.1, 11.9)	11.0 (9.9, 12.2)	0.873	11.2 (10.4, 12.1)	11.2 (10.3, 12.2)	10.7 (9.6, 11.9)	0.772
Free E2	239	0.08 (0.07, 0.09)	0.09 (0.08, 0.09)	0.09 (0.08, 0.10)	0.043	0.08 (0.08, 0.09)	0.08 (0.08, 0.09)	0.09 (0.08, 0.10)	0.306
Adjacent normal prostate tissue (pg/g W)									
T	236	222.2 (204.0, 241.9)	208.6 (189.1, 230.1)	219.9 (194.1, 249.2)	0.622	219.7 (201.3, 239.7)	211.6 (191.2, 234.1)	219.9 (193.4, 250.1)	0.839
DHT	239	6769.1 (6403.8, 7155.3)	6288.2 (5896.0, 6706.5)	6492.1 (5991.6, 7034.3)	0.250	6769.9 (6404.7, 7156.0)	6326.7 (5930.2, 6749.7)	6432.0 (5934.3, 6971.5)	0.303
3α-diol-G	236	2623.5 (2425.9, 2837.3)	2621.9 (2393.2, 2872.5)	2792.0 (2491.7, 3128.5)	0.638	2681.3 (2476.6, 2902.8)	2591.4 (2362.0, 2843.1)	2723.4 (2425.5, 3057.8)	0.775
A	222	578.0 (524.2, 637.3)	574.1 (512.1, 643.6)	616.2 (534.8, 710.0)	0.709	582.4 (527.0, 643.7)	564.8 (502.2, 635.3)	613.1 (530.1, 709.1)	0.685
E1	223	65.8 (60.2, 71.9)	74.1 (66.8, 82.1)	78.0 (68.5, 88.9)	0.082	68.2 (62.5, 74.5)	71.7 (64.7, 79.5)	76.0 (66.7, 86.5)	0.428
E2	223	45.2 (41.1, 49.7)	49.2 (44.1, 54.9)	49.2 (42.8, 56.6)	0.463	46.2 (41.9, 50.9)	48.8 (43.7, 54.6)	47.3 (41.0, 54.5)	0.772
T/E2 ratio	223	4.8 (4.4, 5.3)	4.1 (3.7, 4.59)	4.4 (3.9, 5.1)	0.130	4.6 (4.2, 5.1)	4.2 (3.7, 4.7)	4.6 (4.0, 5.3)	0.378
A/E1 ratio	213	8.9 (8.0, 10.0)	7.8 (6.8, 8.9)	7.9 (6.7, 9.3)	0.277	8.7 (7.7, 9.7)	7.9 (6.9, 9.0)	8.1 (6.9, 9.6)	0.606

A, androstenedione; DHT, dihydrotestosterone; E1, estrone; E2, estradiol; SHBG, sex hormone-binding globulin; T, testosterone; 3α-diol-G, 3α-androstanediol glucuronide.

[a]Adjusted for age at surgery (year, continuous), race (European American, African American, other, unknown), study site (5 sites, not listed here).

[b]Additionally adjusted for BMI (<25.0, 25.0–29.9, ≥30.0 kg/m², unknown), education (less than high school, high school/technical school, college or higher, unknown), smoking status (never, former, current, unknown), and regular alcohol use (never, former, current, unknown).

[c]P-values were calculated for a global test of differences in geometric means.

only) and did not find associations for serum testosterone, estradiol, DHEA-S, or SHBG.[22] Furthermore, another study in the US among 268 prostate cancer cases and controls found that men with vertex balding had higher serum age- and race-adjusted free testosterone levels than those who had little or no hair loss.[47]

This study supports associations of circulating sex hormones with male pattern baldness in an older prostate cancer population. However, comparisons between our results with previously published studies requires caution. First, there is evidence that the presence of prostate cancer may slightly suppress circulating testosterone concentrations through the hypothalamic-pituitary axis.[48–51] Thus, associations observed in this case series may differ from what may be expected in a healthy population. Second, our analytical sample is older, compared to most prior studies, with a mean age of 60 years. It is known that circulating testosterone decreases,[52–54] while male pattern baldness progresses with advancing age.[55] However, we would expect minimal confounding by age in this study because distributions of age were not statistically significantly different by balding status and we adjusted for age in regression models.

Given the strong parallels in androgen dependency and in age-related changes between scalp hair follicles and the prostate, we speculated that male pattern baldness might serve as a proxy for intrinsic enhanced androgenic action in androgen-responsive organs. Such enhanced androgenic action may be partly explained by genetic susceptibility, particularly within the AR signaling pathway. For example, genetic variation in *AR* gene on the X-chromosome has commonly been associated with male pattern baldness in European descendants.[56–58] Meanwhile, genes involved in androgen biosynthesis and metabolism, as well as AR have been associated with prostate cancer risk.[59–61] Despite these shared etiological factors, we did not find robust associations between intraprostatic sex steroid hormones and male pattern baldness, although associations were directionally consistent with our hypothesis. This implies that sex steroid hormone-related factors (eg, AR), rather than the sex steroids hormones themselves, play important roles in organ-specific androgenic actions, and that other overlapping pathways may be involved in associations between these two complex conditions. Although the directional consistency could be explained by the field effect of hormonal carcinogenesis on histologically normal tissue and/or a product of reverse causation from the adjacent cancerous foci—as supported by significantly elevated levels of testosterone, DHT, and estradiol in normal tissue adjacent to Gleason ≥7 tumor foci versus Gleason <7 foci (Supplemental Table S1)—we did not find evidence that Gleason score modified the association between intraprostatic sex hormones and balding status (Supplemental Table S3).

Strengths of this study include central review by an experienced genitourinary pathologist, nurse-assessed dermatological characteristics, and simultaneous measurement of circulating and intraprostatic sex steroid hormones. Limitations include the fact that both circulating and intraprostatic sex hormones were only measured once and, therefore, intra-individual temporal variations could not be assessed. Meanwhile, male pattern baldness at older age may reflect cumulative exposure to circulating sex steroid hormones as opposed to the single time-point we have assessed in serum and tissue at the age of prostate cancer diagnosis (mean = 60, range = 37-86 years), and this mismatched time-window of sex hormone exposure may have reduced statistical power. Second, we combined hair-loss patterns because the number of frontal balding only was relatively small. Although we were unable to specify whether observed associations were modified by hair-loss patterns, the misclassification of balding status was minimized.

In conclusion, this study provides evidence that elevated circulating testosterone, DHT, estradiol, and SHBG are associated with balding status in prostate cancer cases. Male balding serves as a proxy for circulating sex hormone concentrations and may explain prior studies showing an association between male pattern baldness and prostate cancer incidence and specific mortality. Testosterone is the only elevated intraprostatic sex hormone in men with balding; lack of an association between balding and other intraprostatic sex hormones reaffirms differences in organ-specific sex steroid hormone metabolism and cellular response.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Supplemental Table and Figure Legends:

Supplemental Table 1. Distribution of sex steroid hormones and SHBG overall and their geometric means by Gleason score (N=248)

Supplemental Table 2. Adjusted geometric means of sex steroid hormones and SHBG by balding status and Gleason score (N=242)

Supplemental Table 3. Adjusted geometric means of sex steroid hormones and SHBG by balding status and race (N=240)

Supplemental Table 4. Geometric means of sex steroid hormones and SHBG by three-level balding category (N=248)

Supplemental Table 5. Adjusted odds ratios (ORs) and 95% confidence intervals (95%CIs) for tertiles of sex hormones and SHBG using binary logistic regression with balding status as the outcome variable or using ordinal logistic regression with chest hair density as the outcome variable

Supplemental Table 6. Adjusted geometric means of sex steroid hormones and SHBG by chest hair density and Gleason score (N=234)

Supplemental Table 7. Adjusted geometric means of sex steroid hormones and SHBG by chest hair density and race (N=231)

Supplemental Fig 1. Modified Norwood-Hamilton Scale used to score hair loss patterns in NCI Prostate Tissue Study

Supplemental Table 1. Distribution of sex steroid hormones and SHBG overall and their geometric means by Gleason score (N=248)

Sex hormones	N	Lower quartile	Median	Upper quartile	Range Minimum	Range Maximum	Geometric means* Gleason score<7 (N=137)	Geometric means* Gleason score ≥7 (N=105)	P-value[†]
Serum (ng/dl)									
T	248	343.9	473.5	620.2	34.0	1439.6	443.3 (413.2, 475.7)	443.3 (413.2, 475.7)	0.302
DHT	248	38.8	50.4	67.2	6.6	189.9	50.3 (47.2, 53.7)	51.1 (47.4, 55.0)	0.769
3α-diol-G	248	369.0	505.0	720.0	104.0	1892.0	502.1 (459.9, 548.3)	504.0 (455.5, 557.6)	0.958
A	248	52.2	69.5	90.8	24.4	294.4	70.1 (65.4, 75.3)	68.3 (63.0, 74.1)	0.637
E1	248	4.3	5.5	6.8	1.2	17.4	5.3 (5.0, 5.6)	5.3 (5.0, 5.7)	0.984
E2	248	2.4	3.2	4.1	0.7	9.2	3.0 (2.8, 3.2)	3.2 (3.0, 3.4)	0.209
T/E2 Ratio	248	113.3	147.8	196.0	23.8	728.2	147.6 (137.9, 158.0)	147.1 (136.0, 159.1)	0.952
A/E1 Ratio	248	9.5	12.3	17.5	4.7	83.3	13.2 (12.3, 14.2)	12.9 (11.9, 14.0)	0.652
SHBG, nmol/L	248	26.1	33.1	41.9	10.4	129.0	32.3 (30.4, 34.4)	33.0 (30.7, 35.5)	0.680
Free T	248	8.9	11.7	14.2	0.7	23.9	10.9 (10.3, 11.6)	11.5 (10.7, 12.3)	0.304
Free E2	248	0.07	0.09	0.11	0.02	0.23	0.08 (0.08, 0.09)	0.09 (0.08, 0.09)	0.240
Adjacent normal prostate tissue (pg/g W)									
T	245	165.1	215.0	291.1	64.2	1212.6	209.4 (194.1, 226.0)	238.7 (218.3, 260.9)	**0.034**
DHT	248	5318.2	6813.1	8061.6	2149.9	21426.2	6304.0 (6008.5, 6614.0)	6982.8 (6607.4, 7379.5)	**0.008**
3α-diol-G	244	1914.6	2713.5	3572.5	1020.8	7756.2	2583.3 (2412.4, 2766.3)	2819.2 (2605.1, 3050.9)	0.111
A	229	420.6	583.0	817.4	109.5	2772.2	560.6 (514.9, 610.4)	619.6 (560.9, 684.4)	0.144
E1	232	52.6	72.4	98.9	18.2	244.2	71.0 (65.8, 76.5)	74.4 (68.2, 81.2)	0.432

E2	232	35.2	47.2	65.6	12.5	223.0	45.7 (42.0, 49.7)	52.3 (47.4, 57.7)	*0.048*
T/E2 Ratio	232	3.3	4.3	5.8	1.1	16.6	4.4 (4.1, 4.8)	4.5 (4.1, 4.9)	*0.948*
A/E1 Ratio	220	5.4	8.3	12.1	2.2	45.5	8.0 (7.2, 8.8)	8.4 (7.5, 9.5)	*0.494*

Abbreviations: T, testosterone; DHT, dihydrotestosterone; 3α-diol-G, 3α-androstanediol glucuronide; A, androstenedione; E1, estrone; E2, estradiol; SHBG, sex hormone-binding globulin.

[*]Adjusted for age at surgery (year, continuous), race (European American, African American, other, unknown), study site (5 sites, not listed here), BMI (<25.0, 25.5–29.9, ≥30.0 kg/m^2), education (less than high school, high school/technical school, college or higher, unknown), smoking status (never, former, current, unknown), and regular alcohol use (never, former, current, unknown).

[†]P-values were calculated for a global test of differences in geometric means.

Supplemental Table 2. Adjusted[*] geometric means of sex steroid hormones and SHBG by balding status and Gleason score (N=242)

Sex hormones	Gleason score<7 (N=137)					Gleason score≥7 (N=105)					P-value [‡]
	N	No balding (n=56)	Any balding (n=81)	P-value [†]		N	No balding (n=44)	Any balding (n=61)	P-value [†]		
Serum (ng/dl)											
T	137	427.3 (381.0, 479.1)	468.1 (426.1, 514.1)	0.244		105	411.0 (366.0, 461.5)	497.9 (451.9, 548.6)	**0.018**		0.525
DHT	137	48.3 (43.6, 53.4)	52.9 (48.7, 57.4)	0.182		105	44.5 (39.7, 50.0)	54.8 (49.8, 60.4)	**0.010**		0.328
3α-diol-G	137	540.0 (468.6, 622.2)	503.5 (448.3, 565.5)	0.469		105	482.0 (410.3, 566.1)	485.1 (424.1, 554.9)	0.953		0.534
A	137	71.9 (64.0, 80.8)	71.1 (64.6, 78.2)	0.876		105	62.8 (55.4, 71.1)	69.7 (62.8, 77.4)	0.223		0.390
E1	137	5.3 (4.8, 5.9)	5.6 (5.2, 6.1)	0.403		105	4.6 (4.2, 5.1)	5.4 (5.0, 5.8)	**0.013**		0.580
E2	137	3.1 (2.8, 3.4)	3.2 (2.9, 3.4)	0.729		105	2.6 (2.4, 2.9)	3.4 (3.1, 3.7)	**0.001**		0.115
T/E2 Ratio	137	138.6 (124.8, 153.8)	148.2 (136.1, 161.4)	0.343		105	157.0 (138.0, 178.8)	147.9 (132.8, 164.9)	0.503		0.434
A/E1 Ratio	137	13.5 (12.1, 15.2)	12.6 (11.5, 13.8)	0.363		105	13.6 (11.9, 15.5)	12.9 (11.5, 14.4)	0.564		0.684
SHBG, nmol/L	137	29.1 (26.4, 32.1)	34.8 (32.2, 37.7)	**0.008**		105	30.3 (27.0, 34.0)	34.9 (31.7, 38.5)	0.079		0.486
Free T	137	11.0 (10.0, 12.1)	11.2 (10.3, 12.1)	0.781		105	10.3 (9.3, 11.4)	11.9 (10.9, 13.0)	**0.045**		0.265
Free E2	137	0.09 (0.08, 0.10)	0.09 (0.08, 0.09)	0.700		105	0.07 (0.07, 0.08)	0.09 (0.08, 0.10)	**0.005**		0.079
Adjacent normal prostate tissue (pg/g W)											
T	137	196.1 (174.9, 219.9)	228.0 (207.6, 250.5)	0.055		102	214.8 (182.9, 252.3)	242.5 (213.7, 275.1)	0.267		0.767
DHT	137	6422.6 (5923.7, 6963.5)	6330.3 (5924.8, 6763.5)	0.792		105	6499.0 (5981.2, 7061.5)	7189.4 (6707.3, 7706.0)	0.080		0.346
3α-diol-G	136	2528.0 (2262.3, 2824.8)	2607.5 (2379.9, 2856.9)	0.682		103	2699.1 (2365.4, 3079.9)	2927.6 (2609.6, 3284.2)	0.386		0.701
A	127	580.5 (513.9, 655.7)	557.0 (503.9, 615.7)	0.616		96	624.8 (521.8, 748.0)	590.1 (513.0, 678.6)	0.634		0.912
E1	129	68.9 (61.2, 77.5)	76.1 (69.1, 83.8)	0.211		97	64.2 (55.8, 73.9)	75.8 (68.0, 84.5)	0.080		0.985
E2	129	46.6 (40.8, 53.2)	47.3 (42.4, 52.7)	0.874		97	43.1 (36.7, 50.6)	56.4 (49.8, 63.9)	**0.014**		0.129
T/E2 Ratio	129	4.1 (3.7, 4.7)	4.6 (4.2, 5.1)	0.188		97	4.9 (4.1, 5.7)	4.2 (3.7, 4.7)	0.169		0.096
A/E1 Ratio	123	8.6 (7.4, 10.0)	7.3 (6.5, 8.3)	0.118		91	9.7 (8.1, 11.7)	7.7 (6.7, 8.9)	0.063		0.976

Abbreviations: T, testosterone; DHT, dihydrotestosterone; 3α-diol-G, 3α-androstanediol glucuronide; A, androstenedione; E1, estrone; E2, estradiol; SHBG, sex hormone-binding globulin.

[*]Adjusted for age at surgery (year, continuous), race (European American, African American, other, unknown), study site (5 sites, not listed here), BMI (<25.0, 25.0–29.9, ≥30.0 kg/m2), education (less than high school, high school/technical school, college or higher, unknown), smoking status (never, former, current, unknown) and regular alcohol use (never, former, current, unknown).

[†]P-values were calculated for a global test of differences in geometric means.

[‡]P-values were calculated for the multiplicative interaction between balding status and Gleason score.

Supplemental Table 3. Adjusted* geometric means of sex steroid hormones and SHBG by balding status and race (N=240)

Sex hormones		European American (N=134)				African American (N=106)			
	N	No balding (n=61)	Any balding (n=73)	P-value[†]	N	No balding (n=38)	Any balding (n=68)	P-value[†]	P-value[‡]
Serum (ng/dl)									
T	134	387.2 (349.3, 429.2)	449.1 (409.0, 493.2)	*0.043*	106	481.7 (421.6, 550.3)	533.9 (484.4, 588.5)	*0.235*	*0.760*
DHT	134	41.7 (37.9, 45.8)	49.1 (45.1, 53.5)	*0.015*	106	53.7 (47.3, 60.9)	61.5 (56.1, 67.4)	*0.099*	*0.769*
3α-diol-G	134	455.5 (394.5, 525.9)	501.7 (440.3, 571.7)	*0.341*	106	570.5 (490.4, 663.6)	495.7 (443.9, 553.5)	*0.154*	*0.168*
A	134	66.7 (59.8, 74.4)	73.4 (66.5, 81.1)	*0.213*	106	71.1 (62.6, 80.7)	68.5 (62.5, 75.2)	*0.655*	*0.271*
E1	134	4.5 (4.2, 4.9)	5.0 (4.6, 5.4)	*0.091*	106	5.7 (5.1, 6.5)	6.3 (5.8, 6.9)	*0.195*	*0.963*
E2	134	2.5 (2.3, 2.8)	2.8 (2.6, 3.1)	*0.082*	106	3.5 (3.1, 3.9)	3.8 (3.5, 4.2)	*0.190*	*0.990*
T/E2 Ratio	134	152.8 (138.0, 169.2)	157.7 (143.8, 173.0)	*0.659*	106	138.7 (121.6, 158.2)	139.1 (126.3, 153.1)	*0.971*	*0.764*
A/E1 Ratio	134	14.7 (13.2, 16.5)	14.7 (13.2, 16.2)	*0.942*	106	12.4 (10.9, 14.0)	10.8 (9.9, 11.9)	*0.099*	*0.262*
SHBG, nmol/L	134	28.1 (25.7, 30.6)	34.3 (31.7, 37.1)	*0.001*	106	32.4 (28.4, 36.8)	36.3 (33.0, 39.9)	*0.170*	*0.574*
Free T	134	10.0 (9.1, 10.9)	10.8 (9.9, 11.7)	*0.234*	106	12.0 (10.7, 13.4)	12.6 (11.6, 13.6)	*0.508*	*0.775*
Free E2	134	0.07 (0.07, 0.08)	0.08 (0.07, 0.08)	*0.332*	106	0.10 (0.09, 0.11)	0.10 (0.09, 0.11)	*0.447*	*0.973*
Adjacent normal prostate tissue (pg/g W)									
T	132	200.8 (179.3, 224.9)	229.6 (207.6, 254.0)	*0.091*	105	212.7 (180.7, 250.3)	224.3 (199.6, 252.1)	*0.613*	*0.742*
DHT	134	6471.4 (5966.0, 7019.6)	6531.9 (6066.5, 7033.1)	*0.871*	106	6574.9 (6078.8, 7111.5)	6865.6 (6483.4, 7270.4)	*0.396*	*0.589*
3α-diol-G	131	2533.9 (2255.6, 2846.5)	2826.3 (2538.2, 3147.0)	*0.185*	105	2691.1 (2399.4, 3018.4)	2561.2 (2352.8, 2788.0)	*0.509*	*0.092*
A	123	588.7 (513.4, 675.1)	573.3 (509.2, 645.4)	*0.776*	100	581.5 (495.6, 682.3)	580.3 (516.0, 652.7)	*0.985*	*0.590*
E1	128	60.8 (55.0, 67.4)	71.5 (65.3, 78.2)	*0.023*	98	76.8 (65.5, 90.1)	79.4 (70.6, 89.4)	*0.744*	*0.232*
E2	128	41.8 (37.1, 47.0)	50.3 (45.3, 55.8)	*0.025*	98	51.7 (43.5, 61.5)	51.2 (45.0, 58.2)	*0.924*	*0.116*
T/E2 Ratio	128	4.7 (4.2, 5.3)	4.5 (4.0, 4.9)	*0.438*	98	4.0 (3.4, 4.8)	4.2 (3.7, 4.8)	*0.677*	*0.267*
A/E1 Ratio	120	9.9 (8.6, 11.5)	8.0 (7.1, 9.1)	*0.030*	95	7.7 (6.4, 9.2)	7.4 (6.5, 8.5)	*0.730*	*0.148*

Abbreviations: T, testosterone; DHT, dihydrotestosterone; 3α-diol-G, 3α-androstanediol glucuronide; A, androstenedione; E1, estrone; E2, estradiol; SHBG, sex hormone-binding globulin.

*Adjusted for age at surgery (year, continuous), study site (5 sites, not listed here), BMI (<25.0, 25.0–29.9, ≥30.0 kg/m^2), education (less than high school, high school/technical school, college or higher, unknown), smoking status (never, former, current, unknown) and regular alcohol use (never, former, current, unknown).

[†]P-values were calculated for a global test of differences in geometric means.

[‡]P-values were calculated for the multiplicative interaction between balding status and race (European American vs. African American).

Supplemental Table 4. Geometric means of sex steroid hormones and SHBG by three-level balding category (N=248)

Sex hormones	N	Minimally Adjusted *			P-value‡	P-value§	Fully Adjusted †			P-value‡	P-value§
		No (n=104)	Frontal only (n=20)	Vertex + Frontal (n=124)			No (n=104)	Frontal only (n=20)	Vertex + Frontal (n=124)		
Serum (ng/dl)											
T	248	420.0 (387.7, 455.0)	486.5 (403.5, 586.5)	480.8 (447.2, 516.8)	**0.042**	0.907	416.1 (383.8, 451.1)	502.9 (416.1, 607.8)	482.0 (448.2, 518.2)	**0.022**	0.679
DHT	248	46.4 (43.0, 50.0)	53.7 (45.0, 64.0)	53.7 (50.2, 57.5)	**0.016**	0.992	45.9 (42.7, 49.4)	54.2 (45.7, 64.3)	54.1 (50.7, 57.7)	**0.005**	0.980
3α-diol-G	248	505.9 (457.2, 559.7)	574.2 (453.2, 727.5)	481.3 (439.2, 527.3)	0.355	0.170	498.2 (449.7, 551.9)	605.1 (476.0, 769.2)	483.3 (440.9, 529.9)	0.226	0.085
A	248	68.1 (63.0, 73.7)	55.9 (46.6, 67.1)	72.5 (67.6, 77.8)	**0.028**	**0.009**	67.2 (62.0, 72.8)	56.7 (47.0, 68.5)	73.2 (68.1, 78.7)	**0.027**	**0.013**
E1	248	5.0 (4.7, 5.4)	4.9 (4.2, 5.8)	5.6 (5.3, 6.0)	**0.026**	0.108	5.0 (4.7, 5.4)	4.9 (4.2, 5.8)	5.6 (5.3, 6.0)	**0.023**	0.105
E2	248	2.8 (2.7, 3.1)	3.1 (2.6, 3.6)	3.3 (3.1, 3.5)	**0.011**	0.462	2.9 (2.7, 3.1)	3.1 (2.6, 3.6)	3.3 (3.1, 3.5)	**0.029**	0.475
T/E2 Ratio	248	147.5 (135.6, 160.4)	157.4 (129.3, 191.7)	145.6 (135.0, 157.1)	0.765	0.467	144.6 (133.7, 156.6)	163.6 (136.1, 196.6)	147.1 (137.1, 157.9)	0.493	0.288
A/E1 Ratio	248	13.5 (12.4, 14.7)	11.3 (9.4, 13.7)	12.8 (11.9, 13.8)	0.247	0.232	13.3 (12.3, 14.5)	11.5 (9.5, 13.9)	13.0 (12.0, 13.9)	0.393	0.251
SHBG, nmol/L	248	29.8 (27.7, 32.0)	36.5 (30.9, 43.3)	35.2 (33.0, 37.6)	**0.002**	0.686	29.7 (27.6, 31.9)	36.3 (30.6, 42.9)	35.3 (33.1, 37.7)	**0.002**	0.778
Free T	248	10.6 (9.9, 11.4)	11.5 (9.7, 13.5)	11.4 (10.7, 12.2)	0.337	0.979	10.6 (9.8, 11.4)	11.9 (10.0, 14.0)	11.4 (10.7, 12.2)	0.224	0.682
Free E2	248	0.08 (0.08, 0.09)	0.08 (0.07, 0.10)	0.09 (0.08, 0.09)	0.132	0.429	0.08 (0.08, 0.09)	0.08 (0.07, 0.10)	0.09 (0.08, 0.09)	0.248	0.442
Adjacent normal prostate tissue (pg/g W)											
T	245	205.8 (188.4, 224.8)	194.7 (159.0, 238.4)	236.2 (218.5, 255.4)	**0.032**	0.080	205.0 (187.4, 224.1)	201.7 (164.1, 247.7)	235.4 (217.6, 254.7)	0.052	0.167
DHT	248	6445.0 (6092.2, 6818.2)	6000.8 (5260.5, 6845.2)	6767.5 (6431.8, 7120.8)	0.161	0.094	6466.0 (6114.0, 6838.2)	6174.0 (5415.1, 7039.3)	6718.1 (6388.9, 7064.3)	0.370	0.236
3α-diol-G	244	2598.9 (2401.3, 2812.7)	2759.8 (2293.7, 3320.6)	2696.2 (2507.3, 2899.4)	0.744	0.817	2565.3 (2369.4, 2777.4)	2892.5 (2400.8, 3485.0)	2708.4 (2519.3, 2911.6)	0.430	0.515
A	229	594.2 (538.5, 655.6)	531.0 (421.3, 669.2)	586.6 (537.7, 639.8)	0.684	0.427	585.9 (530.4, 647.1)	550.8 (435.7, 696.3)	585.9 (536.9, 639.3)	0.885	0.627
E1	232	67.1 (61.3, 73.4)	70.2 (57.5, 85.8)	76.4 (70.6, 82.8)	0.098	0.442	67.6 (61.9, 73.7)	71.6 (58.8, 87.2)	75.8 (70.1, 81.9)	0.160	0.602

	N				P‡	P§				P‡	P§
E2	232	44.4 (40.3, 49.0)	42.6 (34.2, 53.0)	52.9 (48.5, 57.7)	**0.015**	0.072	45.0 (40.7, 49.6)	44.1 (35.4, 55.1)	51.8 (47.5, 56.6)	0.074	0.186
T/E2 Ratio	232	4.6 (4.1, 5.0)	4.6 (3.7, 5.7)	4.3 (4.0, 4.7)	0.681	0.575	4.5 (4.1, 4.9)	4.7 (3.8, 5.9)	4.4 (4.0, 4.8)	0.804	0.533
A/E1 Ratio	220	9.0 (8.0, 10.1)	7.9 (6.1, 10.3)	7.7 (7.0, 8.5)	0.143	0.831	8.8 (7.9, 9.9)	8.1 (6.2, 10.5)	7.7 (7.0, 8.5)	0.218	0.752

Abbreviations: T, testosterone; DHT, dihydrotestosterone; 3α-diol-G, 3α-androstanediol glucuronide; A, androstenedione; E1, estrone; E2, estradiol; SHBG, sex hormone-binding globulin

[*]Adjusted for age at surgery (year, continuous), race (European American, African American, other, unknown), study site (5 sites, not listed here)

[†]Additionally adjusted for BMI (<25.0, 25.0–29.9, ≥30.0 kg/m^2), education (less than high school, high school/technical school, college or higher, unknown), smoking status (never, former, current, unknown) and regular alcohol use (never, former, current, unknown).

[‡]P-values were calculated for a global test of differences in geometric means.

[§]P-values were calculated for differences in geometric means comparing vertex + frontal with frontal only.

Supplemental Table 5. Adjusted odds ratios (ORs) and 95% confidence intervals (95%CIs) for tertiles of sex hormones and SHBG using binary logistic regression with balding status as the outcome variable or using ordinal logistic regression with chest hair density as the outcome variable

Sex hormones	Balding status (N=248)				Chest hair density (N=239)				
	No	Any	OR (95%CI)*	OR (95%CI)†	None/Sparse	Moderate	Dense	OR (95%CI)*	OR (95%CI)†
Serum (ng/dl)									
T									
<387.0	44	38	1.00 (referent)	1.00 (referent)	30	28	21	1.00 (referent)	1.00 (referent)
387.0–550.9	36	48	1.45 (0.77, 2.74)	1.73 (0.88, 3.38)	38	23	21	1.22 (0.67, 2.23)	1.36 (0.73, 2.54)
≥551.0	24	58	**2.46 (1.23, 4.92)**	**2.87 (1.37, 5.98)**	42	26	10	1.77 (0.91, 3.42)	1.71 (0.86, 3.39)
P-trend‡	104	144	**0.011**	**0.005**	110	77	52	0.090	0.127
DHT									
<44.0	48	35	1.00 (referent)	1.00 (referent)	31	25	25	1.00 (referent)	1.00 (referent)
44.0–60.4	29	54	**2.52 (1.30, 4.90)**	**2.70 (1.34, 5.46)**	36	29	12	1.30 (0.70, 2.42)	1.28 (0.68, 2.41)
≥60.5	27	55	**2.53 (1.27, 5.03)**	**3.04 (1.43, 6.43)**	43	23	15	1.44 (0.76, 2.72)	1.25 (0.64, 2.44)
P-trend‡	104	144	**0.015**	**0.007**	110	77	52	0.286	0.554
3α-diol-G									
<410.0	32	51	1.00 (referent)	1.00 (referent)	43	20	16	1.00 (referent)	1.00 (referent)
410.0–622.9	35	47	0.81 (0.41, 1.60)	0.92 (0.44, 1.93)	33	28	20	0.37 (0.19, 0.73)	0.37 (0.18, 0.75)
≥623.0	37	46	0.80 (0.41, 1.57)	0.85 (0.42, 1.73)	34	29	16	0.64 (0.33, 1.25)	0.66 (0.33, 1.33)
P-trend‡	104	144	0.573	0.655	110	77	52	0.558	0.750
A									
<58.4	33	50	1.00 (referent)	1.00 (referent)	39	25	17	1.00 (referent)	1.00 (referent)
58.4–83.6	38	45	0.81 (0.42, 1.56)	0.98 (0.49, 1.95)	35	27	16	0.92 (0.49, 1.72)	0.93 (0.48, 1.79)
≥83.7	33	49	0.93 (0.48, 1.81)	1.11 (0.55, 2.21)	36	25	19	0.94 (0.50, 1.76)	1.00 (0.52, 1.89)
P-trend‡	104	144	0.875	0.753	110	77	52	0.866	0.988
E1									
<4.6	39	40	1.00 (referent)	1.00 (referent)	35	22	19	1.00 (referent)	1.00 (referent)
4.6–6.3	41	50	1.24 (0.63, 2.44)	1.35 (0.66, 2.74)	40	28	19	0.86 (0.44, 1.66)	0.82 (0.41, 1.61)

≥6.4	24	54	2.09 (1.00, 4.39)	2.21 (0.99, 4.96)	35	27	14	0.64 (0.32, 1.29)	0.69 (0.33, 1.46)
P-trend‡	104	144	**0.046**	0.051	110	77	52	0.199	0.335
E2									
<2.7	47	35	1.00 (referent)	1.00 (referent)	33	24	21	1.00 (referent)	1.00 (referent)
2.7–3.7	31	56	**2.58 (1.31, 5.07)**	**2.70 (1.33, 5.50)**	35	30	18	0.79 (0.42, 1.48)	0.82 (0.43, 1.57)
≥3.8	26	53	**2.74 (1.29, 5.83)**	**2.94 (1.33, 6.51)**	42	23	13	0.97 (0.48, 1.98)	1.08 (0.52, 2.25)
P-trend‡	104	144	**0.010**	**0.009**	110	77	52	0.976	0.804
T/E2 Ratio									
<124.9	34	48	1.00 (referent)	1.00 (referent)	37	25	19	1.00 (referent)	1.00 (referent)
124.9–180.8	37	47	0.87 (0.46, 1.66)	0.96 (0.48, 1.90)	31	28	18	1.23 (0.67, 2.28)	1.14 (0.60, 2.19)
≥180.9	33	49	0.98 (0.50, 1.91)	1.13 (0.55, 2.36)	42	24	15	**2.18 (1.14, 4.18)**	1.94 (0.96, 3.94)
P-trend‡	104	144	0.982	0.707	110	77	52	**0.017**	0.056
A/E1 Ratio									
<10.3	28	52	1.00 (referent)	1.00 (referent)	36	27	16	1.00 (referent)	1.00 (referent)
10.3–15.3	42	43	0.65 (0.33, 1.26)	0.66 (0.33, 1.34)	38	23	16	1.63 (0.85, 3.13)	1.71 (0.88, 3.35)
≥15.4	34	49	0.88 (0.44, 1.76)	0.99 (0.47, 2.08)	36	27	20	1.51 (0.79, 2.89)	1.53 (0.77, 3.03)
P-trend‡	104	144	0.977	0.720	110	77	52	0.328	0.391
SHBG (nmol/L)									
<28.0	45	37	1.00 (referent)	1.00 (referent)	32	23	23	1.00 (referent)	1.00 (referent)
28.0–39.4	39	44	1.26 (0.67, 2.39)	1.22 (0.62, 2.40)	33	31	16	1.28 (0.69, 2.37)	1.14 (0.61, 2.16)
≥39.5	20	63	**3.49 (1.69, 7.24)**	**3.81 (1.75, 8.31)**	45	23	13	**2.23 (1.14, 4.35)**	1.80 (0.90, 3.59)
P-trend‡	104	144	**0.001**	**<0.001**	110	77	52	**0.016**	0.086
Free T									
<9.9	41	42	1.00 (referent)	1.00 (referent)	32	30	18	1.00 (referent)	1.00 (referent)
9.9–13.1	38	43	1.08 (0.57, 2.04)	1.25 (0.64, 2.45)	39	19	21	1.12 (0.61, 2.06)	1.25 (0.66, 2.34)
≥13.2	25	59	**2.08 (1.06, 4.11)**	**2.53 (1.23, 5.23)**	39	28	13	1.12 (0.59, 2.11)	1.05 (0.54, 2.06)

	104	144							
P-trend‡			**0.033**	**0.012**	110	77	52	0.737	0.876
Free E2									
<0.074	43	39	1.00 (referent)	1.00 (referent)	39	21	19	1.00 (referent)	1.00 (referent)
0.074–0.103	30	53	1.94 (1.00, 3.78)	1.87 (0.93, 3.77)	29	30	19	0.50 (0.26, 0.95)	0.56 (0.29, 1.08)
≥0.104	31	52	1.66 (0.81, 3.41)	1.57 (0.73, 3.37)	42	26	14	0.60 (0.30, 1.20)	0.69 (0.33, 1.43)
	104	144							
P-trend‡			0.239	0.352	110	77	52	0.242	0.470
Adjacent normal prostate tissue (pg/g W)									
T									
<181.8	32	49	1.00 (referent)	1.00 (referent)	34	27	17	1.00 (referent)	1.00 (referent)
181.8–255.4	39	44	0.74 (0.38, 1.43)	0.76 (0.39, 1.51)	36	29	17	1.25 (0.67, 2.32)	1.36 (0.72, 2.56)
≥255.5	30	51	1.19 (0.60, 2.39)	1.25 (0.61, 2.57)	39	21	16	1.16 (0.61, 2.22)	1.17 (0.60, 2.27)
	101	144							
P-trend‡			0.531	0.466	109	77	50	0.690	0.691
DHT									
<6065.5	39	44	1.00 (referent)	1.00 (referent)	30	30	20	1.00 (referent)	1.00 (referent)
6065.5–7492.6	33	49	1.13 (0.59, 2.17)	1.10 (0.56, 2.16)	41	23	15	1.87 (0.99, 3.50)	1.88 (0.98, 3.58)
≥7492.7	32	51	1.24 (0.65, 2.38)	1.29 (0.65, 2.57)	39	24	17	1.60 (0.86, 3.00)	1.75 (0.91, 3.39)
	104	144							
P-trend‡			0.514	0.473	110	77	52	0.129	0.087
3α-diol-G									
<2254.2	37	44	1.00 (referent)	1.00 (referent)	41	21	16	1.00 (referent)	1.00 (referent)
2254.2–3198.8	33	48	1.12 (0.57, 2.17)	1.14 (0.57, 2.29)	33	31	16	0.73 (0.39, 1.37)	0.80 (0.42, 1.55)
≥3198.9	34	48	1.18 (0.60, 2.29)	1.35 (0.67, 2.74)	35	24	19	0.89 (0.47, 1.67)	1.05 (0.54, 2.03)
	104	140							
P-trend‡			0.639	0.401	109	76	51	0.790	0.798
A									
<473.4	26	51	1.00 (referent)	1.00 (referent)	33	27	15	1.00 (referent)	1.00 (referent)
473.4–726.3	31	44	0.79 (0.40, 1.57)	0.90 (0.44, 1.84)	36	22	14	1.06 (0.55, 2.04)	1.10 (0.56, 2.14)
≥726.4	37	40	0.67 (0.33, 1.36)	0.70 (0.34, 1.45)	34	22	19	0.99 (0.51, 1.92)	1.10 (0.55, 2.18)
	94	135							
P-trend‡			0.280	0.326	103	71	48	0.950	0.808
E1									

10

Category									
<59.1	40	38	1.00 (referent)	1.00 (referent)	40	21	16	1.00 (referent)	1.00 (referent)
59.1–86.1	29	48	1.69 (0.86, 3.30)	1.75 (0.87, 3.53)	33	26	17	0.78 (0.41, 1.48)	0.87 (0.45, 1.67)
≥86.2	27	50	**2.13 (1.04, 4.37)**	2.13 (0.99, 4.59)	30	26	14	0.57 (0.29, 1.14)	0.72 (0.35, 1.47)
P-trend[‡]	96	136	**0.043**	0.058	103	73	47	0.111	0.365
E2									
<40.7	38	40	1.00 (referent)	1.00 (referent)	42	21	14	1.00 (referent)	1.00 (referent)
40.7–57.5	32	44	1.34 (0.69, 2.63)	1.31 (0.65, 2.64)	30	26	18	0.71 (0.37, 1.35)	0.79 (0.41, 1.52)
≥57.6	26	52	1.95 (0.98, 3.89)	1.94 (0.93, 4.01)	31	26	15	0.65 (0.34, 1.27)	0.77 (0.39, 1.54)
P-trend[‡]	96	136	0.058	0.075	103	73	47	0.228	0.481
T/E2 Ratio									
<3.8	31	47	1.00 (referent)	1.00 (referent)	30	29	15	1.00 (referent)	1.00 (referent)
3.8–5.1	32	43	0.91 (0.47, 1.78)	0.88 (0.43, 1.78)	32	22	17	1.10 (0.59, 2.08)	1.01 (0.52, 1.95)
≥5.2	33	46	1.02 (0.52, 1.97)	1.19 (0.60, 2.37)	41	22	15	1.66 (0.88, 3.15)	1.57 (0.82, 3.01)
P-trend[‡]	96	136	0.917	0.548	103	73	47	0.105	0.145
A/E1Ratio									
<6.1	22	51	1.00 (referent)	1.00 (referent)	29	29	10	1.00 (referent)	1.00 (referent)
6.1–10.3	29	44	0.67 (0.32, 1.37)	0.68 (0.32, 1.44)	32	20	20	1.00 (0.52, 1.94)	1.01 (0.51, 1.99)
≥10.4	39	35	**0.42 (0.20, 0.88)**	**0.45 (0.21, 0.97)**	37	20	16	1.55 (0.76, 3.13)	1.45 (0.70, 3.00)
P-trend[‡]	90	130	**0.022**	**0.042**	98	69	46	0.191	0.282

Abbreviations: T, testosterone; DHT, dihydrotestosterone; 3α-diol-G, 3α-androstanediol glucuronide; A, androstenedione; E1, estrone; E2, estradiol; SHBG, sex hormone-binding globulin.

[*]Adjusted for age at surgery (year, continuous), race (European American, African American, other, unknown), study site (5 sites, not listed here)

[†]Additionally adjusted for BMI (<25.0, 25.0–29.9, ≥30.0 kg/m^2), education (less than high school, high school/technical school, college or higher, unknown), smoking status (never, former, current, unknown) and regular alcohol use (never, former, current, unknown).

[‡]P-trend was calculated by assigning median values for each tertile of sex hormones and SHBG as a continuous variable in logistic regression models.

Supplemental Table 6. Adjusted[*] geometric means of sex steroid hormones and SHBG by chest hair density and Gleason score (N=234)

Sex hormones	N	Gleason score<7 (N=130) None/Sparse (n=57)	Gleason score<7 (N=130) Moderate/Dense (n=73)	P-value[†]	N	Gleason score≥7 (N=104) None/Sparse (n=48)	Gleason score≥7 (N=104) Moderate/Dense (n=56)	P-value[†]	P-value[‡]
Serum (ng/dl)									
T	130	469.2 (417.0, 527.9)	439.9 (397.2, 487.1)	0.449	104	472.7 (418.5, 533.9)	447.3 (400.3, 499.8)	0.544	0.553
DHT	130	52.1 (46.9, 57.9)	50.7 (46.2, 55.5)	0.706	104	50.5 (44.7, 57.1)	50.0 (44.7, 55.9)	0.906	0.493
3α-diol-G	130	510.2 (442.9, 587.9)	544.0 (481.3, 614.9)	0.532	104	461.6 (392.0, 543.7)	498.0 (429.0, 578.1)	0.535	0.491
A	130	74.1 (65.5, 83.8)	70.2 (63.2, 78.1)	0.548	104	67.5 (59.3, 76.7)	66.1 (58.8, 74.4)	0.836	0.725
E1	130	5.5 (4.9, 6.1)	5.5 (5.0, 6.0)	0.990	104	4.7 (4.3, 5.2)	5.4 (5.0, 5.9)	**0.049**	0.451
E2	130	3.2 (2.9, 3.6)	3.1 (2.8, 3.4)	0.699	104	2.9 (2.6, 3.3)	3.1 (2.8, 3.4)	0.521	0.185
T/E2 Ratio	130	147.1 (131.8, 164.1)	142.1 (129.2, 156.2)	0.662	104	160.7 (140.9, 183.3)	144.1 (127.8, 162.4)	0.268	0.529
A/E1 Ratio	130	13.5 (11.9, 15.2)	12.8 (11.5, 14.2)	0.555	104	14.3 (12.5, 16.4)	12.2 (10.8, 13.8)	0.116	0.794
SHBG, nmol/L	130	32.8 (29.5, 36.4)	32.3 (29.5, 35.4)	0.852	104	34.4 (30.5, 38.7)	31.7 (28.4, 35.4)	0.381	0.861
Free T	130	11.5 (10.4, 12.7)	10.8 (9.9, 11.8)	0.379	104	11.3 (10.2, 12.6)	11.1 (10.0, 12.2)	0.759	0.416
Free E2	130	0.09 (0.08, 0.10)	0.09 (0.08, 0.09)	0.748	104	0.08 (0.07, 0.09)	0.09 (0.08, 0.10)	0.347	0.163
Adjacent normal prostate tissue (pg/g W)									
T	130	210.5 (189.0, 234.6)	209.7 (191.0, 230.2)	0.958	101	243.1 (207.4, 284.8)	219.6 (190.6, 253.0)	0.388	0.937
DHT	130	6667.3 (6148.5, 7229.9)	6095.1 (5682.5, 6537.6)	0.128	104	6993.5 (6419.9, 7618.4)	6781.6 (6272.4, 7332.0)	0.630	0.074
3α-diol-G	129	2644.1 (2362.7, 2959.0)	2531.8 (2296.8, 2791.0)	0.594	102	2906.3 (2541.3, 3323.8)	2734.7 (2417.8, 3093.0)	0.543	0.882
A	122	555.1 (489.4, 629.6)	583.6 (521.3, 653.4)	0.588	95	631.9 (527.9, 756.5)	574.5 (490.1, 673.4)	0.473	0.308
E1	122	73.9 (65.2, 83.7)	69.5 (62.3, 77.5)	0.495	96	65.4 (57.0, 75.0)	75.6 (66.8, 85.5)	0.155	**0.049**
E2	122	46.9 (41.2, 53.5)	45.0 (40.1, 50.4)	0.651	96	49.0 (41.7, 57.6)	51.8 (44.8, 59.9)	0.648	0.171
T/E2 Ratio	122	4.4 (3.8, 5.0)	4.5 (4.0, 5.0)	0.760	96	4.8 (4.1, 5.7)	4.1 (3.6, 4.8)	0.192	0.140
A/E1 Ratio	118	7.5 (6.4, 8.8)	8.5 (7.4, 9.8)	0.272	90	9.8 (8.2, 11.7)	7.5 (6.3, 8.8)	**0.044**	**0.012**

Abbreviations: T, testosterone; DHT, dihydrotestosterone; 3α-diol-G, 3α-androstanediol glucuronide; A, androstenedione; E1, estrone; E2, estradiol; SHBG, sex hormone-binding globulin.

[*]Adjusted for age at surgery (year, continuous), race (European American, African American, other, unknown), study site (5 sites, not listed here), BMI (<25.0, 25.0–29.9, ≥30.0 kg/m2), education (less than high school, high school/technical school, college or higher, unknown), smoking status (never, former, current, unknown) and regular alcohol use (never, former, current, unknown).

[†]P-values were calculated for a global test of differences in geometric means.

[‡]P-values were calculated for the multiplicative interaction between balding status and Gleason score.

Supplemental Table 7. Adjusted[*] geometric means of sex steroid hormones and SHBG by chest hair density and race (N=231)

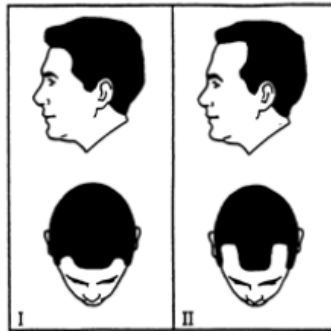| Sex hormones	N	European American (N=126)			N	African American (N=105)			P-value[‡]
		None/Sparse (n=40)	Moderate/Dense (n=86)	P-value[†]		None/Sparse (n=66)	Moderate/Dense (n=39)	P-value[†]	
Serum (ng/dl)									
T	126	407.4 (358.4, 463.1)	422.4 (387.9, 460.0)	0.652	105	538.4 (486.7, 595.6)	479.0 (418.2, 548.7)	0.198	0.100
DHT	126	45.5 (40.4, 51.4)	45.6 (42.1, 49.4)	0.994	105	60.0 (54.4, 66.0)	56.6 (49.7, 64.5)	0.508	0.403
3α-diol-G	126	430.3 (362.5, 510.7)	513.8 (458.5, 575.8)	0.100	105	534.3 (475.9, 600.0)	498.4 (426.5, 582.3)	0.502	0.068
A	126	76.9 (66.9, 88.4)	68.0 (62.0, 74.6)	0.163	105	67.0 (60.9, 73.8)	73.5 (64.6, 83.5)	0.285	0.086
E1	126	4.7 (4.2, 5.2)	4.8 (4.4, 5.1)	0.780	105	5.8 (5.3, 6.4)	6.6 (5.9, 7.5)	0.108	0.492
E2	126	2.6 (2.3, 3.0)	2.7 (2.5, 2.9)	0.722	105	3.6 (3.3, 4.0)	3.8 (3.4, 4.3)	0.516	0.811
T/E2 Ratio	126	155.2 (136.6, 176.4)	156.6 (143.8, 170.5)	0.913	105	147.6 (133.8, 162.8)	124.7 (109.3, 142.3)	0.057	0.142
A/E1 Ratio	126	16.4 (14.2, 18.9)	14.2 (12.9, 15.7)	0.116	105	11.5 (10.4, 12.7)	11.1 (9.7, 12.6)	0.677	0.259
SHBG, nmol/L	126	30.4 (27.1, 34.1)	31.6 (29.2, 34.0)	0.606	105	36.9 (33.5, 40.7)	31.9 (27.9, 36.3)	0.093	**0.040**
Free T	126	10.1 (9.0, 11.4)	10.5 (9.7, 11.3)	0.666	105	12.7 (11.7, 13.8)	11.8 (10.6, 13.3)	0.369	0.222
Free E2	126	0.07 (0.07, 0.08)	0.08 (0.07, 0.08)	0.787	105	0.10 (0.09, 0.11)	0.11 (0.09, 0.12)	0.230	0.712
Adjacent normal prostate tissue (pg/g W)									
T	124	214.4 (188.2, 244.3)	210.9 (193.4, 229.9)	0.837	104	224.9 (199.2, 253.9)	211.1 (179.0, 248.8)	0.560	0.979
DHT	126	6575.4 (5958.2, 7256.5)	6419.8 (6012.7, 6854.5)	0.698	105	7069.3 (6670.1, 7492.5)	6277.4 (5805.7, 6787.4)	**0.024**	0.335
3α-diol-G	124	2586.4 (2245.5, 2979.1)	2732.5 (2485.6, 3003.9)	0.535	104	2743.2 (2516.3, 2990.5)	2394.2 (2133.6, 2686.7)	0.078	0.067
A	117	626.5 (530.2, 740.2)	557.5 (497.7, 624.5)	0.268	99	562.5 (498.0, 635.3)	614.5 (521.0, 724.8)	0.420	0.117
E1	120	59.0 (52.0, 66.8)	67.8 (62.3, 73.9)	0.077	97	78.7 (69.5, 89.1)	77.5 (65.6, 91.4)	0.888	0.283
E2	120	44.6 (38.8, 51.3)	44.8 (40.7, 49.3)	0.961	97	49.0 (42.8, 56.0)	55.1 (46.0, 65.9)	0.331	0.330
T/E2 Ratio	120	4.8 (4.2, 5.5)	4.6 (4.2, 5.0)	0.622	97	4.4 (3.9, 5.0)	3.8 (3.2, 4.5)	0.175	0.520
A/E1 Ratio	114	10.8 (9.1, 12.8)	8.2 (7.3, 9.3)	**0.015**	94	7.2 (6.3, 8.4)	8.0 (6.6, 9.7)	0.428	**0.033**

Abbreviations: T, testosterone; DHT, dihydrotestosterone; 3α-diol-G, 3α-androstanediol glucuronide; A, androstenedione; E1, estrone; E2, estradiol; SHBG, sex hormone-binding globulin.

[*]Adjusted for age at surgery (year, continuous), study site (5 sites, not listed here), BMI (<25.0, 25.0–29.9, ≥30.0 kg/m^2), education (less than high school, high school/technical school, college or higher, unknown), smoking status (never, former, current, unknown) and regular alcohol use (never, former, current, unknown).
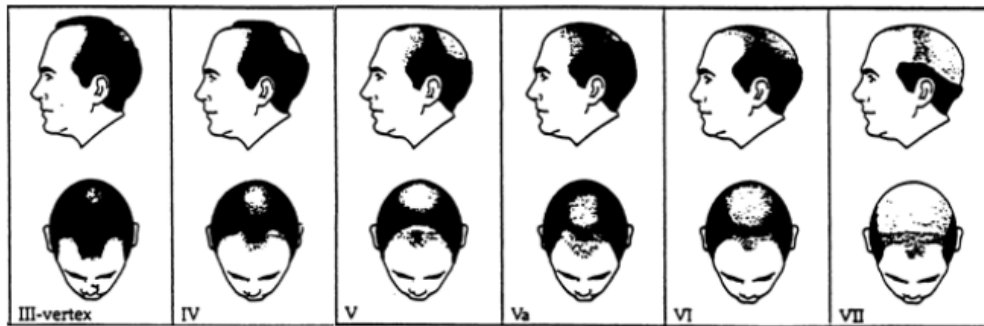
[†]P-values were calculated for a global test of differences in geometric means.

[‡]P-values were calculated for the multiplicative interaction between balding status and race (European American vs. African American).
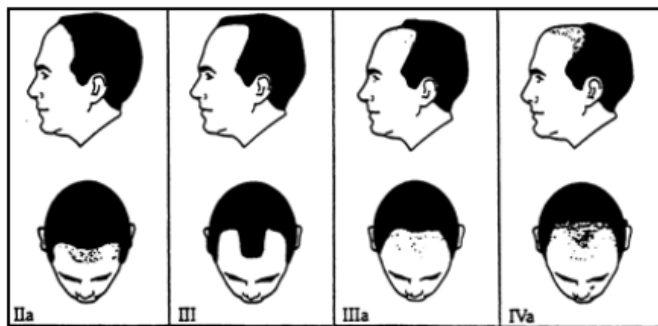
Supplemental Fig 1. Modified Norwood-Hamilton Scale used to score hair loss patterns in NCI Prostate Tissue Study

No baldness

Vertex + Frontal baldness

Frontal baldness