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The association between serum sex steroid hormone concentrations and intraprostatic inflammation in men without prostate cancer and irrespective of clinical indication for biopsy in the placebo arm of the Prostate Cancer Prevention Trial

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Abstract

Background: Intraprostatic inflammation is an emerging prostate cancer risk factor. Estrogens are pro-inflammatory while androgens are anti-inflammatory. Thus, we investigated whether serum sex steroid hormone concentrations are associated with intraprostatic inflammation to inform mechanistic links among hormones, inflammation, and prostate cancer.

Methods: We conducted a cross-sectional study among 247 men in the placebo arm of the Prostate Cancer Prevention Trial who had a negative end-of-study biopsy, most (92.7%) performed without clinical indication per trial protocol. Serum estradiol, estrone, and testosterone were previously measured by immunoassay in pooled baseline and Year 3 serum. Free estradiol and free

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SUPPORTING INFORMATION

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testosterone were calculated. Inflammation was visually assessed (median of three prostate biopsy cores per man). Polytomous or logistic regression was used to estimate the odds ratio (OR) and 95% confidence interval (CI) of some or all cores inflamed (both vs none) or any core inflamed (vs none) by hormone tertile, adjusting for age, race, and family history. We evaluated effect modification by waist circumference and body mass index (BMI). Results: In all, 51.4% had some and 26.3% had all cores inflamed. Free (*P*-trend = .11) but not total estradiol was suggestively inversely associated with all cores inflamed. In men with waist circumference greater than or equal to 102 cm (*P*-trend = .021) and BMI ≥ 27.09 kg/m^2 (*P*-trend = .0037) free estradiol was inversely associated with any core inflamed. Estrone was inversely associated with all cores inflamed (T3: OR = 0.36, 95% CI 0.14–0.95, *P*-trend = .036). Total (T3: OR = 1.91, 95% CI 0.91–4.02, *P*-trend = .11) and free (T3: OR = 2.19, 95% CI 1.01–4.74, *P*-trend = .05) testosterone were positively associated with any core inflamed, especially free testosterone in men with waist circumference less than 102 cm (T3: OR = 3.51, 95% CI 1.03–12.11, *P*-trend = .05).

Conclusions: In this first study in men without prostate cancer and irrespective of clinical indication for biopsy, contrary to the hypothesis, circulating estrogens appeared to be inversely associated, especially in heavy men, whereas androgens appeared to be positively associated with intraprostatic inflammation.

Keywords

estradiol; estrone; inflammation; prostate; testosterone

1 | INTRODUCTION

Intraprostatic inflammation, described pathologically as immune cell infiltrates, is commonly observed in prostate tissue resected for prostate cancer, suspicion of prostate cancer, and symptomatic benign prostatic hyperplasia (summarized in Umbehr et al.[1]), and in prostate biopsy tissue in men without clinical indication in the Prostate Cancer Prevention Trial (PCPT).[2,3] Evidence from observational studies, most notably the PCPT,[2,3] in which men with persistently low prostate-specific antigen (PSA) levels in the placebo arm had protocol-directed prostate biopsies (ie, without clinical indication), suggests that intraprostatic inflammation is a likely contributor to prostate carcinogenesis.

Other than infectious agents, few factors have been associated with intraprostatic inflammation.[4,5] We hypothesize that sex steroid hormones may influence intraprostatic inflammation.

Estrogens are known to be pro-inflammatory, while androgens are anti-inflammatory.[6,7] These links are also observed for circulating markers, such as C-reactive protein (CRP), an acute-phase reactant that is a nonspecific indicator of systemic inflammation. For example, in a nationally representative sample of US men, higher plasma estradiol levels were associated with higher plasma CRP concentration, while higher plasma testosterone levels were associated with lower CRP levels.[8]

To our knowledge, no study has investigated whether circulating concentrations of estrogens and androgens are associated with intraprostatic inflammation in a setting unbiased by any

links of intraprostatic inflammation and/or testosterone with PSA, a clinical indication for biopsy that is under androgenic regulation.

Thus, we investigated whether circulating sex steroid hormones are associated with intraprostatic inflammation in the PCPT to inform mechanistic links among hormones, inflammation, and prostate cancer. Given that men with excess body fat have higher estrogen and reduced androgen levels,[9] as well as higher circulating markers of systemic inflammation[8] than leaner men, we assessed whether measures of body fatness modify the association between these hormones and intraprostatic inflammation.

2. | METHODS

2.1 | Study population and design

We included 247 men who were randomized to the placebo arm of the PCPT, who were not diagnosed with prostate cancer on the end-of-study biopsy (controls), and for whom we previously measured hormones[10] and inflammation.[2] The PCPT was a randomized, placebo-controlled trial that examined the potential of finasteride to reduce the period prevalence of prostate cancer over 7 years.[11] From 1993 to 1997, the PCPT randomized 18 882 men over 55 years old with PSA ≤ 3 mg/mL, a normal digital-rectal examination (DRE), and with an American Urological Association Symptom Index < 20. At entry, men reported demographics, family history of prostate cancer, cigarette smoking history, weight, height, and other lifestyle and medical factors. Men were screened for prostate cancer at each annual visit. During the trial, if PSA level was greater than 4 ng/mL or the DRE was abnormal, a biopsy was recommended. At the end of the trial and regardless of PSA or DRE, men who were not diagnosed with prostate cancer during the trial were asked to undergo a biopsy as a component of the trial protocol. Of the 247 men included in the current study, the majority (92.7%) did not have a clinical indication for biopsy.

2.2 | Hormone concentration measurements

Concentrations of estradiol (pg/mL), estrone (pg/mL), testosterone (ng/dL), 5α-androstane-3α,17β-diol glucuronide (androstanediol glucuronide; ng/mL), and sex hormone binding globulin (SHBG; nmol/L) were previously measured in serum specimens from baseline and Year 3, which were pooled to reduced intra-individual variability. Estradiol and estrone were measured using radioimmunoassay following organic solvent extraction and Celite column partition chromatography.[10] Testosterone was measured by a direct solid-phase, competitive chemiluminescent enzyme immunoassay, androstanediol glucuronide by direct competitive radioimmunoassay, and SHBG by a direct solid-phase, two-site chemiluminescent immunometric assay.[12] Free estradiol and free testosterone concentrations were calculated using mass action equations, measured SHBG, and total testosterone or total estradiol, and assuming the average concentration for albumin.[13,14] Coefficients of variation for pooled blinded quality control samples were estradiol 14.9%, estrone 15.2%, testosterone 10.5%, androstanediol glucuronide 14.0%, and SHBG 12.2%.[12]

2.3 | Intraprostatic inflammation assessment

Inflammation in benign tissue from prostate biopsy cores was previously assessed by a pathologist trained to review for inflammation.[2] Briefly, one or more of the six to ten biopsy cores taken per man were embedded in each tissue block. Tissue blocks were selected to achieve a median of three cores per man for review (of the controls, 6.1% had 2, 67.2% had 3, 15.8% had 4, 7.7% had 5%, and 3.2% had 6–8 cores). One hematoxylin and eosin stained section per selected block was digitally imaged and visually reviewed. We previously classified each man with respect to the prevalence of inflammation—any core inflamed, and the extent of inflammation—none, some, or all biopsy cores with inflammation.[2,5]

2.4 | Overweight/obesity and other covariate measurement

Weight and baseline height were measured by trained staff annually. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared as a measure of overall body fatness. Age and race were taken during the trial registration. Waist circumference, as a measure of central adiposity, was measured in centimeters a year after randomization. At trial entry, the men completed a questionnaire on alcohol consumption, education, history of diabetes, smoking history, and family history. Attained education was later classified as high school or lower, some college or college graduate, or a postgraduate education. Smoking status was categorized as never (<100 cigarettes in a lifetime), current, or past smoker. Participants were asked how physically active (ie, walking, swimming, dancing, recreational sports) they were in the past 4 weeks and were classified as sedentary, light, moderate, or active. Meat intake was assessed via a food frequency questionnaire administered a year after randomization, from which intake of red meat (g/d) was calculated. Serum PSA was measured at every annual visit and serum total cholesterol was measured at trial entry.

2.5 | Statistical analysis

Geometric mean concentrations of serum total estradiol, free estradiol, estrone, total testosterone, free testosterone, androstanediol glucuronide, SHBG, testosterone-to-estradiol ratio, and estrone-to-estradiol ratio were computed by the prevalence and extent of inflammation using generalized linear models adjusting for age, race, and family history of prostate cancer (these were sampling and matching factors from our prior nested case-control study[2]). To test for trend in hormone concentration across the extent of inflammation, we entered into the model the extent of inflammation as an ordinal variable, the coefficient for which we tested using the Type III Sums of Squares F test statistic. We estimated the odds ratio (OR) and 95% confidence interval (CI) for the association of any biopsy core with inflammation (vs none; logistic regression) or some or all biopsy cores with inflammation (vs none; nominal polytomous logistic regression) with tertiles of sex steroid hormones adjusting for age, race, and family history of prostate cancer. To test for trend across hormone tertiles, we entered into the model the median for each tertile, the coefficient for which we tested using the Wald test. We repeated these analyses stratified by BMI using the median as the cutpoint (<27.09, ≥27.09 kg/m^2) and by waist circumference using a standard cutpoint (<102, ≥102 cm).[15] We tested for statistical interaction by entering a cross-product term for BMI or waist circumference and inflammation along with their

main effects terms in the model; we tested the coefficient for the cross-product term using the Wald test.

3 | RESULTS

Baseline characteristics of the 247 men by prevalence and extent of inflammation are shown in Table 1. Of the men, 22.3% had none, 51.4% had some, and 26.3% had all biopsy cores inflamed. The prevalence of diabetes decreased across the extent of inflammation (none: 12.7%, some: 8.7%, all: 6.2%). Mean PSA at baseline (none: 0.88, some: 1.21, all: 1.35 ng/mL) and at biopsy (none: 1.24, some: 1.53, all: 3.42 ng/mL) increased across the extent of inflammation. None of the lifestyle characteristics differed notably by the presence or extent of cores with inflammation.

Adjusted geometric mean hormone and SHBG concentrations and ratios of testosterone-to-estradiol and estrone-to-estradiol are shown in Table 2. Mean estrone and androstanediol glucuronide concentrations statistically significantly decreased across the extent of cores inflamed. None of the other concentrations or ratios differed across the extent of inflammation.

Adjusted geometric mean concentrations stratified by BMI and waist circumference are shown in Supporting Information Tables S1 and S2. In men with BMI < 27.09 kg/m^2 or waist circumference less than 102 cm, no clear patterns were observed aside from the ratio of estrone-to-estradiol being possibly lower for all vs no cores inflamed in men with BMI < 27.09 kg/m^2 (*P*-trend = .029; Supporting Information Table S1). In men with BMI ≥ 27.09 kg/m^2 or waist circumference greater than or equal to 102 cm, compared with no cores inflamed, mean total estradiol, free estradiol, and estrone concentrations were lower in those with any or all cores inflamed, and mean testosterone-to-estradiol ratio was higher in men with any core inflamed (Supporting Information Tables S1 and S2). Additionally, in men with BMI ≥ 27.09 kg/m^2 or waist circumference greater than or equal to 102 cm, androstanediol glucuronide concentration tended to be lower in men with all or any core inflamed compared with no cores inflamed (Supporting Information Table S2).

Table 3 shows the OR of the prevalence and extent of inflammation by tertile of serum sex hormone concentration adjusting for age, race, and family history of prostate cancer. Free (*P*-trend = .11) but not total estradiol concentration, was possibly inversely, and estrone concentration (*P*-trend = .036) was inversely associated with all cores inflamed. Total and free testosterone concentrations tended to be positively associated with any (*P*-trend = .11, .05, respectively) or some (*P*-trend = .10, .047, respectively) cores inflamed. The ratio of testosterone-to-estradiol tended to be positively associated with any (*P*-trend = .08) or some (*P*-trend = .056) cores inflamed. Adjusting for physical activity slightly strengthened the association of total (T3 vs T1: OR = 2.09, 95% CI 0.98– 4.47) and free (T3 vs T1: OR = 2.40, 95% CI 1.10–5.27; T2 vs T1: OR = 1.97, 95% CI 1.10–5.27) testosterone concentrations with any core inflamed. These results did not notably change after excluding 18 men who had a PSA > 4 ng/mL or abnormal DRE at the time of the end-of-study biopsy. Results were similar after further adjustment for other lifestyle factors and after mutual adjustment for the sex steroid hormones (data not shown).

Tables 4 and 5 show the OR of the prevalence of inflammation by tertile of serum sex hormone concentration adjusting for age, race, and family history of prostate cancer stratified by BMI and waist circumference. In heavier men, total (BMI ≥ 27.09 kg/m^2: *P*-trend = .079, waist ≥ 102: *P*-trend = .13) and free (BMI ≥ 27.09 kg/m^2: *P*-trend = .0037, waist ≥ 102: *P*-trend = .021) estradiol concentrations were inversely associated with any core inflamed, and these associations were stronger than overall. Contrary to overall, in men with BMI < 27.09 kg/m^2, free estradiol concentration was possibly positively associated with any core inflamed, although based on small numbers (*P*-trend = .10; Table 4). Estrone concentration appeared to be inversely associated with any core inflamed in both men with higher and lower BMI. Total and free testosterone concentrations appeared to be positively associated with any core inflamed in both heavier and leaner men, especially free testosterone concentration in men with waist circumference less than 102 cm (*P*-trend = .05; Table 5). SHBG concentration in men with BMI ≥ 27.09 kg/m^2 (*P*-trend = .08), and the ratio of testosterone-to-estradiol in men with BMI ≥ 27.09 kg/m^2 (*P*-trend = .027) or waist circumference ≥ 102 cm (*P*-trend = .10) (Tables 4 and 5) tended to be positively associated with any core inflamed. We observed statistically significant interactions of estradiol and free estradiol concentration with BMI (*P*-interaction= .016 and .0012, respectively) and waist circumference (*P*-interaction= .038 and .022, respectively).

4 | DISCUSSION

Our hypotheses were that men with higher serum estradiol (vs lower) and lower testosterone (vs higher) levels would have a greater prevalence and extent of inflammation in benign prostate tissue from men without a prostate cancer diagnosis and irrespective of clinical indication for biopsy. Our results do not support these hypotheses. Instead, we observed that circulating estrogens, including estrone (a weak estrogen) appeared to be inversely associated, whereas circulating androgens appeared to be positively associated with intraprostatic inflammation. For free and total estradiol, the inverse associations with inflammation tended to be stronger in men with higher BMI or waist circumference than overall. Total and free testosterone appeared to be positively associated with inflammation irrespective of BMI or waist circumference. We do not have direct explanations for these findings. Despite these findings contrary to our hypothesis, this is the first investigation of the association between serum hormones and intraprostatic inflammation in men without prostate cancer and irrespective of clinical indication for biopsy, which was possible because of a unique feature of the PCPT.

Estrogens have been hypothesized to be a risk factor for prostate cancer because circulating estrogen levels have been associated with inflammation and the immune response,[6] and their metabolites can produce DNA damage,[16,17] which in turn could produce an inflammatory response, and based on animal studies (reviewed in Nelles et al[6]). We previously found that intraprostatic inflammation was associated with prostate cancer in men.[2,3] Thus, we expected to observe a positive association between serum estrogens and intraprostatic inflammation. Neither the inverse estrogen-inflammation association we observed nor the hypothesized positive association can account for the null results for circulating levels of estrogens and prostate cancer risk in a collaborative analysis of world-wide prospective cohort data[18] or in the placebo arm of the PCPT.[10]

Androgens have been hypothesized to be a risk factor for prostate cancer because lowering dihydrotestosterone by blocking its conversion from testosterone reduced the period prevalence of prostate cancer in the PCPT,[11] and androgen-deprivation therapies are used to manage advanced prostate cancer.[19] Given that androgens are considered to be anti-inflammatory,[7] and given our prior finding for intraprostatic inflammation and prostate cancer,[2,3] we expected to observe an inverse association between serum androgens and intraprostatic inflammation. Neither the positive testosterone-inflammation association we observed, nor the hypothesized inverse association, can account for the null results for the association of serum total testosterone and androstanediol glucuronide with prostate cancer in the collaborative analysis of world-wide prospective cohort data,[18] or the null results for serum total and free testosterone and androstanediol glucuronide and prostate cancer in the placebo arm of the PCPT.[20] The collaborative analysis did show a lower risk of prostate cancer in men with very low free testosterone (bottom tenth vs higher).[21] In the current study, the sample size was too small to investigate whether inflammation is substantially reduced in men with very low free testosterone.

Overweight and obese individuals tend to have higher estrogen and lower testosterone levels,[9] and are more likely to have more systemic inflammation.[8] For our PCPT data, heavier men with no cores inflamed did have higher estradiol and lower testosterone. However, the highest tertile of estradiol and free estradiol concentrations tended to be positively associated with inflammation in leaner men, which is consistent with our hypothesis, and inversely associated with inflammation in heavier men, which is not consistent with our hypothesis. In contrast, the inverse association for estrone did not clearly differ by measures of body fatness. To understand this observation and given that estrone and estradiol interconvert in men in adipose tissue, we additionally investigated their ratio with intraprostatic inflammation and found no association overall or when stratified by BMI and waist circumference.

We also investigated the ratio between testosterone and estradiol concentrations and intraprostatic inflammation because animal studies support that coadministration of estrogens and androgens promoted development of pre-malignant lesions, adenocarcinoma, and inflammation in the prostate (reviewed in Nelles et al[6]). The testosterone-to-estradiol ratio tended to be positively associated with intraprostatic inflammation, and similar in magnitude for testosterone alone; this pattern was also observed in heavy men, but not in lean men. The estradiol-to-testosterone ratio was not associated with prostate cancer in the PCPT.[20]

A unique strength of this study is that it is the only study of its kind to examine the association of serum estrogen and testosterone levels and inflammation in benign prostate tissue from men without a prostate cancer diagnosis irrespective of clinical indication for biopsy and in which the majority (92.7%) had no clinical indication. Restricting to men only with a clinical indication, specifically elevated PSA, can lead to observation bias because intraprostatic inflammation can cause elevated PSA,[1] which in turn increases the likelihood of biopsy and the finding of inflammation. To our knowledge, no epidemiologic studies have been able to investigate the association of circulating estrogen and intraprostatic inflammation in men irrespective of clinical indication and/or in men without clinical

indication for biopsy. The findings counter to our hypotheses do not appear to be due to confounding by lifestyle factors.

Other aspects of this study warrant discussion. We used hormone levels measured in mid- and older adulthood. Although we are aware that androgen levels decline[22] and estrogen levels tend to either remain stable or increase with age,[23] we were not able to address how the change in hormone levels with aging may be associated with intraprostatic inflammation. We measured circulating hormone levels; we cannot rule out that local levels, whether from circulation or locally produced, may be more relevant, although circulating levels have been shown to weakly correlate with prostate tissue levels in benign prostate tissue adjacent to cancerous tissue.[24] We used hormone levels from more than 4 years before the end-of-study biopsies; we cannot rule out that more recent levels may be more relevant. Controls in this analysis were not a random sample of all men in the PCPT who had a negative end-of-study biopsy; thus, we cannot be certain that the results we observed would be comparable to what we would have observed if all controls had been studied. The smaller sample sizes after stratification by waist circumference and BMI restricted power to statistically observe effect modification by body fatness for the extent of inflammation; we presented stratified results only for any core inflamed vs none. Also, while we observed some associations that were conventionally statistically significant ($P < .05$), we did perform multiple statistical tests. Using the Bon-ferroni correction, for the main results that compelled the subsequent analyses (Table 2, N = 9 tests for trend, .05/9 = .0056), neither estrone (P-trend = .0072) nor androstanediol glucuronide (P-trend = .43) would be considered statistically significant.

In summary, in this first study in men without prostate cancer and irrespective of clinical indication for biopsy, contrary to the hypotheses, circulating estrogens appeared to be inversely associated, especially in heavy men, and circulating androgens appeared to be positively associated with intraprostatic inflammation. Further studies are needed to uncover mechanistic reasons for our observations, including possibly by investigating estrogenicity and androgenicity measured as sex steroid hormone receptor numbers or polymorphisms in those receptors and transcriptional activity in the prostate.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Characteristics of 247 controls in the placebo arm of PCPT by the prevalence and extent of inflammation in prostate biopsy cores

		Prostate biopsy cores with inflammation			
	Overall	**None**	**Any**[a]	**Some**	**All**
N	247	55	192	127	65
Mean age, y	64	63	65	64	65
White, %	83.4	85.5	82.8	82.7	83.1
Smoking status, %					
Current	5.3	5.4	5.2	4.7	6.2
Former	62.4	65.5	61.5	60.6	63.1
Never	32.4	29.1	33.3	34.7	30.8
Attained education, %					
High school or lower	18.6	10.9	20.8	20.5	21.5
Some college, college graduate	46.2	61.8	41.7	41.7	41.5
Graduate school	35.2	27.3	37.5	37.8	36.9
Mean BMI, kg/m^2	27.5	27.8	27.4	27.3	27.7
Mean waist circumference, cm	102	102	102	102	103
Activity level, %					
Sedentary or light	55.9	49.9	57.8	58.3	56.9
Moderate or active	44.1	50.9	42.2	41.7	43.1
History of diabetes, %	8.9	12.7	7.8	8.7	6.2
Mean cholesterol concentration, mg/dL	205	206	204	204	205
Mean alcohol intake, g/d	7.7	9.1	7.3	7.1	7.5
Mean red meat intake, g/d	0.65	0.58	0.65	0.66	0.64
Family history of prostate cancer, %	17.8	16.4	18.2	17.3	20.0
Mean baseline PSA concentration, ng/mL	1.17	0.88	1.26	1.21	1.35
Mean biopsy PSA concentration, ng/mL	1.97	1.24	2.17	1.53	3.42

[a]Some or all cores inflamed.

TABLE 2

Adjusted geometric mean[a] sex steroid hormone concentrations by the prevalence and extent of inflammation in prostate biopsy cores in 247 controls in the placebo arm of the PCPT

	Prostate biopsy cores with inflammation				
	None	**Any**	**Some**	**All**	***P*-trend[b]**
N	55	192	127	65	
Estradiol, pg/mL	33.2	32.3	32.5	31.8	.52
Free estradiol, pg/mL	0.70	0.66	0.66	0.65	.21
Estrone, pg/mL	44.3	41.6	43.4	38.2	.0072
Testosterone, ng/dL	335.0	364.8	371.1	353.0	.48
Free testosterone, pg/mL	77.5	80.0	82.9	74.5	.52
Androstanediol glucuronide, ng/mL	6.16	5.54	5.85	5.00	.043
SHBG, nmol/L	34.8	38.1	38.3	37.6	.31
Testosterone/ estradiol ratio	101	113	114	111	.21
Estrone/estradiol ratio	1.33	1.29	1.34	1.20	.053

[a] From a linear model adjusting for age, race, and family history of prostate cancer.

[b] Across none, some, all biopsy cores with inflammation.

TABLE 3

Adjusted associations of tertiles of sex steroid hormones with the prevalence and extent of inflammation in prostate biopsy cores in 247 controls in the placebo arm of the PCPT

	Prostate biopsy cores with inflammation						
	None	Any		Some		All	
	N	N	OR (95% CI)[a]	N	OR (95% CI)	N	OR (95% CI)
Estradiol							
T1	17	64	1 (Ref)	39	1 (Ref)	25	1 (Ref)
T2	21	61	0.70 (0.33–1.48)	44	0.83 (0.38–1.84)	17	0.48 (0.19–1.21)
T3	17	65	0.96 (0.44–2.06)	44	1.07 (0.47–2.39)	21	0.78 (0.31–1.93)
P-trend			0.92		0.87		0.58
Free estradiol							
T1	15	66	1 (Ref)	42	1 (Ref)	24	1 (Ref)
T2	18	64	0.74 (0.34–1.63)	41	0.75 (0.33–1.71)	23	0.72 (0.29–1.82)
T3	22	60	0.63 (0.29–1.33)	44	0.71 (0.32–1.57)	16	0.46 (0.18–1.17)
P-trend			0.23		0.41		0.11
Estrone							
T1	14	66	1 (Ref)	36	1 (Ref)	30	1 (Ref)
T2	23	58	0.49 (0.23–1.05)	41	0.63 (0.28–1.43)	17	0.30 (0.12–0.75)
T3	18	63	0.75 (0.34–1.66)	49	1.06 (0.46–2.43)	14	0.36 (0.14–0.95)
P-trend			0.57		0.75		0.036
Testosterone							
T1	25	57	1 (Ref)	35	1 (Ref)	22	1 (Ref)
T2	14	68	1.95 (0.92–4.16)	48	2.26 (1.02–5.02)	20	1.45 (0.59–3.61)
T3	16	66	1.91 (0.91–4.02)	44	2.06 (0.94–4.54)	22	1.67 (0.69–4.07)
P-trend			0.11		0.10		0.26
Free testosterone							
T1	24	58	1 (Ref)	37	1 (Ref)	21	1 (Ref)
T2	16	67	1.79 (0.86–3.76)	44	1.84 (0.84–4.03)	23	1.71 (0.71–4.16)
T3	15	67	2.19 (1.01–4.74)	46	2.31 (1.02–5.21)	21	1.97 (0.77–5.00)
P-trend			0.050		0.047		0.16

	Prostate biopsy cores with inflammation						
	None	Any		Some		All	
	N	N	OR (95% CI)[a]	N	OR (95% CI)	N	OR (95% CI)
SHBG							
T1	23	59	1 (Ref)	43	1 (Ref)	16	1 (Ref)
T2	17	65	1.43 (0.68–2.97)	39	1.18 (0.55–2.56)	26	2.11 (0.86–5.19)
T3	15	67	1.46 (0.68–3.12)	45	1.38 (0.62–3.06)	22	1.67 (0.65–4.30)
P-trend			0.35		0.41		0.37
Androstanediol glucuronide							
T1	15	67	1 (Ref)	40	1 (Ref)	27	1 (Ref)
T2	20	63	0.70 (0.33–1.51)	44	0.82 (0.37–1.84)	19	0.52 (0.21–1.28)
T3	20	62	0.77 (0.36–1.67)	43	0.89 (0.39–2.00)	19	0.59 (0.24–1.47)
P-trend			0.58		0.83		0.31
Testosterone/estradiol ratio							
T1	24	57	1 (Ref)	34	1 (Ref)	23	1 (Ref)
T2	16	66	1.65 (0.79–3.44)	47	1.97 (0.90–4.30)	19	1.15 (0.47–2.80)
T3	15	67	1.96 (0.93–4.14)	46	2.24 (1.01–4.94)	21	1.53 (0.63–3.74)
P-trend			0.083		0.056		0.33
Estrone/estradiol ratio							
T1	17	63	1 (Ref)	37	1 (Ref)	26	1 (Ref)
T2	18	63	1.05 (0.49–2.27)	42	1.17 (0.52–2.65)	21	0.88 (0.36–2.17)
T3	20	61	0.94 (0.44–1.99)	47	1.20 (0.55–2.65)	14	0.53 (0.21–1.35)
P-trend			0.85		0.66		0.19

Cutoffs for tertiles T1, T2, and T3, respectively, of hormone concentrations were the following: testosterone: <306, 306 to <407, ≥407 ng/dL; free testosterone: <71.5, 71.5 to <88.4, ≥88.4 pg/mL; SHBG < 31.8, 31.8 to <43.6, ≥43.6 nmol/L; androstanediol glucuronide < 4.71, 4.71 to <6.83, ≥6.83 ng/mL; estradiol: <29.6, 29.6 to 36.7, ≥36.7 pg/mL; free estradiol: <0.59, 0.59 to <0.75, ≥0.75 pg/mL; estrone: <37.2; 37.2 to <47.2, ≥47.2 pg/mL; testosterone/estradiol: <95.8, 95.8 to 129, ≥129; estrone/estradiol: <1.15, 1.15 to <1.47, ≥1.47.

Abbreviations: CI, confidence interval; OR, odds ratio; PCPT, Prostate Cancer Prevention Trial; SHBG, sex hormone binding globulin.

[a]OR calculated using logistic regression (any vs no [ref] cores with inflammation) and polytomous logistic regression (none [ref], some, all cores with inflammation) and adjusted for age, race, and family history of prostate cancer.

TABLE 4

Adjusted associations of tertiles of sex steroid hormones with the prevalence and extent of inflammation in prostate biopsy cores among controls in the placebo arm of the PCPT by BMI

	BMI< 27.09 kg/m^2 Prostate biopsy cores with inflammation			**BMI ≥ 27.09 kg/m^2 Prostate biopsy cores with inflammation**			
	None	**Any**		**None**	**Any**		
	N	**N**	**OR (95% CI)**[a]	**N**	**N**	**OR (95% CI)**	***P*-interaction**
Estradiol							.016
T1	11	31	1 (Ref)	6	33	1 (Ref)	
T2	7	29	1.04 (0.35–3.10)	14	31	0.45 (0.15–1.38)	
T3	5	38	2.61 (0.81–8.44)	12	24	0.35 (0.11–1.11)	
P-trend			0.11			0.079	
Free estradiol							.0012
T1	10	34	1 (Ref)	5	31	1 (Ref)	
T2	10	28	0.73 (0.26–2.06)	8	35	0.68 (0.19–2.40)	
T3	3	36	2.62 (0.74–9.28)	19	24	0.22 (0.07–0.71)	
P-trend			0.10		“/>	**0.0037**	
Estrone							.68
T1	7	36	1 (Ref)	7	30	1 (Ref)	
T2	10	29	0.44 (0.14–1.40)	13	27	0.53 (0.18–1.56)	
T3	6	31	0.79 (0.24–2.56)	12	32	0.75 (0.25–2.26)	
P-trend			0.92			0.57	
Testosterone							.99
T1	7	19	1 (Ref)	18	38	1 (Ref)	
T2	7	37	1.56 (0.45–5.42)	7	31	2.30 (0.83–6.38)	
T3	9	42	1.68 (0.53–5.31)	7	22	1.68 (0.58–4.92)	
P-trend			0.43			0.31	
Free testosterone							.82
T1	8	25	1 (Ref)	16	32	1 (Ref)	
T2	7	29	1.28 (0.40–4.13)	9	38	2.49 (0.92–6.74)	
T3	8	45	2.05 (0.65–6.46)	7	21	1.79 (0.60–5.35)	
P-trend			0.22			0.25	

	BMI< 27.09 kg/m^2 Prostate biopsy cores with inflammation			BMI ≥ 27.09 kg/m^2 Prostate biopsy cores with inflammation			
	None	Any		None	Any		
	N	N	OR (95% CI)[a]	N	N	OR (95% CI)	*P*-interaction
SHBG							.21
T1	6	24	1 (Ref)	17	35	1 (Ref)	
T2	8	37	0.98 (0.29–3.40)	9	27	1.57 (0.59–4.16)	
T3	9	37	0.79 (0.23–2.70)	6	29	2.02 (0.69–5.94)	
P-trend			0.67			0.080	
Androstanediol glucuronide							.78
T1	7	38	1 (Ref)	8	28	1 (Ref)	
T2	8	33	0.91 (0.30–2.73)	12	30	0.62 (0.20–1.89)	
T3	8	29	0.82 (0.27–2.55)	12	33	0.76 (0.26–2.26)	
P-trend			0.60			0.90	
Testosterone/estradiol ratio							.093
T1	3	26	1 (Ref)	21	31	1 (Ref)	
T2	11	30	0.33 (0.081–1.31)	5	34	4.15 (1.37–12.54)	
T3	9	42	0.58 (0.14–2.39)	6	25	3.01 (1.03–8.82)	
P-trend			0.82			0.027	
Estrone/estradiol ratio							.63
T1	8	36	1 (Ref)	9	26	1 (Ref)	
T2	6	30	1.25 (0.38–4.15)	12	32	1.07 (0.37–3.09)	
T3	9	30	0.79 (0.27–2.35)	11	31	1.17 (0.41–3.42)	
P-trend			0.66			0.75	

Cutoffs for tertiles T1, T2, and T3, respectively, of hormone concentrations were the following: testosterone: <306, 306 to <407, ≥407 ng/dL; free testosterone: <71.5, 71.5 to <88.4, ≥88.4 pg/mL; SHBG < 31.8, 31.8 to <43.6, ≥43.6 nmol/L; androstanediol glucuronide <4.71, 4.71 to <6.83, ≥6.83 ng/mL; estradiol: <29.6, 29.6 to 36.7, ≥36.7 pg/mL; free estradiol: <0.59, 0.59 to <0.75, ≥0.75 pg/mL; estrone: <37.2; 37.2 to <47.2, ≥47.2 pg/mL; testosterone/ estradiol: <95.8, 95.8 to 129, ≥129; estrone/estradiol: <1.15, 1.15 to <1.47, ≥1.47.

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio; PCPT, Prostate Cancer Prevention Trial; SHBG, sex hormone binding globulin.

[a]Adjusted for age, race, and family history of prostate cancer.

TABLE 5

Adjusted associations of tertiles of sex steroid hormones with the prevalence and extent of inflammation in prostate biopsy cores among controls in the placebo arm of the PCPT by waist circumference

	Waist circumference < 102 cm Prostate biopsy cores with inflammation			**Waist circumference ≥102cm Prostate biopsy cores with inflammation**			
	None	**Any**		**None**	**Any**		
	N	**N**	**OR (95% CI)[a]**	**N**	**N**	**OR (95% CI)**	***P*-interaction**
Estradiol							.038
T1	11	30	1 (Ref)	5	29	1 (Ref)	
T2	8	27	0.91 (0.29–2.79)	11	31	0.50 (0.15–1.69)	
T3	5	31	2.21 (0.66–7.41)	11	28	0.39 (0.12–1.30)	
P-trend			0.22			0.13	
Free estradiol							.022
T1	10	34	1 (Ref)	4	27	1 (Ref)	
T2	9	25	0.70 (0.23–2.11)	7	34	0.70 (0.18–2.78)	
T3	5	29	1.73 (0.51–5.90)	16	27	0.27 (0.078–0.92)	
P-trend			0.44			0.021	
Estrone							.46
T1	8	31	1 (Ref)	5	29	1 (Ref)	
T2	11	30	0.63 (0.21–1.90)	10	23	0.37 (0.11–1.27)	
T3	5	25	1.14 (0.31–4.12)	12	35	0.57 (0.17–1.85)	
P-trend			0.89			0.47	
Testosterone							.34
T1	10	18	1 (Ref)	15	35	1 (Ref)	
T2	6	30	2.16 (0.63–7.42)	5	33	2.65 (0.85–8.25)	
T3	8	41	2.89 (0.93–8.94)	7	20	1.31 (0.43–4.01)	
P-trend			0.085			0.59	
Free testosterone							.44
T1	9	19	1 (Ref)	15	33	1 (Ref)	
T2	8	31	1.94 (0.59–6.34)	5	30	3.19 (0.97–10.47)	
T3	7	40	3.51 (1.03–12.11)	7	25	1.93 (0.66–5.70)	
P-trend		“/>	**0.050**			0.22	

	Waist circumference < 102 cm Prostate biopsy cores with inflammation			Waist circumference ≥102cm Prostate biopsy cores with inflammation			
	None	Any		None	Any		
	N	N	OR (95% CI)[a]	N	N	OR (95% CI)	*P*-interaction
SHBG							.74
T1	9	21	1 (Ref)	12	34	1 (Ref)	
T2	8	36	1.67 (0.52–5.34)	9	28	1.14 (0.41–3.16)	
T3	7	32	1.53 (0.46–5.12)	6	26	1.13 (0.35–3.62)	
P-trend			0.55			0.83	
Androstanediol glucuronide							.66
T1	9	21	1 (Ref)	6	30	1 (Ref)	
T2	8	36	1.67 (0.52–5.34)	10	28	0.58 (0.18–1.93)	
T3	7	32	1.53 (0.46–5.12)	11	30	0.59 (0.19–1.87)	
P-trend			0.55			0.43	
Testosterone/estradiol ratio							.56
T1	6	19	1 (Ref)	17	34	1 (Ref)	
T2	9	28	1.02 (0.30–3.55)	5	32	2.96 (0.96–9.18)	
T3	9	41	1.57 (0.47–5.31)	5	22	2.38 (0.75–7.57)	
P-trend			0.40			0.10	
Estrone/estradiol ratio							.68
T1	9	30	1 (Ref)	7	24	1 (Ref)	
T2	5	28	2.43 (0.67–8.90)	11	32	1.07 (0.34–3.33)	
T3	10	28	0.99 (0.33–2.98)	9	31	1.24 (0.39–3.97)	
P-trend			0.91			0.71	

Cutoffs for tertiles T1, T2, and T3, respectively, of hormone concentrations were the following: testosterone: <306, 306 to <407, ≥407 ng/dL; free testosterone: <71.5, 71.5 to <88.4, ≥88.4 pg/mL; SHBG < 31.8, 31.8 to <43.6, ≥43.6 nmol/L; androstanediol glucuronide < 4.71, 4.71 to <6.83, ≥6.83 ng/mL; estradiol: <29.6, 29.6 to 36.7, ≥36.7 pg/mL; free estradiol: <0.59, 0.59 to <0.75, ≥0.75 pg/mL; estrone: <37.2; 37.2 to <47.2, ≥47.2 pg/mL; testosterone/estradiol: <95.8, 95.8 to 129, ≥129; estrone/estradiol: <1.15, 1.15 to <1.47, ≥1.47.

[a]Adjusted for age, race, and family history of prostate cancer.