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Published in final edited form as:
Eur Urol. 2014 April ; 65(4): 683–689. doi:10.1016/j.eururo.2013.01.003.

Prediagnostic Circulating Sex Hormones Are Not Associated with Mortality for Men with Prostate Cancer

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Abstract

Background—Sex hormones play an important role in the growth and development of the prostate, and low androgen levels have been suggested to carry an adverse prognosis for men with prostate cancer (PCa).

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Author contributions: Lorelei A. Mucci had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Drafting of the manuscript: Gershman, Shui, Mucci, Giovannucci.
Critical revision of the manuscript for important intellectual content: Gershman, Shui, Mucci, Giovannucci, Sesso, Platz, Gann, Stampfer.
Statistical analysis: Gershman, Shui, Mucci.
Obtaining funding: Mucci, Giovannucci, Stamper.
Administrative, technical, or material support: Mucci, Giovannucci, Stamper.
Supervision: Mucci, Giovannucci, Shui.
Other (specify): None.

Financial disclosures: Lorelei A. Mucci certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/ affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Objective—To examine the association between prediagnostic circulating sex hormones and lethal PCa in two prospective cohort studies, the Physicians' Health Study (PHS) and the Health Professionals Follow-up Study (HPFS).

Design, setting, and participants—We included 963 PCa cases (700 HPFS; 263 PHS) that provided prediagnostic blood samples, in 1982 for PHS and in 1993–1995 for HPFS, in which circulating sex hormone levels were assayed.

Outcome measures and statistical analysis—The primary end point was lethal PCa (defined as cancer-specific mortality or development of metastases), and we also assessed total mortality through March 2011. We used Cox proportional hazards models to evaluate the association of prediagnostic sex hormone levels with time from diagnosis to development of lethal PCa or total mortality.

Results and limitations—PCa cases were followed for a mean of 12.0 ± 4.9 yr after diagnosis. We confirmed 148 cases of lethal PCa and 421 deaths overall. Using Cox proportional hazard models, we found no significant association between quartile of total testosterone, sex hormone binding globulin (SHBG), SHBG-adjusted testosterone, free testosterone, dihydrotestosterone, androstanediol glucuronide, or estradiol and lethal PCa or total mortality. In subset analyses stratified by Gleason score, TNM stage, age, and interval between blood draw and diagnosis, there was also no consistent association between lethal PCa and sex hormone quartile.

Conclusions—We found no overall association between prediagnostic circulating sex hormones and lethal PCa or total mortality. Our null results suggest that reverse causation may be responsible in prior studies that noted adverse outcomes for patients with low circulating androgens.

Keywords

Prostate cancer; Testosterone; Androgens; Sex hormones; Mortality

1. Introduction

Sex hormones play an important role in the normal development, growth, and regulation of the prostate [1]. Testosterone has historically been implicated in the pathogenesis of prostate cancer (PCa), although epidemiologic studies generally have not observed an association between circulating androgen levels and risk of developing PCa [2,3]. In contrast, among men with PCa, studies have found an association between low pretreatment testosterone levels and higher Gleason score [3-5], advanced pathologic stage [6-8], and positive surgical margins [8] as well as worse overall survival for men diagnosed with metastatic disease [9-11]. Pretreatment estrogen levels have also been associated with high-grade PCa [12], and there is evidence that the relationship between sex hormones and high-grade PCa may be nonlinear [13].

To our knowledge, no study has examined the association between prediagnostic circulating sex hormone levels and clinical outcomes for men with PCa. We conducted this secondary analysis of two large, prospective cohort studies—the Health Professionals Follow-up Study (HPFS) and the Physicians' Health Study (PHS)—to examine the association of prediagnostic circulating sex hormone levels with lethal PCa and overall survival among men with PCa.

2. Patients and methods

2.1. Study populations

2.1.1. Health Professionals Follow-up Study—The HPFS is an ongoing prospective cohort study of 51 529 US men aged 40–75 yr at enrollment in 1986 and followed with biennial questionnaires described previously [14]. Between 1993 and 1995, 18 018 men provided a blood specimen that was that was stored and used for subsequent analysis.

2.1.2. Physicians' Health Study—The PHS I was a double-blind, placebo-controlled trial that randomized 22 071 healthy US male physicians aged 40–84 yr to either aspirin and/or β-carotene in 1982, as described previously [15]. Prior to randomization, 14 916 men provided a blood sample that was stored and used for subsequent analysis.

2.2. Case selection and follow-up

We had biomarker data on 963 participants from the two cohorts (700 in HPFS and 263 in PHS) who were diagnosed with PCa and had provided prediagnostic blood in which circulating sex hormone levels were assayed. Participants in the HPFS were diagnosed between 1993 and 2000, and participants in the PHS were diagnosed between 1982 and 1992. Of the 963 men, 219 (23%) were diagnosed with PCa within 2 yr of blood collection.

Study investigators verified reporting of PCa by review of medical records and pathology reports. Clinical TNM stage was used when pathologic TNM stage was unavailable, and biopsy Gleason score was used when pathologic Gleason score was unavailable. We were able to obtain medical and pathology records for approximately 90% of the HPFS cases and 96% of the PHS cases, with high validity of self-reported diagnosis.

Men were followed from date of cancer diagnosis until death, development of bone or organ metastases, or end of study follow-up (March 2011). Follow-up information was obtained via questionnaires that asked participants to report on treatments and clinical progression. Medical record review was used to verify report of metastases. Deaths were initially identified either by family member report, via follow-up questionnaire, or through a search of the National Death Index [16]. Cause of death was centrally verified by study investigators using review of medical records and death certificates.

2.3. Laboratory measurements

Frozen blood samples were analyzed as previously described [3,17]. Blood samples were stored at −82°C from blood draw until analyses, and the original samples were aliquoted in multiple vials to minimize freeze-thaw cycles. Frozen blood samples were shipped on dry ice to the laboratory and assayed for total testosterone, free testosterone (HPFS only), dihydrotestosterone (DHT), androstanediol glucuronide (AAG), sex hormone-binding globulin (SHBG), and estradiol (E2) in a single analytic run in December 1994 for PHS and in three separate analytic runs for HPFS. DHT was unavailable for the third HPFS analytic run, and free testosterone was not measured in the PHS.

2.4. Statistical analysis

We calculated batch-specific quartiles for each sex hormone to control for interassay variation. The primary study end point was lethal PCa (defined as cancer-specific mortality or development of metastases), and we also assessed total mortality. We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for lethal PCa or death from any cause. For men who died of PCa, time to event was calculated as time from date of cancer diagnosis to cancer-specific death. For men who developed metastatic disease but did not die of PCa (n = 14), time to event was calculated as

time to metastasis plus median time from metastasis to cancer-specific death for the cohort. The lowest quartile of each sex hormone was used as the reference level, and we also tested for trends across quartiles by treating the quartile as an ordinal variable. Models were adjusted for age at diagnosis, cigarette smoking status (current, past, never), body mass index (BMI; <25 kg/m^2, 25–30 kg/m^2, ≥30 kg/m^2), level of physical activity (low, moderate, high), Gleason score, and TNM stage. Because bioavailable testosterone depends on levels of SHBG, we created an additional Cox model for total testosterone using the two cohorts combined that adjusted for SHBG by including a batch-adjusted continuous measure of SHBG as a covariate to estimate bioavailable testosterone. Results for lethal PCa and total mortality were similar among cohorts, and we present the results for the two cohorts combined except when otherwise noted. We also conducted subset analyses stratified by Gleason score, TNM stage, age (<65 yr vs ≥65 yr), and time between blood draw and diagnosis (<2 yr and ≥2 yr). Because of small numbers, we conducted only subset analyses with the two cohorts combined, using a batch-adjusted continuous measure of each hormone. All p values were two-sided and considered significant at $p < 0.05$. Statistical analysis was performed using SAS v.9.0 (SAS Institute, Cary, NC, USA).

3. Results

The 963 men with PCa were followed for a mean plus or minus standard deviation of 12.0 ± 4.9 yr after diagnosis (Table 1). Mean age at blood draw and diagnosis were 64.7 ± 7.6 yr and 69.1 ± 7.3 yr, respectively. During follow-up, we confirmed 421 deaths overall, 134 deaths due to PCa, and 14 men alive with bone or organ metastases. Deaths due to PCa and men alive with metastatic disease were combined into a single category of lethal PCa (n = 148).

Using Cox proportional hazards models adjusted for age at diagnosis (HR1); further adjusted for BMI, physical activity, and smoking status (HR2); and further adjusted for Gleason score and TNM stage (HR3), we found no significant association between quartile of total testosterone, SHBG, SHBG-adjusted total testosterone, free testosterone, DHT, AAG, or estradiol and lethal PCa or total mortality (Table 2a and 2b). Results were similarly null when age at blood draw was substituted for age at diagnosis in the models as well as when clinical stage and Gleason score at diagnosis were substituted for best available stage or Gleason score (data not shown).

In separate analyses of the HPFS and PHS cohorts, there was no association between any of the sex hormones and lethal PCa or total mortality, with the following exceptions: SHBG-adjusted testosterone in HPFS (HR1 1.00/0.85/0.75/0.63, p_{trend} = 0.04 for total mortality), AAG in HPFS (HR3 1.00/1.15/1.10/1.52, p_{trend} = 0.04 for total mortality), and estradiol in HPFS (HR1 1.00/1.58/1.23/2.30, p_{trend} = 0.02; HR2 1.00/1.53/1.26/2.12, p_{trend} = 0.04 for lethal PCa). Subset analyses were performed on the combined cohort, and in general, we did not see heterogeneity in the results (Table 3). However, for men with Gleason 8 10 disease, there was an increased risk of lethal PCa with increasing DHT (HR: 1.87; 95% CI, 1.26–2.78). There was also an increased risk of lethal PCa for men with stage T3 disease associated with increasing DHT (HR: 1.98; 95% CI, 1.30–3.00) and SHBG (HR: 1.59; 95% CI, 1.05–2.41), and for men with <2 yr between blood draw and diagnosis associated with increasing DHT (HR: 1.69; 95% CI, 1.17–2.44).

4. Discussion

In this analysis of two large, prospective PCa cohorts with long-term follow-up, we found no overall association between prediagnostic circulating sex hormone levels and lethal PCa or total mortality. In addition, we did not find any consistent association when men were

stratified by age at diagnosis, Gleason score, TNM stage, and time from blood draw to diagnosis, with several exceptions.

To our knowledge, no study has evaluated the relationship between prediagnostic sex hormone levels and clinical outcomes for men with PCa. In contrast, several studies have examined men with metastatic disease and noted an association between lower pretreatment testosterone levels and increased cancer-specific mortality [9,11,18,19]. For example, Ribeiro et al [11] observed that low pretreatment serum testosterone was associated with a poor response to androgen deprivation therapy. The concept that more aggressive, androgen-independent PCa may develop in a low-androgenicity milieu has also been suggested by other authors [7,9,20]. An additional study also noted increased biochemical recurrence associated with low pretreatment testosterone in men undergoing radical prostatectomy for localized disease [21].

There are several obvious differences between these studies and the present one. Most important, these studies used pretreatment testosterone levels (ie, taken at or after diagnosis) rather than prediagnostic levels, and their observations may reflect reverse causality: that low pretreatment testosterone levels are a consequence of PCa itself rather than that aggressive PCa is a result of the hormonal milieu in which it develops. Indeed, several studies have suggested that PCa may result in suppression of circulating total testosterone and free testosterone, noting an increase in these hormones following radical prostatectomy [22-24]. Such changes are not seen following suprapubic prostatectomy [25], transurethral resection of the prostate, or for men with PCa on watchful waiting [22]. Moreover, two of these studies [22,23] noted a concomitant increase in luteinizing hormone and follicle-stimulating hormone following radical prostatectomy, suggesting central suppression related to PCa. Interestingly, the glycoprotein inhibin is produced by testis and prostate and has been suggested as a potential inhibitor of pituitary gonadotropins in this setting [23].

Men with metastatic disease represent a selected subset of all PCa cases, and since primary therapy consists of androgen deprivation, outcomes may be more associated with circulating sex hormone levels than for men with nonmetastatic disease. Interestingly, when we stratified patients by TNM stage, we did not observe an association between lethal PCa and any sex hormone for men with T4/N1/M1 disease. This appears to contradict the results of prior studies, and these differences may again be due to the use of prediagnostic rather than pretreatment hormone levels.

Only one small study [26] has previously evaluated the association of circulating DHT with PCa outcomes. In this prospective study, the authors observed a decreased risk of cancer-specific mortality with increasing pretreatment DHT level. Our overall null results contradict these observations. In addition, we noted an increased risk of lethal PCa with increasing DHT level for men diagnosed within 2 yr of blood draw or with Gleason 8–10 disease. As discussed above, the use of prediagnostic rather than pretreatment DHT levels may explain the differing results, as low pretreatment DHT levels may be a consequence of aggressive PCa and not the reverse. Several studies have observed that higher pretreatment SHBG is associated with worse pathologic outcomes [27,28]. In contrast, we found no overall relationship between SHBG and lethal PCa, with the exception of patients with T3 disease, in whom higher SHBG was associated with lethal PCa. These differences may be explained by the use of prediagnostic hormone levels or could be due to chance because of the smaller numbers and multiple comparisons.

Other considerations may explain our null results despite biologic plausibility. For instance, circulating sex hormone levels may correlate with potential confounders such as age, BMI [29], and level of physical activity [30], all of which were included in our multivariate

models but may have confounded results in some prior studies. In addition, some error may be introduced from measuring sex hormone levels at a single time point. Multiple measurements over time would be able to provide a better estimate of long-term exposure or allow us to better assess different etiologic periods of exposure. However, levels of blood sex hormones have been found to have good correlation when measured 3 yr apart [3]. Moreover, the results remained consistent when we compared cases diagnosed within 2 yr and >2 yr after diagnosis.

This study has several potential limitations. The possibility of residual or unmeasured confounding by comorbid conditions cannot be excluded. Due to the sample size, we did not test for nonlinear associations or use alternate modeling techniques to evaluate for fine associations at the tail ends of the exposure range. Interestingly, a recent study has suggested that the relationship between sex hormones and PCa may be nonlinear [13]. However, we did not observe any evidence of a nonlinear relationship when we categorized the exposures into batch and study-specific quartiles. As with any null study, it is possible that a larger sample size may be required to detect smaller associations.

This study has a number of strengths. It is an analysis of two large, prospective studies with long-term, complete follow-up and excellent ascertainment of centrally verified end points. More important, the use of prediagnostic blood samples allows us to examine the association between circulating sex hormone levels and development of lethal PCa, greatly reducing the possibility that changes in hormone levels are a consequence of the cancer itself. Strict quality control measures were in place for the biomarker assessments, and the coefficients of variation in the hormones across batches were relatively low, suggesting precise assessment of the marker. Finally, this study is the first to evaluate long-term clinical outcomes such as PCa-specific mortality in relation to prediagnostic sex hormone levels.

5. Conclusions

We found no association between prediagnostic circulating sex hormones and lethal PCa or total mortality. Prior studies that observed an adverse prognosis for patients with metastatic PCa and low androgen levels may reflect an effect of the cancer itself, possibly mediated through suppression of pituitary gonadotropins. Although likely not etiologic, pretreatment hormone levels may nonetheless have clinical utility in risk stratification and prognostication, and further prospective studies are needed to investigate this area.

Acknowledgments

We are grateful to the ongoing participation of men in the Health Professionals Follow-up Study (HPFS) and Physicians' Health Study. We would like to thank the participants and staff of the HPFS for their valuable contributions as well as the following US state cancer registries for their help: Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Delaware Florida, Georgia, Idaho, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Nebraska, New Hampshire, New Jersey, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Virginia, Washington, Wyoming.

Funding/Support and role of the sponsor: This study was funded in part by grants from the National Institutes of Health/National Cancer Institute (RO1 CA136578 PI: Mucci; P01 CA055075 PI: Willett; R01 CA133891 PI: Giovannucci; R01 CA141298 PI: Stampfer; DF/HCC SPORE in Prostate Cancer NIH/NCI P50 CA90381 PI: Kantoff). Lorelei A. Mucci was a Milken Young Investigator of the Prostate Cancer Foundation. Irene M. Shui is supported by the National Cancer Institute NRSA T32 CA09001 (PI: Stampfer) and a US Army Prostate Cancer Postdoctoral Fellowship.

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Take-home message

We found no overall association between prediagnostic circulating sex hormones and lethal prostate cancer or total mortality. Our null results suggest that reverse causation may be responsible in prior studies that noted adverse outcomes for patients with low circulating androgens.

Table 1

Characteristics of men with prostate cancer in the Health Professionals Follow-up Study (1993–2000) and the Physicians' Health Study (1982–1992)

	Combined cohort	HPFS	PHS
No. of cases	963	700	263
Age at blood draw, yr, mean (SD)	64.7 (7.6)	65.8 (7.4)	61.7 (7.5)
Age at diagnosis, yr, mean (SD)	69.1 (7.3)	68.9 (7.3)	69.6 (7.5)
Follow-up, yr, mean (SD)	12.0 (4.9)	11.6 (3.8)	13.0 (6.8)
Gleason score, no. (%)			
2–6	467 (54)	353 (53)	114 (56)
7	296 (34)	238 (36)	58 (29)
8–10	103 (12)	73 (11)	30 (15)
Missing	97	36	61
TNM stage, no. (%)			
T1/T2	753 (81)	575 (85)	178 (72)
T3	118 (13)	81 (12)	37 (15)
T4/N1/M1	55 (6)	22 (3)	33 (13)
Missing	37	22	15
Smoking status, no. (%)			
Never	418 (45)	310 (46)	108 (41)
Past	468 (50)	335 (50)	133 (51)
Current	53 (6)	31 (5)	22 (8)
Missing	24	24	0
BMI, kg/m^2, no. (%)			
<25	445 (46)	293 (42)	152 (58)
25–29	435 (45)	335 (48)	100 (38)
≥30	83 (9)	72 (10)	11 (4)
Physical activity, no. (%)			
Low	354 (37)	288 (41)	66 (25)
Moderate	349 (36)	202 (29)	147 (57)
High	257 (27)	210 (30)	47 (18)
Missing	3	0	3
Deaths, no. (%)	421 (44)	246 (35)	175 (67)
Deaths from PCa, no. (%)	134 (14)	72 (10)	62 (24)
"Lethal" PCa, no. (%)	148 (15)	82 (12)	66 (25)

BMI = body mass index; HPFS = Health Professionals Follow-up Study; PCa = prostate cancer; PHS = Physicians' Health Study; SD = standard deviation.

[1] Percentages may not add to 100% due to rounding.

Table 2

Association between sex hormone quartile (a) and lethal prostate cancer (defined as development of metastases or cancer-specific mortality) (b) and total mortality; combined cohort of the Health Professionals Follow-up Study and the Physicians' Health Study (n = 963), 1982–2010

(a)

	Quartile[5]				
	Q1 (low)	**Q2**	**Q3**	**Q4 (high)**	p_{trend}
Total T					
No. events/cases	36/240	39/240	45/243	28/240	
HR1[1] (95% CI)	1.00	1.09 (0.70–1.72)	1.25 (0.81–1.94)	0.77 (0.47–1.26)	0.48
HR2[2] (95% CI)	1.00	1.29 (0.81–2.07)	1.42 (0.91–2.23)	0.94 (0.56–1.58)	0.97
HR3[3] (95% CI)	1.00	1.38 (0.86–2.23)	1.18 (0.74–1.88)	0.98 (0.58–1.67)	0.83
SHBG					
No. events/cases	35/238	38/243	32/242	43/240	
HR1[1] (95% CI)	1.00	1.12 (0.71–1.77)	0.86 (0.53–1.38)	1.25 (0.80–1.96)	0.55
HR2[2] (95% CI)	1.00	1.26 (0.79–2.01)	0.93 (0.57–1.51)	1.46 (0.92–2.31)	0.26
HR3[3] (95% CI)	1.00	1.02 (0.63–1.65)	0.69 (0.42–1.14)	0.95 (0.58–1.54)	0.50
SHBG-adjusted T[4]					
No. events/cases	36/240	39/240	45/243	28/240	
HR1[1] (95% CI)	1.00	0.99 (0.62–1.57)	1.04 (0.65–1.66)	0.53 (0.29–0.97)	0.09
HR2[2] (95% CI)	1.00	1.16 (0.72–1.87)	1.17 (0.72–1.89)	0.65 (0.36–1.20)	0.27
HR3[3] (95% CI)	1.00	1.39 (0.85–2.27)	1.19 (0.72–1.96)	0.99 (0.54–1.82)	0.89
Free T[6]					
No. events/cases	23/172	20/174	20/174	18/173	
HR1[1] (95% CI)	1.00	0.81 (0.44–1.47)	0.93 (0.51–1.71)	0.81 (0.44–1.51)	0.63
HR2[2] (95% CI)	1.00	1.08 (0.57–2.04)	1.24 (0.66–2.34)	1.10 (0.57–2.12)	0.69
HR3[3] (95% CI)	1.00	1.53 (0.80–2.94)	1.36 (0.69–2.66)	1.50 (0.76–2.96)	0.30
DHT[7]					
No. events/cases	32/175	28/187	31/180	35/181	
HR1[1] (95% CI)	1.00	0.82 (0.49–1.36)	0.89 (0.54–1.46)	1.06 (0.65–1.72)	0.74

(a)

	Quartile[5]				
	Q1 (low)	**Q2**	**Q3**	**Q4 (high)**	p_{trend}
HR2[2] (95% CI)	1.00	0.89 (0.53–1.49)	1.02 (0.61–1.70)	1.22 (0.74–2.01)	0.37
HR3[3] (95% CI)	1.00	0.80 (0.47–1.37)	0.82 (0.48–1.39)	1.22 (0.72–2.04)	0.46
AAG					
No. events/cases	35/238	43/241	35/243	35/239	
HR1[1] (95% CI)	1.00	1.17 (0.75–1.83)	0.95 (0.59–1.52)	1.06 (0.66–1.71)	0.96
HR2[2] (95% CI)	1.00	1.24 (0.79–1.95)	0.99 (0.62–1.59)	1.10 (0.69–1.77)	0.94
HR3[3] (95% CI)	1.00	1.14 (0.71–1.82)	0.96 (0.59–1.56)	1.04 (0.64–1.70)	0.93
E2					
No. events/cases	31/234	40/242	33/243	44/244	
HR1[1] (95% CI)	1.00	1.28 (0.80–2.04)	1.04 (0.64–1.70)	1.47 (0.93–2.33)	0.19
HR2[2] (95% CI)	1.00	1.24 (0.77–1.98)	1.00 (0.61–1.64)	1.32 (0.83–2.11)	0.40
HR3[3] (95% CI)	1.00	1.27 (0.79–2.05)	1.34 (0.81–2.23)	1.38 (0.86–2.21)	0.19

(b)

	Quartile[5]				
	Q1 (low)	Q2	Q3	Q4 (high)	p_{trend}
Total T					
No. events/cases	108/240	106/240	110/243	97/240	
HR1[1] (95% CI)	1.00	1.01 (0.77–1.32)	1.03 (0.79–1.34)	0.87 (0.66–1.15)	0.37
HR2[2] (95% CI)	1.00	1.18 (0.89–1.56)	1.17 (0.89–1.54)	1.08 (0.81–1.44)	0.60
HR3[3] (95% CI)	1.00	1.16 (0.88–1.54)	1.07 (0.81–1.41)	1.07 (0.80–1.44)	0.78
SHBG					
No. events/cases	100/238	107/243	97/242	117/240	
HR1[1] (95% CI)	1.00	1.13 (0.86–1.49)	0.86 (0.65–1.14)	1.12 (0.86–1.47)	0.84
HR2[2] (95% CI)	1.00	1.25 (0.95–1.66)	0.91 (0.68–1.21)	1.29 (0.98–1.70)	0.33
HR3[3] (95% CI)	1.00	1.19 (0.90–1.58)	0.83 (0.62–1.11)	1.14 (0.85–1.51)	0.99

(a)

	Quartile[5]				
	Q1 (low)	**Q2**	**Q3**	**Q4 (high)**	p_{trend}
SHBG-adj T[4]					
No. events/cases	108/240	106/240	110/243	97/240	
HR1[1] **(95% CI)**	1.00	0.96 (0.73–1.26)	0.93 (0.70–1.24)	0.72 (0.51–1.01)	0.08
HR2[2] **(95% CI)**	1.00	1.11 (0.84–1.48)	1.05 (0.79–1.41)	0.89 (0.63–1.26)	0.52
HR3[3] **(95% CI)**	1.00	1.14 (0.86–1.52)	1.03 (0.77–1.39)	1.01 (0.71–1.44)	0.91
Free T[6]					
No. events/cases	73/172	61/174	58/174	50/173	
HR1[1] **(95% CI)**	1.00	0.74 (0.53–1.04)	0.89 (0.63–1.26)	0.72 (0.50–1.03)	0.15
HR2[2] **(95% CI)**	1.00	0.92 (0.65–1.32)	1.15 (0.80–1.66)	0.94 (0.64–1.37)	0.96
HR3[3] **(95% CI)**	1.00	0.99 (0.69–1.43)	1.15 (0.80–1.67)	0.99 (0.67–1.46)	0.83
DHT[7]					
No. events/cases	81/175	94/187	84/180	94/181	
HR1[1] **(95% CI)**	1.00	1.07 (0.80–1.45)	0.89 (0.65–1.21)	0.99 (0.73–1.34)	0.65
HR2[2] **(95% CI)**	1.00	1.23 (0.91–1.66)	1.02 (0.74–1.40)	1.17 (0.86–1.59)	0.56
HR3[3] **(95% CI)**	1.00	1.27 (0.93–1.73)	0.98 (0.71–1.36)	1.25 (0.91–1.72)	0.43
AAG					
No. events/cases	108/238	106/241	100/243	107/239	
HR1[1] **(95% CI)**	1.00	0.92 (0.70–1.20)	0.89 (0.68–1.17)	1.19 (0.91–1.56)	0.29
HR2[2] **(95% CI)**	1.00	0.98 (0.75–1.29)	0.94 (0.71–1.24)	1.23 (0.94–1.62)	0.21
HR3[3] **(95% CI)**	1.00	1.02 (0.77–1.35)	0.94 (0.70–1.24)	1.19 (0.90–1.57)	0.34
E2					
No. events/cases	108/234	106/242	94/243	113/244	
HR1[1] **(95% CI)**	1.00	1.00 (0.77–1.31)	0.88 (0.67–1.17)	1.18 (0.91–1.54)	0.39
HR2[2] **(95% CI)**	1.00	0.98 (0.75–1.28)	0.86 (0.65–1.14)	1.09 (0.83–1.43)	0.75
HR3[3] **(95% CI)**	1.00	0.93 (0.71–1.23)	0.84 (0.63–1.12)	1.09 (0.83–1.43)	0.71

AAG = androstanediol glucuronide; BMI = body mass index; CI = confidence interval; DHT = dihydrotestosterone; E2 = estradiol; HPFS = Health Professionals Follow-up Study; HR = hazard ratio; SHBG = sex hormone binding globulin; T = testosterone.
PHS = Physicians' Health Study; SHBG = sex hormone binding globulin; T = testosterone.

[1] HR1: adjusted for age at diagnosis.

[2] HR2: adjusted for age at diagnosis, BMI, physical activity, smoking status.

[3] HR3: adjusted for age at diagnosis, BMI, physical activity, smoking status, Gleason score, and TNM stage.

[4] HRs as above but further adjusted for SHBG using a batch-adjusted continuous measure of SHBG.

[5] Quartiles calculated separately for each batch to control for interassay variation.

[6] Free testosterone not measured in PHS.

[7] DHT data not available for third HPFS batch.

Table 3

Association between sex hormone level and lethal prostate cancer (defined as development of metastases or cancer-specific mortality), stratified by Gleason score, TNM stage, age at diagnosis, and interval from blood draw to diagnosis; combined cohort of the Health Professionals Follow-up Study and the Physicians' Health Study[1] (*n* = 963), 1982–2010

	No. events/cases[2]	HR[3]	*p* value
Gleason score ≤6			
T	32/447	0.90 (0.58–1.40)	0.64
SHBG	32/447	1.07 (0.70–1.63)	0.77
SHBG-adjusted T[4]	32/447	0.77 (0.43–1.38)	0.38
Free T	20/336	1.06 (0.63–1.77)	0.83
DHT[5]	26/326	0.99 (0.62–1.57)	0.95
AAG	32/446	1.13 (0.83–1.55)	0.44
Estradiol	32/447	1.08 (0.72–1.63)	0.71
Gleason score 7			
T	42/295	0.93 (0.66–1.31)	0.68
SHBG	42/295	1.14 (0.77–1.69)	0.50
SHBG-adjusted T[4]	42/295	0.82 (0.49–1.36)	0.44
Free T	22/223	0.96 (0.55–1.68)	0.88
DHT[5]	37/211	0.86 (0.55–1.34)	0.50
AAG	42/294	1.08 (0.84–1.39)	0.55
Estradiol	42/295	1.06 (0.75–1.49)	0.75
Gleason score 8–10			
T	37/98	1.06 (0.72–1.56)	0.78
SHBG	37/98	1.04 (0.77–1.40)	0.81
SHBG-adjusted T[4]	37/98	1.05 (0.63–1.73)	0.86
Free T	23/68	1.36 (0.74–2.52)	0.32
DHT[5]	30/75	***1.87 (1.26–2.78)**	***0.002**
AAG	37/98	1.21 (0.84–1.74)	0.31
Estradiol	37/98	1.31 (0.83–2.08)	0.25
Stage T1/T2			
T	75/750	0.87 (0.66–1.15)	0.33
SHBG	75/750	1.02 (0.78–1.34)	0.88
SHBG-adjusted T[4]	75/750	0.79 (0.55–1.14)	0.21
Free T	45/569	1.05 (0.73–1.51)	0.79
DHT[5]	62/546	0.98 (0.72–1.32)	0.87
AAG	75/749	1.14 (0.93–1.39)	0.21
Estradiol	75/750	0.96 (0.73–1.27)	0.79
Stage T3			
T	24/115	1.12 (0.57–2.20)	0.75
SHBG	24/115	***1.59 (1.05–2.41)**	***0.03**

	No. events/cases[2]	HR[3]	*p* value
SHBG-adjusted T[4]	24/115	0.63 (0.26–1.52)	0.31
Free T	14/77	0.93 (0.39–2.23)	0.87
DHT[5]	21/93	***1.98 (1.30–3.00)**	***0.001**
AAG	24/115	1.12 (0.80–1.56)	0.52
Estradiol	24/115	1.38 (0.74–2.57)	0.32
Stage T4/N1/M1			
T	44/53	1.14 (0.65–2.02)	0.65
SHBG	44/53	0.77 (0.54–1.10)	0.15
SHBG-adjusted T[4]	44/53	1.56 (0.82–2.98)	0.18
Free T[6]	–	–	–
DHT[5]	40/47	1.11 (0.70–1.78)	0.66
AAG	44/52	0.73 (0.45–1.20)	0.21
Estradiol	44/53	0.93 (0.72–1.21)	0.61
Age <65 yr			
T	34/252	1.02 (0.73–1.42)	0.92
SHBG	34/252	1.21 (0.83–1.77)	0.33
SHBG-adjusted T[4]	34/252	0.94 (0.60–1.47)	0.79
Free T	8/173	1.08 (0.51–2.26)	0.84
DHT[5]	31/193	1.36 (0.96–1.94)	0.09
AAG	34/251	0.81 (0.59–1.12)	0.21
Estradiol	34/252	0.82 (0.53–1.26)	0.36
Age ≥65 yr			
T	111/684	0.97 (0.77–1.23)	0.83
SHBG	111/684	1.17 (0.96–1.44)	0.13
SHBG-adjusted T[4]	111/684	0.79 (0.58–1.07)	0.13
Free T	67/489	1.01 (0.73–1.40)	0.95
DHT[5]	92/512	1.16 (0.93–1.46)	0.19
AAG	111/683	1.12 (0.94–1.34)	0.21
Estradiol	111/684	1.17 (0.96–1.44)	0.13
Interval <2 yr			
T	39/219	0.91 (0.54–1.51)	0.70
SHBG	39/219	1.18 (0.81–1.74)	0.39
SHBG-adjusted T[4]	39/219	0.75 (0.42–1.35)	0.34
Free T	28/197	1.05 (0.65–1.67)	0.86
DHT[5]	38/213	***1.69 (1.17–2.44)**	***0.005**
AAG	39/219	0.92 (0.66–1.29)	0.63
Estradiol	39/219	1.05 (0.77–1.42)	0.77
Interval ≥2 yr			
T	106/717	0.95 (0.78–1.16)	0.62

	No. events/cases[2]	HR[3]	*p* value
SHBG	106/717	1.19 (0.96–1.46)	0.11
SHBG-adjusted T[4]	106/717	0.80 (0.60–1.08)	0.15
Free T	50/472	0.88 (0.60–1.29)	0.50
DHT[5]	85/492	1.08 (0.84–1.37)	0.56
AAG	106/715	1.04 (0.88–1.23)	0.66
Estradiol	106/717	1.08 (0.86–1.35)	0.51

AAG = androstanediol glucuronide; BMI = body mass index; DHT = dihydrotestosterone; HPFS = Health Professionals Follow-up Study; HR = hazard ratio; PHS = Physicians' Health Study; SHBG = sex hormone binding globulin; T = testosterone.

[1] Free T not measured in PHS.

[2] When possible, men with missing values were included in the analysis using a missing indicator variable. In some subsets the number of men with missing values was too small (≤5%) to ensure model convergence, so these men were excluded from the analysis.

[3] HR: adjusted for age at diagnosis, BMI, physical activity, and smoking status. HR represents change per unit interquartile range in batch-adjusted continuous measure of each hormone.

[4] HR as above but further adjusted for SHBG.

[5] DHT data not available for third HPFS batch.

[6] Analysis not performed due to insufficient sample size for subset.