Androgens, Growth Factors, and Risk of Prostate Cancer: The Multiethnic Cohort

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BACKGROUND. Androgens and growth factors are thought to be associated with prostate cancer risk, although past research has produced mixed results.
METHODS. We conducted a nested case–control study of biomarkers of prostate cancer risk within the Multiethnic Cohort. We compared prediagnostic levels of testosterone, dihydrotestosterone (DHT), sex hormone-binding globulin (SHBG), 3α-androstanediol glucuronide (3α-diol G), insulin-like growth factor I (IGF-I), IGF-II, IGF-binding protein 1 (IGFBP-1), and IGFBP-3 in serum from 467 incident prostate cancer cases and 934 cancer-free controls. Controls were matched to the cases on geographic site (HI, LA), ethnicity, age at specimen collection (±1 year), date (±1 month) and time of day (±2 hr) of sample collection, and fasting status (<6, 6–7, 8–9, >10 hr). Multivariate conditional logistic regression models were used to compute adjusted odds ratios (ORs) and 95% confidence intervals (CIs).
RESULTS. Serum concentrations of testosterone, DHT, SHBG, 3α-diol G, IGF-I, IGF-II, IGFBP-1, and IGFBP-3 were not associated with risk of prostate cancer. Tests for trend of quartiles of serum concentrations also did not show any association. Results were relatively unchanged for men with advanced prostate cancer and their matched controls. However, the follow-up period was relatively short (mean of 1.9 years). Analysis by ethnic group showed an increased risk for Latino men in the second (OR = 3.67, 95% CI: 1.63–8.24) and third (OR = 2.96, 95% CI: 1.19–7.40) tertiles of IGF-I serum levels compared with the first tertile.
CONCLUSIONS. The suggested increased risk for IGF-I in Latino men merits further study, with greater statistical power.

KEY WORDS: **IGFs; androgens; prostate cancer; risk; ethnicity**

INTRODUCTION

Although prostate cancer is the leading cancer among males in the US, there are few established risk factors for this neoplasm. Because hormones and growth factors stimulate cell proliferation and have been linked to other cancers, many research studies have examined the association of androgens and/or growth factors with the risk of prostate cancer. The results, however, have been inconsistent with regard to which, if any, of the androgens and growth factors alter prostate cancer risk. Two recent pooled analyses of 12 [1] and 18 [2] prospective studies, respectively, found no overall association of

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testosterone, dihydrotestosterone (DHT), 3α-androstanediol gluconoride (3α-diol G), and insulin-like growth factor II (IGF-II) with the risk of prostate cancer. However, they did observe a statistically significant negative association of sex hormone-binding globulin (SHBG) with prostate cancer risk and statistically significant positive associations of insulin-like growth factor I (IGF-I) and IGF-binding protein 3 (IGFBP-3) with prostate cancer risk.

In this analysis, we examined serum levels of several androgens and growth hormones—3α-diol G, SHBG, testosterone, DHT, IGF-II, IGF-I, IGFBP-1, and IGFBP-3—in a nested case–control study of prostate cancer. Cases and controls were identified through the prospective Multiethnic Cohort Study of African-Americans, Caucasians, Japanese-Americans, Latinos, and Native Hawaiians.

MATERIALS AND METHODS

Study Population

Details of the Multiethnic Cohort (MEC) were described previously [3]. In brief, data were collected between 1993 and 1996 using a 26-page self-administered mail questionnaire sent to residents of Hawaii and California, mainly Los Angeles County. Subjects were identified through drivers' license records in both locations, supplemented with voter registration records in Hawaii and Health Care Financing Administration (Medicare) files in California. African-Americans, Caucasians, Japanese-Americans, Latinos, and Native Hawaiians were the primary targets for recruitment, but a small number of persons of other ethnicities were also enrolled in the study. Participation in the cohort was limited to people between the ages of 45 and 75 years in 1993, except for Native Hawaiians who were recruited at 42 years and older. The MEC dataset consists of 215,251 people, including 96,382 men. The Institutional Review Boards of both the University of Hawaii and the University of Southern California approved the study.

Biospecimen Subcohort

Participants for this nested case–control study were men from the MEC who had provided prediagnostic blood specimens primarily between 2001 and 2006. Cohort members were contacted by letter, and then by phone, to request biological specimens (blood and urine). For those who agreed, a short screening questionnaire (use of anticoagulants, blood clotting disorders, etc.) and updated information on a few items (including current smoking habits, weight, vitamin supplement use, prostate-specific antigen (PSA)) were administered. Specimens were collected at a clinical laboratory or in the subjects' home and were processed within 4 hr of collection. Blood samples were drawn in a fasting state of eight or more hours for most cases (94%), and were separated into components (serum, plasma, buffy coat, and red cells) and stored in multiple 0.5 cm^3 aliquots in the vapor phase of liquid nitrogen freezers.

Selection of Cases and Controls

Cases of invasive prostate cancer, diagnosed after specimen collection, were identified through linkages with the Los Angeles County Cancer Surveillance Program, the State of California Cancer Registry, and the Hawaii Tumor Registry, all members of the Surveillance, Epidemiology, and End Results program supported by the National Cancer Institute. Advanced prostate cancer cases were defined as: (i) having either regional or distant spread and/or (ii) having a Gleason score ≥ 7 irrespective of tumor stage. A total of 467 prostate cancer cases were identified for this study. Controls were selected among the male biorepository participants who were alive and free of prostate cancer at the age of diagnosis of the case. A control pool that met the matching criteria was created for each case, from which two controls were randomly selected. Matching criteria included geographic site (HI, LA), ethnicity, age at specimen collection (± 1 year), date (± 1 month) and time of day (± 2 hr) of sample collection, and fasting status (<6, 6–7, 8–9, >10 hr).

Assay Methods

Serum levels of testosterone and DHT were measured using radioimmunoassay (RIA) methods [4,5]. After adding appropriate internal standards (^{3}H-testosterone and ^{3}H-DHT) to each sample to follow procedural bases, testosterone and DHT were extracted from the serum using ethyl acetate:hexane (1:1). Following evaporation of the organic solvents, the extract was redissolved in *iso*-octane and applied on a Celite partition column impregnated with ethylene glycol. DHT was eluted from the column with 10% toluene in isooctane, whereas 40% toluene in isooctane was used to elute testosterone. After evaporating the eluates, the residues were reconstituted in assay buffer and aliquots were taken for the RIA procedure and for determining procedural losses. The RIAs for testosterone and DHT utilized specific antisera in conjunction with the appropriate iodinated testosterone or DHT derivative as the radioligand. Testosterone and DHT were incubated for 16–18 hr. Subsequently, separation of antibody-bound testosterone or DHT was achieved by use of a second antibody. After centrifugation, the antibody-bound fraction was counted in a gamma

counter and the concentration of each androgen was calculated and corrected for procedural losses.

3α-Diol G, SHBG, and PSA were quantified by direct immunoassays. 3α-Diol G was measured by RIA using a commercial kit obtained from Beckman-Coulter Diagnostic Systems Laboratories (Webster, TX) [6], whereas SHBG and PSA were measured by chemiluminescent immunoassay on the Immulite analyzer (Siemens Medical Solutions, Los Angeles, CA).

Insulin-like growth factors, including IGF-I, IGF-II, IGFBP-1, and IGFBP-3 were measured by an enzyme-linked immunoabsorbent assay (ELISA) method. The analytic laboratory has validated the IGF-I, IGF-II, IGFBP-1, and IGFBP-3 ELISA methodology using reagents from Diagnostic Systems Laboratories (Webster, TX) against regular RIA s following acid extraction. The results obtained with the ELISA methodology, which is more suitable for large numbers of specimens, were highly correlated with the more labor-intensive methods ($r = 0.82$). All assays were performed with standards and controls that include recombinant proteins, as well as a pooled serum sample. For IGF-I and IGF-II, the absolute sensitivity of the assay was 0.3 ng/ml.

Serum analysis was performed on 394 (84%) cases, 792 (85%) controls for 3α-diol G, 463 (99%) cases, 931 (99%) controls for SHBG, testosterone, and DHT, 326 (70%) cases, 657 (70%) controls for IGF-II and 386 (83%) cases, 777 (83%) controls for IGF-I, IGFBP-1, and IGFBP-3. The percentages vary because of the availability of sample and the requirement of a fasting sample for the growth factor measures. Additionally, IGF-II was not performed on all samples because of the temporary cessation of the assay material by the manufacturer. The intra-assay coefficients of variation were 3.4% for 3α-diol G, 3.0% for SHBG, 3.5% for testosterone, 3.8% for DHT, 1.8% for IGF-II, 2.1% for IGF-I, 2.2% for IGFBP-I, and 2.5% for IGFBP-3.

Statistical Analysis

We applied multivariate conditional logistic regression models of prostate cancer incidence, with case–control matched sets as the strata variable, to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs). We created quartiles for each variable based on the distribution of cases and controls combined, and represented them with three indicator variables. Individual trend variables were created by assigning them the median values of each quartile grouping. We adjusted for the following covariates in our models: body mass index (≤ 25, >25 to ≤ 30, $>30\,kg/m^2$), family history of prostate cancer in father and/or brother(s) (yes, no), years of education (continuous), age at blood draw (continuous), and number of fasting hours prior to blood draw (continuous). The first three variables were selected because they were found to be related to prostate cancer risk or screening in the MEC. The last two variables accounted for any systematic differences in these variables within matched sets. We repeated the analyses using only controls with PSA values less than or equal to 4.0 ng/ml and their matched cases to minimize any potential bias as a result of disease misclassification. We also performed analyses using only advanced prostate cases and their matched controls. Additionally, we performed analyses using tertiles of each variable for the three ethnic groups with adequate sample size (African-Americans, Japanese-Americans, and Latinos). We tested the interaction of ethnicity and BMI ($\geq 25\,kg/m^2$ versus $<25\,kg/m^2$) with the trend variable for each androgen/growth factor variable using the Wald test for the cross-product terms.

RESULTS

Cases and controls had similar median values for all the analytes (Table I), although there were slight variations in median values of IGFBP-3 and IGF-II.

We observed no association between serum 3α-diol G or SHBG and prostate cancer risk (Table II); the ORs for the fourth quartile compared to the first quartile of serum concentration were 1.03 (95% CI: 0.71–1.48) and 0.83 (95% CI: 0.59–1.18), respectively. The ORs for serum concentrations of testosterone and DHT were similar and both were not associated with prostate cancer risk. The ORs were: 0.87 (95% CI: 0.61–1.22) for testosterone, 0.81 (95% CI: 0.57–1.15) for DHT, and 1.04 (95% CI: 0.74–1.48) for the ratio of testosterone to DHT for the fourth quartile compared with the first quartile. Risk estimates for testosterone did not change materially with further adjustment for serum SHBG levels. We observed no trends in risk for any of the hormones or SHBG.

Serum IGF-I concentrations were not associated with prostate cancer risk. However, the ORs across quartiles are not close to the null. Risk estimates for the second, third, and fourth quartiles compared with the first quartile were respectively: 1.43 (95% CI: 0.99–2.06), 0.97 (0.67–1.41) and 1.23 (95% CI: 0.85–1.78). We observed no association of serum IGFBP-I levels and prostate cancer risk. The OR for the fourth quartile compared with the first quartile was close to the null ($OR = 0.98$, 95% CI: 0.65–1.49). The risk estimates for IGF-II increased somewhat across the quartiles, but there was no statistically significant trend (P trend $= 0.36$). The OR for IGF-II was 1.17 (95% CI: 0.78–1.76) for the fourth quartile compared with the first quartile. The results for IGFBP-3 were interesting. We observed a 66% increased risk of prostate cancer

TABLE I. Characteristics of Cases and Controls*

Characteristics	Cases (n = 467)	Controls (n = 936)
Covariates		
Body mass index (kg/m^2), mean (SD)	26.2 (4.0)	26.5 (4.1)
Age at blood draw (years), mean (SD)	68.9 (7.1)	68.7 (7.1)
Fasting hours prior to blood draw, mean (SD)	11.8 (4.8)	11.9 (4.9)
High school education or less, %	34.0	34.4
Family history of prostate cancer, %	12.6	8.3
Ethnicity, %		
African-American	46.9	46.8
Caucasian	13.1	13.1
Japanese-American	18.8	18.8
Latino	17.8	17.7
Native Hawaiian	3.4	3.5
Analytes median (interquartile range)		
Testosterone (ng/dl)	550 (422–689)	541 (425–683)
Dihydrotestosterone (ng/dl)	58 (42–78)	57 (43–75)
3α-Androstanediol glucuronide (ng/ml)	4.71 (3.15–6.69)	4.47 (3.18–6.63)
Sex hormone-binding globulin (nmol/L)	36 (28–45)	35 (27–46)
Insulin-like growth factor I (ng/ml)	182 (148–217)	180 (151–222)
Insulin-like growth factor II (ng/ml)	876 (728–1,039)	900 (744–1,062)
Insulin-like growth factor binding protein 1 (ng/ml)	21 (11–36)	20 (11–38)
Insulin-like growth factor binding protein 3 (ng/ml)	3,892 (3,201–4,664)	3,971 (3,387–4,591)

*Cases and controls were matched on geographic site (Hawaii/Los Angeles, CA), ethnicity, age at specimen collection (±1 year), date (±1 month), and time of day (±2 hr) of sample collection, and fasting status (<6, 6–7, 8–9, >10 hr).

(95% CI: 1.14–2.41) for men in the third quartile of serum IGFBP-3 compared with the first quartile. However, the OR decreased for men in the fourth quartile of serum concentration, OR = 1.15 (95% CI: 0.77–1.71) and there was no trend (P trend = 0.35). The ratio of IGF-I to IGFBP-3 was not associated with risk of prostate cancer; the OR was 0.90 (95% CI: 0.61–1.33) for the fourth quartile compared with the first quartile.

When all of the analyses were restricted to control subjects with PSA values less than or equal to 4.0 and their matched cases, our conclusions were unchanged (data not shown). We also examined effect modification by BMI (<25 and ≥25 kg/m^2) and found no statistical evidence for differences across the strata (data not shown).

We repeated the analyses by ethnic group (Table III) to see whether the findings in Table II appeared consistent. Because of a limited sample size, we were unable to perform analyses on Native Hawaiians and Caucasians. As shown in Table II, serum concentrations of testosterone, DHT, 3α-diol G, and SHBG, were not associated with risk of prostate cancer for African-Americans, Japanese-Americans, or Latinos. However, we observed an increase in risk of prostate cancer with serum IGF-I levels for Latino men; in contrast, African-American men had a decrease in risk of prostate cancer (P interaction for ethnicity < 0.001). Latino men in the second tertile of IGF-I had an OR = 3.67 (95% CI: 1.63–8.24) compared with men in the first tertile of serum IGF-I. The corresponding OR was close to threefold greater for Latino men in the third tertile of IGF-I (OR = 2.96, 95% CI: 1.19–7.40). For African-American men, those in the third tertile of IGF-I serum concentration had a 46% lower risk of prostate cancer (95% CI: 0.32–0.90) compared with men in the first tertile of IGF-I. We observed statistically significant trends in risk estimates for Latino men and African-American men (P trend = 0.02 for both groups). Latino men also had an increased risk of prostate cancer, as IGFBP-3 levels increased (P trend = 0.02). Men in the highest tertile of IGFBP-3 had 2.75 times the risk (95% CI: 1.20–6.32) of prostate cancer compared with men in the first tertile. Like the Latino men, Japanese-American men also had risk estimates above 1, but none were statistically significant. We observed no statistically significant interaction between IGFBP-3 levels and ethnicity, although there was a suggestion of a possible interaction (P interaction = 0.09).

Table IV shows results of an analysis restricted to men with advanced prostate cancer and their matched controls. The lack of association between any of the biomarkers and risk of prostate cancer persisted although the risk estimates were higher for

TABLE II. Odds Ratios and 95% Confidence Intervals for Risk of Prostate Cancer Across Quartiles of Serum Androgens, SHBG and Growth Factors

	Quartiles of serum concentration levels				
Variable	1	2	3	4	*P* trend
Testosterone					
Median level (ng/dl)	348	486	608	832	0.38
No. of cases[a]	111	119	109	113	
Unadjusted OR[b]	1	1.02 (0.73–1.41)	0.93 (0.66–1.3)	0.98 (0.70–1.36)	
Multivariate OR[c]	1	0.98 (0.70–1.37)	0.84 (0.59–1.18)	0.87 (0.61–1.22)	
Dihydrotestosterone					
Median level (ng/dl)	33	50	66	94	0.14
No. of cases	110	120	117	105	
Unadjusted OR	1	1.15 (0.83–1.59)	1.05 (0.75–1.46)	0.91 (0.66–1.27)	
Multivariate OR	1	1.12 (0.80–1.56)	0.97 (0.69–1.37)	0.81 (0.57–1.15)	
Testosterone/dihydrotestosterone ratio					
Median level	6.5	8.6	10.3	13.2	0.95
No. of cases	113	120	106	113	
Unadjusted OR	1	1.12 (0.81–1.53)	0.93 (0.67–1.29)	1.02 (0.72–1.43)	
Multivariate OR	1	1.13 (0.82–1.55)	0.94 (0.67–1.3)	1.04 (0.74–1.48)	
3α-diol G					
Median level (ng/ml)	2.30	3.94	5.52	8.38	0.72
No. of cases	95	110	89	91	
Unadjusted OR	1	1.30 (0.91–1.84)	0.93 (0.65–1.34)	0.97 (0.68–1.39)	
Multivariate OR	1	1.31 (0.92–1.87)	1.00 (0.69–1.44)	1.03 (0.71–1.48)	
SHBG					
Median level (nmol/L)	23	32	40	55	0.42
No. of cases	122	107	109	115	
Unadjusted OR	1	0.84 (0.61–1.15)	0.88 (0.63–1.22)	0.94 (0.67–1.31)	
Multivariate OR	1	0.80 (0.58–1.11)	0.81 (0.58–1.13)	0.83 (0.59–1.18)	
IGF-I					
Median level (ng/ml)	124	166	197	248	0.62
No. of cases	87	108	84	97	
Unadjusted OR	1	1.43 (0.99–2.05)	0.97 (0.67–1.41)	1.19 (0.83–1.72)	
Multivariate OR	1	1.43 (0.99–2.06)	0.97 (0.67–1.41)	1.23 (0.85–1.78)	
IGFBP-1					
Median level (ng/ml)	6.3	15.8	27.9	51.1	0.94
No. of cases	92	99	84	101	
Unadjusted OR	1	1.06 (0.73–1.52)	0.85 (0.58–1.25)	1.11 (0.75–1.66)	
Multivariate OR	1	1.00 (0.69–1.44)	0.78 (0.52–1.16)	0.98 (0.65–1.49)	
IGF-II					
Median level (ng/ml)	627	810	962	1,176	0.36
No. of cases	78	74	78	88	
Unadjusted OR	1	0.94 (0.63–1.38)	1.05 (0.70–1.56)	1.21 (0.81–1.81)	
Multivariate OR	1	0.91 (0.61–1.35)	1.05 (0.70–1.57)	1.17 (0.78–1.76)	
IGFBP-3					
Median level (ng/ml)	2,792	3,626	4,295	5,162	0.35
No. of cases	79	101	109	87	
Unadjusted OR	1	1.42 (0.99–2.04)	1.67 (1.15–2.41)	1.15 (0.78–1.70)	
Multivariate OR	1	1.35 (0.94–1.95)	1.66 (1.14–2.41)	1.15 (0.77–1.71)	
IGF-1/IGFBP-3					
Median level (ng/ml)	0.036	0.043	0.050	0.059	0.34
No. of cases	93	110	89	84	
Unadjusted OR	1	1.27 (0.89–1.81)	0.94 (0.66–1.35)	0.85 (0.58–1.25)	
Multivariate OR	1	1.28 (0.90–1.83)	0.93 (0.64–1.33)	0.90 (0.61–1.33)	

[a]Sample size for cases varies by analyte as a result of differences in the number of samples analyzed for each analyte and due to missing values for some covariates.
[b]Adjusted by conditional logistic regression for matched sets as strata and age at blood draw and fasting hours prior to blood draw as continuous measures.
[c]Adjusted by conditional logistic regression for matched sets as strata and for age at blood draw, fasting hours prior to blood draw, body mass index, family history of prostate cancer, and education as covariates in the log-linear model.

TABLE III. Odds Ratios and 95% Confidence Intervals for Risk of Prostate Cancer by Ethnicity, Across Tertiles of Serum Androgens, SHBG, and Growth Factors

	Tertiles of serum concentration levels									
	African-Americans			Japanese-Americans			Latinos			
Variable	1	2	3	1	2	3	1	2	3	*P* interaction*
Testosterone										
No. of cases	75	68	63	24	28	36	22	30	26	0.21
Multivariate OR[a]	1	0.99 (0.64–1.54)	0.86 (0.54–1.38)	1	0.61 (0.31–1.20)	0.81 (0.42–1.55)	1	1.68 (0.79–3.57)	1.34 (0.61–2.94)	
P-trend		0.51			0.76			0.55		
Dihydrotestosterone										
No. of cases	65	66	75	28	26	34	23	34	21	0.66
Multivariate OR	1	1.02 (0.65–1.61)	0.93 (0.59–1.47)	1	0.73 (0.37–1.45)	1.16 (0.61–2.18)	1	1.81 (0.87–3.79)	1.17 (0.56–2.47)	
P-trend		0.71			0.55			0.82		
Testosterone/dihydrotestosterone ratio										
No. of cases	84	57	65	25	31	32	19	33	26	0.45
Multivariate OR	1	0.89 (0.59–1.36)	1.12 (0.72–1.72)	1	0.88 (0.45–1.72)	0.72 (0.36–1.47)	1	1.53 (0.73–3.21)	1.21 (0.54–2.74)	
P-trend		0.63			0.36			0.81		
3α-diol G										
No. of cases	57	58	59	44	22	12	15	18	24	0.56
Multivariate OR	1	0.84 (0.52–1.37)	0.87 (0.54–1.40)	1	0.78 (0.41–1.47)	0.96 (0.43–2.17)	1	1.40 (0.57–3.44)	1.03 (0.47–2.25)	
P-trend		0.63			0.76			0.82		
SHBG										
No. of cases	66	67	73	24	27	37	29	29	20	0.99
Multivariate OR	1	0.90 (0.58–1.39)	0.99 (0.62–1.58)	1	0.80 (0.40–1.61)	0.84 (0.38–1.85)	1	1.21 (0.62–2.36)	0.82 (0.39–1.71)	
P-trend		0.96			0.73			0.58		
IGF-I										
No. of cases	58	55	39	30	25	27	15	33	21	<0.001
Multivariate OR	1	0.77 (0.47–1.26)	0.54 (0.32–0.90)	1	0.91 (0.46–1.83)	1.11 (0.53–2.35)	1	3.67 (1.63–8.24)	2.96 (1.19–7.40)	
P-trend		0.02			0.75			0.02		
IGFBP-I										
No. of cases	64	54	34	15	18	49	27	25	17	0.21
Multivariate OR	1	1.26 (0.76–2.08)	0.77 (0.43–1.39)	1	0.41 (0.17–1.01)	0.95 (0.41–2.19)	1	0.68 (0.33–1.44)	0.60 (0.25–1.42)	
P-trend		0.34			0.30			0.28		
IGF-II										
No. of cases	53	43	32	18	28	27	15	18	15	0.15
Multivariate OR	1	1.05 (0.62–1.79)	0.91 (0.50–1.67)	1	1.53 (0.71–3.28)	1.10 (0.51–2.37)	1	1.78 (0.75–4.21)	1.52 (0.59–3.88)	
P-trend		0.80			0.94			0.34		
IGFBP-3										
No. of cases	57	55	40	20	31	31	22	21	26	0.09
Multivariate OR	1	1.02 (0.64–1.64)	1.00 (0.57–1.76)	1	1.56 (0.75–3.25)	1.34 (0.64–2.78)	1	1.72 (0.77–3.83)	2.75 (1.20–6.32)	
P-trend		0.98			0.53			0.02		
IGF-I/IGFBP-3										
No. of cases	40	62	50	30	30	22	21	24	24	0.03
Multivariate OR	1	1.73 (1.00–2.97)	0.87 (0.50–1.51)	1	0.90 (0.46–1.74)	1.26 (0.61–2.62)	1	1.23 (0.58–2.62)	2.13 (0.83–5.44)	
P-trend		0.35			0.54			0.12		

[a]Adjusted by conditional logistic regression for matched sets as strata and for age at blood draw, fasting hours prior to blood draw, body mass index, family history of prostate cancer, and education as covariates in the log-linear model.

**P*-value for Wald test of interaction between the three ethnic groups and each biomarker trend variable.

TABLE IV. Odds Ratios and 95% Confidence Intervals for Risk of Advanced Prostate Cancer Across Quartiles of Serum Androgens, SHBG and Growth Factors

	Quartiles of serum concentration levels				
Variable	1	2	3	4	*P* trend
Testosterone					
No. of cases	29	38	33	25	0.79
Multivariate OR[a]	1	1.24 (0.68–2.26)	1.06 (0.55–2.05)	0.96 (0.48–1.95)	
Dihydrotestosterone					
No. of cases	29	34	33	29	0.73
Multivariate OR	1	1.48 (0.76–2.86)	1.66 (0.83–3.29)	0.94 (0.47–1.90)	
Testosterone/dihydrotestosterone ratio					
No. of cases	34	35	31	25	0.52
Multivariate OR	1	1.17 (0.64–2.15)	1.00 (0.53–1.92)	0.84 (0.42–1.68)	
3α-diol G					
No. of cases	13	22	19	19	0.75
Multivariate OR	1	2.22 (0.91–5.43)	1.74 (0.75–4.06)	1.46 (0.60–3.53)	
SHBG					
No. of cases	38	29	32	26	0.44
Multivariate OR	1	0.75 (0.40–1.42)	0.92 (0.50–1.69)	0.71 (0.36–1.40)	
IGF-I					
No. of cases	28	26	25	28	0.38
Multivariate OR	1	1.47 (0.72–3.02)	1.24 (0.63–2.45)	1.39 (0.71–2.72)	
IGFBP-I					
No. of cases	30	24	22	31	0.20
Multivariate OR	1	0.88 (0.42–1.84)	0.71 (0.33–1.54)	1.44 (0.68–3.07)	
IGF-II					
No. of cases	21	12	14	11	0.16
Multivariate OR	1	0.35 (0.13–0.94)	0.77 (0.28–2.13)	0.40 (0.14–1.14)	
IGFBP-3					
No. of cases	36	28	30	13	0.57
Multivariate OR	1	1.15 (0.61–2.19)	1.95 (0.97–3.92)	0.53 (0.23–1.23)	
IGF-I/IGFBP-3					
No. of cases	17	34	23	33	0.44
Multivariate OR	1	2.33 (1.08–5.00)	1.40 (0.67–2.89)	1.75 (0.79–3.87)	

[a]Adjusted by conditional logistic regression for matched sets as strata and for age at blood draw, fasting hours prior to blood draw, body mass index, family history of prostate cancer, and education as covariates in the log-linear model.

DHT, 3α-diol G, IGF-I, and the ratio of IGF-I/IGFBP-3 and lower for IGF-II compared with those in Table II. Risk estimates remained relatively similar for SHBG, testosterone, testosterone/DHT ratio. For IGFBP-3, the risk estimate decreased when restricted to the advanced prostate cancer cases and their matched controls; the lack of association remained. Although we observed changes in the values of risk estimates for the advanced prostate cancer cases, we observed no statistically significant trends.

DISCUSSION

In this study, we observed no clear associations between serum levels of testosterone, DHT, 3α-diol G, SHBG, IGF-I, IGF-II, IGFBP-1, and IGFBP-3 and the risk of prostate cancer. We did observe an interaction between ethnicity and levels of IGF-I; Latino men were at increased risk of prostate cancer and African-American men had a decreased risk of prostate cancer. Latino men also had a higher risk of prostate cancer with increasing levels of IGFBP-3. Our overall findings were relatively unchanged when analyses were restricted to controls with normal PSA values and their matched cases. Analyses restricted to advanced prostate cancer cases and their matched controls did not change the overall conclusions although some risk estimates were higher.

Our null results for 3α-diol G agree with several prospective studies [7–13] that also found no association with prostate cancer. One study [13] did find an inverse association with aggressive prostate cancer cases ≥65 years old (OR = 0.52, 95% CI: 0.28–0.97). In contrast, the risk estimates for our advanced cases were

all greater than 1.0, although none were statistically significant. Serum testosterone, DHT and SHBG levels were not associated with the risk of prostate cancer in this study, a finding that is consistent with the results of several prospective studies of testosterone [7–18], DHT [7,9,11,16], and SHBG [7–15,17,18]. Three prospective studies also examined the ratio of testosterone to DHT. Two studies [7,16] reported no association with prostate cancer, in concordance with our results, while the Physician's Health Study [11] observed an increase in risk of prostate cancer (OR = 2.35, 95% CI: 1.22–4.53 for the fourth quartile compared with the first). The discrepancy of this finding compared with other studies, including ours, could be due to differences in the hormone levels of the study populations. For example, the median value for the fourth quartile of testosterone in the Physician's Health Study was slightly lower than the median value in this study (7.02 and 8.32 ng/ml, respectively) and the median value of the fourth quartile of DHT was much lower in the Physician's Health Study (0.68 ng/ml) compared with this study (0.94 ng/ml). Furthermore, this difference remained when we restricted our comparison to white cases in this study (mean DHT level of 0.59 ng/ml compared with a mean of 0.34 ng/ml in the Physician's Health Study). Therefore, the values for the testosterone to DHT ratios would be very different. One possible explanation for the differences may be attributed to differences in assay methodology. In this study, testosterone and DHT were measured in the same aliquot of serum by RIA with preceding extraction and chromatography steps whereas in the Physicians' Health Study, testosterone was measured by direct RIA with a commercial kit and DHT was measured by RIA with preceding purification steps similar to the ones we used.

This study observed no overall association between IGF-I levels and risk of prostate cancer. Other prospective studies [19–24] are in agreement with our null results. However, the Physician's Health Study [25] results were again discrepant, with an increased risk of advanced prostate cancer (RR = 5.1, 95% CI: 2.0–13.2) for men in the fourth quartile compared with men in the first quartile. Our risk estimates for IGF-I were greater than 1.0 for men with advanced prostate cancer; however, none of the estimates were statistically significant. We did, however, observe a statistically significant positive association of IGF-I and prostate cancer among Latino men and a statistically significant inverse association among African-American men. We did perform the analysis restricting cases (and their matched controls) to those with blood drawn more than a year before diagnosis, but the results did not change materially. A case–control study [26] of African-American men and prostate cancer reported a non-statistically significant inverse association (OR = 0.67, 95% CI: 0.29–1.50) for the fourth quartile of serum IGF-I compared with the first quartile. However, as the blood was collected post-diagnostically, this may reflect reverse causation. No other prospective research studies with results for African-American or Latino men were found. Therefore, our results for IGF-I should be interpreted with caution until more research is carried out.

The role of IGF-I in the development of prostate cancer remains debatable. It may be that early studies, such as the Physician's Health Study, which took place before PSA screening was commonplace observed the association of growth factors with risk for progression to clinical significance rather than risk of prostate cancer diagnosis. A recent pooled analysis [1] concluded that high circulating IGF-I levels are associated with an increase in risk of prostate cancer (OR = 1.38, 95% CI: 1.19–1.60), but results from most prospective studies, taken separately, showed no association implying that the association may be weak [19–24]. Our observed increased risk for Latino men is interesting. The Latino men in this study had the lowest mean IGF-I levels of all ethnic groups (176 ng/ml compared with 186 ng/ml for African-American men and 185 ng/ml for Japanese-American men) which is contrary to the current belief that high IGF-I levels should be related to increased risk of prostate cancer because of IGF-I's cell proliferative and anti-apoptotic effects. Furthermore, it was the African-American group, not the Latinos that made up the majority of our advanced prostate cancer cases, another inconsistency that is hard to reconcile with the strong positive results from the Physicians Health Study [25], given that IGF-I had a negative association with prostate cancer for the African-Americans.

We observed no association between IGFBP-3 and the risk of prostate cancer. Several prospective studies support our null findings [19,20,23,24,27]. However, two studies [21,22] reported a positive association between prostate cancer and IGFBP-3 levels. The Health Professionals Follow-up Study reported a 62% increased risk of prostate cancer (95% CI: 1.07–2.46) for men in the fourth quartile of serum IGFBP-3 compared with men in the first quartile [21]. Results from the Melbourne Collaborative Cohort study [22] also showed an increased risk of prostate cancer for men in the fourth quartile of serum IGFBP-3 compared with the first quartile (HR: 1.49, 95% CI: 1.11–2.00). The reasons for the discrepancies in research of IGFBP-3 and prostate cancer are difficult to pinpoint. Both positive studies reported mean or median IGFBP-3 plasma levels lower than ours, but that is probably not the source of the differences in results because studies that have null results had similar

IGFBP-3 values to the studies that found associations [19,20,24,27].

Few prospective studies have examined levels of IGFBP-I and IGF-II. A prospective study of Chinese men with prostate cancer [28] reported no associations of IGFBP-I or IGF-II and risk of prostate cancer, a finding confirmed by our results.

This study had several strengths. It is a prospective study and specimens were collected before prostate cancer diagnosis. We were able to examine the consistency of risk estimates for three ethnic groups: African-Americans, Latinos, and Japanese-Americans. Other prospective studies consisted mainly of Caucasian men. A limitation of this study was the lack of power in the analysis of advanced prostate cancer and the analysis by ethnic groups.

Overall, this study found no association of testosterone, DHT, 3α-diol G, SHBG, IGF-I, IGF-II, IGFBP-1, and IGFBP-3 and the risk of prostate cancer. The observed negative association of IGF-I with prostate cancer in African-Americans and the positive association of IGF-I with prostate cancer in Latino men are interesting, but need to be validated in other studies.

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