

Research Article

Insulin-Like Growth Factors and Insulin-Like Growth Factor-Binding Proteins and Prostate Cancer Risk: Results from the Prostate Cancer Prevention Trial

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Abstract

The role of the insulin-like growth factor (IGF) axis and whether IGFs interact with androgen-suppressing agents in relation to prostate carcinogenesis is unclear. This nested case-control study ($n = 1,652$ cases/1,543 controls) examined whether serum IGF1, IGF2, IGFBP2, IGFBP3, and the IGF1:IGFBP3 ratio were associated with prostate cancer in the Prostate Cancer Prevention Trial (PCPT), a randomized, placebo-controlled trial of finasteride for prostate cancer prevention. Presence or absence of cancer was determined by prostate biopsy. Baseline serum was assayed for IGF-axis analytes using ELISA. Logistic regression estimated ORs and 95% confidence intervals for risk of total, low-grade (Gleason 2–6) and high-grade (Gleason 7–10) cancers. Results were stratified by intervention assignment. In both the placebo and finasteride arms, serum IGF1, IGF2, IGFBP3, and the IGF1:IGFBP3 ratio were not associated with prostate cancer. However, men in the highest versus lowest quartile of serum IGFBP2 had a 48% ($P_{\text{trend}} = 0.02$) and 55% ($P_{\text{trend}} = 0.01$) increased risk for total and low-grade cancers, respectively. These IGFBP2 associations were attenuated and no longer statistically significant in the finasteride arm. Our results suggest that in general, serum IGF-axis analytes were not associated with prostate cancer risk in the PCPT in which presence or absence of all cancers was biopsy-determined. The exception was the finding that high serum IGFBP2 is a risk factor for low-grade disease, which was attenuated for men on finasteride. Further research is needed to understand better the risk incurred by high IGFBP2 and whether androgen-suppressing agents such as finasteride influence aspects of IGFBP2 physiology relevant to prostate carcinogenesis. *Cancer Prev Res*; 6(2); 91–99. ©2013 AACR.

Introduction

The insulin-like growth factors (IGF) are potent mitogens and antiapoptotic factors (1). Unlike other regulatory peptides, they have characteristics of both tissue growth factors and circulating growth hormones. Thus, while they are expressed in many tissues in which they have local actions, they are also present in the circulation, in which levels are physiologically regulated and vary with both genetic and lifestyle factors (2). The bioactivity of IGFs is modulated by a

family of high-affinity binding proteins (IGFBPs), which are also expressed in most tissues and are present in the circulation (3).

Relationships between circulating concentrations of IGFs and IGFBPs with cancer risk in general and prostate cancer risk in particular have been investigated for more than a decade. The first prospective study related to prostate cancer, based on the Physicians' Health Study cohort, showed an approximate 4-fold increase in risk from the lowest to highest quartile of serum IGF1 concentrations, and decreased risk with increasing serum IGFBP3 concentrations (4) but did not investigate IGFBP2 or the IGF1:IGFBP3 molar ratio. Many (5–11), but not all (12, 13), subsequent studies confirmed increased risk of prostate cancer with increasing serum IGF1 concentrations, although the effect size was considerably lower than that observed in the original Physicians' Health Study. The European Prospective Investigation into Cancer and Nutrition (EPIC) recently reported a prostate cancer OR of 1.69 for men in the highest versus the lowest quartile of serum IGF1, but no other IGF-axis analytes were reported (14). The Endogenous Hormones and Prostate Cancer Collaborative Group pooled data from 12 prospective cohort studies to examine

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associations of serum IGF1, IGF2, IGFBP2, and IGFBP3 with prostate cancer risk (15). Men in the top quintile of serum IGF1 had a modest, but significant, increased risk of prostate cancer compared with the lowest quintile [OR = 1.38; 95% confidence interval (CI), 1.19–1.60; $P_{\text{trend}} < 0.001$; ref. 15]. The authors noted marked heterogeneity across the studies for associations of serum IGFBP3 with prostate cancer risk, consistent with previous findings showing considerable variation across studies with respect to the direction and magnitude of association of IGFBPs with prostate cancer risk (5, 7, 9). Still, the pooled OR for IGFBP3 reported by the Collaborative group was modestly elevated (OR = 1.23; 95% CI, 1.06–1.43; ref. 15). The Collaborative group found no association of serum IGF2 or IGFBP2 with prostate cancer risk, but fewer data were available on these analytes, thereby limiting power to detect associations (15).

Here, we examine associations of serum concentrations of IGF1, IGF2, IGFBP2, IGFBP3, and the IGF1:IGFBP3 ratio with prostate cancer risk using a nested case–control study in the Prostate Cancer Prevention Trial (PCPT) in both the intervention and placebo arms of the trial (16). Despite the strong biologic plausibility and the many studies that have previously examined associations of IGF-axis analytes and prostate cancer risk, several aspects of the PCPT are unique rendering it an optimal setting in which to examine these and other questions about prostate cancer risk. Specifically, willing and eligible men ($n = 9,060$ of 18,882 PCPT participants) had a prostate biopsy either during or at the conclusion of the study to detect the presence or absence of prostate cancer. The remaining participants did not have a biopsy due to the early cessation of the trial or because they elected not to undergo a biopsy (16). For those with biopsies, centralized and uniform pathologic grading was used to categorize prostate cancer endpoints. While almost all prostate cancer cases in PCPT were diagnosed as local stage, detection bias was minimized and pathologic grading of cases was rigorous and standardized. In addition, we have the important opportunity within this randomized controlled trial to test whether associations of IGF analytes with prostate cancer risk varies by randomization to the PCPT intervention agent, finasteride (a 5- α -reductase inhibitor), or placebo.

Materials and Methods

Study design and study population

The PCPT was a randomized, placebo-controlled trial testing whether the 5- α -reductase inhibitor, finasteride, could reduce the 7-year period prevalence of prostate cancer. Details about study design and participant characteristics have been described previously (16). Briefly, at 221 clinical centers across the United States 18,880 men of ages 55 years and older with a normal digital rectal examination (DRE) and prostate-specific antigen (PSA) level 3.0 ng/mL or less, as well as no history of prostate cancer, severe benign prostatic hyperplasia, or clinically significant comorbid conditions that would have precluded successful completion of the study protocol, were randomized to receive finasteride (5 mg/d) or placebo. During the course of the

PCPT, men underwent annual DRE and PSA measures and a prostate biopsy was recommended for all men with an abnormal DRE or a finasteride-adjusted PSA of 4.0 ng/mL or more (17). At the final study visit, all men without a previous diagnosis of prostate cancer were offered an end-of-study biopsy. Biopsies were collected under transrectal ultrasonographic guidance and a minimum of 6 biopsy specimens (cores) were collected from each participant. All biopsies were reviewed both by a local study pathologist and a central study pathologist (18, 19). Discordant pathology interpretations were arbitrated by a referee pathologist and concordance was achieved in all cases (16, 18, 19). Pathologists were blinded to the randomization arm of all participants. Tumors were graded with the Gleason system by central pathology review at the Prostate Diagnostic Laboratory (Denver, CO). Study procedures were approved by Institutional Review Boards at each of the participating clinical centers, the Southwest Oncology Group (SWOG, San Antonio, TX) and the SWOG Statistical Center (Fred Hutchinson Cancer Research Center, Seattle, WA). All men signed informed consent. An independent data safety and monitoring committee met every 6 months throughout the course of the trial to review data on safety, adherence, and diagnosis of prostate cancer (16).

This report presents data from a nested case–control study in the PCPT. Cases were men with biopsy-determined prostate cancer identified either during a for-cause interim biopsy prompted by abnormal DRE or elevated PSA or an end-of-study biopsy (for-cause and not for-cause) and who had baseline serum available for analysis ($n = 1,803$). Tumors were classified as low-grade = Gleason 2–6; high-grade = Gleason 7–10 as was done in the original trial report (16). Controls were selected from men who completed the end-of-study biopsy procedure, had no evidence of prostate cancer and had available baseline serum samples ($n = 1,797$). Controls were frequency matched to cases by age (in 5-year age groups), PCPT treatment arm (finasteride vs. placebo), and positive family history for first-degree relative with prostate cancer. Controls were oversampled to include all eligible non-White men. Men with self-reported diabetes, reported at any time before cancer diagnosis or negative biopsy, were further excluded from these analyses due to dysregulation of the insulin and IGF-axis among diabetics (20, 21) leaving $n = 1,652$ cases and $n = 1,543$ controls for analysis.

Data collection

Blood collection and processing. Nonfasting blood specimens were collected at screening (approximately 3 months before randomization) and yearly thereafter. Venous blood was drawn into collection tubes without anticoagulant, refrigerated, and shipped via overnight courier to the PCPT specimen repository in which they were centrifuged, aliquotted, and stored at -70°C until analysis (22).

Laboratory analysis. Concentrations of IGF1, IGF2, IGFBP2, and IGFBP3 were assayed in the baseline serum samples with a standard ELISA using a single production lot of reagents (Diagnostic Systems Limited, Webster, TX). All

assays were conducted in duplicate and the mean of the duplicate measures are reported. Two sets of quality control (QC) samples (from pooled specimens) were included for quality control and the coefficients of variation from these QC pools were as follows: IGF1 (7.1% and 5.3%), IGF2 (5.0% and 4.2%), IGFBP2 (5.5% and 8.9%), and IGFBP3 (4.2% and 4.8%). Laboratory technicians were blinded to both the randomization assignment and case-control status of all participants. The primary analyses in this report are from baseline measures of the entire case-control sample. Year 2 serum samples from a randomly selected subset of $n = 244$ participants (121 cases and 123 controls) were used to assess potential finasteride associated change in IGF-axis analytes.

Other data. Demographic characteristics, personal medical history, family history of prostate cancer, and lifestyle habits, such as smoking, usual diet, alcohol, and physical activity habits were collected by self-report at baseline. The measurement characteristics of many of these self-assessment tools are published (23–25). Height and weight were assessed at the baseline clinic visit using a standard protocol (26) and weight was assessed annually thereafter. Body mass index (BMI) was computed as [weight (kg)/height (m²)] and standard cutoff points categorized BMI as normal = BMI < 25.0 kg/m²; overweight = BMI 25.0 to <30.0 kg/m²; and obese = BMI ≥30.0 kg/m² (27). Circumferences of the abdomen, waist, hip, and thigh were measured at 1-year postrandomization (28). As the body circumference measurements were voluntary, some clinical centers did not participate, resulting in missing data for 10% ($n = 319$) of the participants.

Statistical analysis

We compared baseline demographic and lifestyle characteristics of prostate cancer cases and controls by t tests for continuous variables and χ^2 tests for categorical variables. We compared baseline and year 2 serum concentrations of IGF-axis analytes using a paired t test in the subset of participants who had values at both time points. We used logistic and polytomous logistic regression models to estimate associations of serum IGF1, IGF2, IGFBP2, IGFBP3, and the IGF1:IGFBP3 molar ratio with risks of total, low-grade, and high-grade prostate cancer. Results are given separately for the finasteride and the placebo arms because we hypothesized *a priori* that finasteride treatment could modify associations between the IGF-axis and prostate cancer risk. Models were adjusted for the matching factors (age, family history of first-degree relative with prostate cancer), the oversampling of non-White men, and other covariates selected on the basis of *a priori* information (age, race, family history) and evidence for potential confounding in this cohort based on our data diagnostics procedures (protein intake, smoking, BMI; refs. 29–31). The final covariates were age, race (White/non-White), family history of prostate cancer, protein intake (g/d, continuous), BMI (continuous), and cigarette smoking (pack-years of smoking). Other variables examined, but determined noninfluential on the results and

therefore not included, were physical activity, education, waist circumference, and waist:hip ratio. Serum concentrations of IGFs and IGFBPs were categorized into quartiles based on the distribution in the controls. Tests for linear trend across the quartiles were based on an ordinal variable taking values of 1, 2, 3, and 4 corresponding to rank from lowest to highest category (32). Exploratory analyses used the Wald test to investigate multiplicative interactions by entering cross-product terms of IGF-axis analytes with treatment arm. These subgroup analyses examined whether risk estimates differed between for-cause and not-for-cause cancers, when stratified by BMI (<25.0, 25.0–29.9, ≥30.0 kg/m²) and when stratified by

Table 1. Demographic, health and lifestyle characteristics of PCPT prostate cancer cases and controls ($n = 3,195$)

Characteristic ^a	Cases ($n = 1,652$)	Controls ($n = 1,543$)
	Mean (SD)	
Age, y	63.6 (5.6)	63.6 (5.6)
Waist circumference, cm	101.2 (9.8)	101.4 (10.3)
Height, inches	70 (2.9)	69.8 (2.8)
Waist:hip ratio	1.0 (0.1)	1.0 (0.1)
Smoking, pack-years	13.8 (16.2)	14.9 (16.8)
Alcohol intake, g/d	10.1 (15.5)	9.3 (13.8)
Protein intake, g/d	92.8 (37.6)	92.7 (37.9)
Dairy intake, svg/wk	10.3 (8.8)	9.7 (8.2)
	n (%)	
Race/ethnicity		
White	1,541 (93.3)	1,268 (82.2)
Non-White	111 (6.7)	275 (17.8)
Family history of prostate cancer	358 (21.7)	338 (21.9)
BMI, kg/m ²		
Normal (<25.0)	485 (29.6)	413 (27.0)
Overweight (25.0–29.9)	848 (51.8)	821 (53.8)
Obese (≥30.0)	304 (18.6)	293 (19.2)
Education		
High school or less	271 (16.4)	290 (18.8)
Some college	444 (26.9)	453 (29.4)
Graduate/professional school	927 (56.7)	799 (51.8)
Alcohol intake		
Nondrinker	344 (20.8)	336 (21.8)
<30 g/d	1,151 (69.7)	1,072 (69.5)
≥30 g/d	157 (9.5)	135 (8.7)
Prostate cancer characteristics		
Low grade (Gleason 2–6)	1,138 (68.9)	N/A
High grade (Gleason 7–10)	445 (26.9)	N/A

^aAll characteristics were assessed at baseline, excluding dietary intake (protein, dairy, alcohol), waist circumference and hip circumference, which were assessed at year 1.

Table 2. Baseline and year 2 comparisons of serum IGF-axis analytes in cases and controls by PCPT intervention arm^a

Analyte	n	Finasteride		n	Placebo		P value ^b
		Baseline	Follow-up		Baseline	Follow-up	
IGF1, ng/mL							
Controls	57	223.3 (203.9, 242.7)	204.9 (188.9, 221.0)	66	192.3 (177.5, 207.1)	189 (175.2, 202.7)	0.03
All prostate cancer	56	212.7 (195.0, 230.4)	199.2 (185.4, 212.9)	65	202.1 (188.4, 215.7)	198.6 (183.3, 213.8)	0.16
High-grade prostate cancers	24	207.8 (182.9, 232.6)	197.7 (172, 223.4)	14	208.5 (181.2, 235.8)	195.8 (162.5, 229.1)	0.79
IGF2, ng/mL							
Controls	57	1,779.0 (1,666.5, 1,891.5)	1,696.3 (1,585.1, 1,807.4)	66	1,679.2 (1,554.9, 1,803.4)	1,584.6 (1,455.9, 1,713.4)	0.79
All prostate cancer	56	1,657.8 (1,551.4, 1,764.2)	1,601.8 (1,501.5, 1,702.2)	65	1,743.3 (1,644.8, 1,841.8)	1,671.1 (1,567.1, 1,775)	0.68
High-grade prostate cancer	24	1,695.6 (1,536.3, 1,854.9)	1,587.9 (1,434.7, 1,741.1)	14	1,934.7 (1,755.4, 2,114.1)	1,856.1 (1,663.1, 2,049)	0.70
IGFBP2, ng/mL							
Controls	57	557.2 (473.0, 641.4)	592.5 (486.8, 698.1)	66	586.2 (510.7, 661.8)	660.3 (576.3, 744.3)	0.31
All prostate cancer	56	608.9 (510.7, 707.1)	662.9 (553.2, 772.6)	65	536.5 (458, 614.9)	601.7 (515.4, 688.0)	0.75
High-grade prostate cancer	24	594.1 (416.6, 771.5)	616.5 (452.0, 781.0)	14	515.0 (388.1, 642.0)	524.4 (415.0, 633.8)	0.78
IGFBP3, ng/mL							
Controls	57	4,221.1 (3,953.8, 4,488.5)	3,934.4 (3,677, 4,191.8)	66	3,882.1 (3,607.2, 4,156.9)	3,694.1 (3,414.4, 3,973.8)	0.28
All prostate cancer	56	3,962.9 (3,706.4, 4,219.4)	3,802.8 (3,561.9, 4,043.8)	65	4,029.0 (3,800.7, 4,257.3)	3,890.5 (3,639.8, 4,141.2)	0.79
High-grade prostate cancer	24	4,000.7 (3,582.2, 4,419.1)	3,848.7 (3,459.3, 4,238.1)	14	4,486.3 (4,107.9, 4,864.6)	4,191.8 (3,700.9, 4,682.8)	0.43

^an = 244 randomly selected participants had follow-up measures using bloods drawn at year 2. Values are means (95% CI).

^bP values are from *t* tests comparing change from baseline with follow-up values between finasteride and treatment arms.

baseline serum PSA (for IGFBP3 only since PSA cleaves IGFBP3). All statistical tests were 2-sided with $P < 0.05$ considered statistically significant. SAS (version 9.2) was used for all statistical analyses.

Results

Table 1 gives demographic and health-related characteristics of the study population by case-control status. Because of the sampling design for this nested case-control study, there were more non-White controls compared with cases and no differences between cases and controls with respect to the matching factors of age, family history of prostate cancer, and intervention arm. Cases and controls did not differ by measures of adiposity (BMI, body circumferences), dietary intake of dairy and protein or alcohol use, and smoking history, but a greater proportion of cases had advanced college degrees compared with controls. Two thirds (68.9%) of prostate cancer cases were low-grade (Gleason < 7).

Table 2 compares finasteride versus placebo baseline with year 2 values for serum IGF1, IGF2, IGFBP2, and IGFBP3 (mean and 95% CI). Serum concentrations of IGF1 decreased from baseline to year 2 significantly more among controls on finasteride than on placebo ($P = 0.03$). Decreases in serum IGF1 were of suggestively greater magnitude for all prostate cancer cases on finasteride compared with placebo ($P = 0.16$), but there were no differences for high-grade disease. There were no other differences in

baseline to follow-up measures of IGF-axis analytes by study arm in either cases or controls.

Table 3 gives associations of serum concentrations of IGF1, IGF2, IGFBP3, IGFBP2, and the IGF1:IGFBP3 molar ratio with total, low-grade, and high-grade prostate cancer risk stratified by PCPT treatment arm (placebo or finasteride). In both the placebo and finasteride arms, we found no associations between serum IGF1, IGF2, IGFBP3, and the IGF1:IGFBP3 with prostate cancer risk. However, higher versus lower serum IGFBP2 was associated with a 48% increased risk ($P_{\text{trend}} = 0.02$) of total prostate cancer and a 55% increased risk ($P_{\text{trend}} = 0.01$) of low-grade prostate cancer for men randomized to placebo. These associations were attenuated and no longer statistically significant for men using finasteride. Despite these differences in risk estimates by PCPT treatment arm, none of the P values was statistically significant from the models testing the interaction of IGF analytes with treatment in relation to prostate cancer risk.

Additional subgroup analyses revealed neither differences between cases diagnosed for-cause and not-for-cause nor any differences by BMI or baseline PSA in either the placebo or finasteride arms (data not shown).

Discussion

In the PCPT, the majority of prostate cancer cases were low-grade and asymptomatic and the presence or absence of all cancers was determined by prostate biopsy. Neither

Table 3. Associations between serum IGF1, IGF2, IGFBP3, and IGF1:IGFBP3 with risk of total and high-grade prostate cancer by treatment arm in the PCPT

	ORs (95% CI)				<i>P</i> _{trend}
	Serum IGF1 (ng/mL) ^a				
	Q1 <167.1 ng/mL	Q2 167.1 to <203.7 ng/mL	Q3 203.7 to <250.2 ng/mL	Q4 ≥250.2 ng/mL	
Placebo					
All cases	1.0 (ref.)	0.89 (0.67–1.20)	1.10 (0.83–1.45)	1.06 (0.79–1.42)	0.39
No. of cases	184	179	240	210	
Gleason 2–6	1.0 (ref.)	0.83 (0.60–1.14)	1.07 (0.79–1.45)	1.11 (0.81–1.52)	0.24
No. of cases	138	129	181	172	
Gleason 7–10	1.0 (ref.)	1.14 (0.70–1.86)	1.28 (0.80–2.05)	0.90 (0.53–1.53)	0.90
No. of cases	37	42	52	31	
Finasteride					
All cases	1.0 (ref.)	0.92 (0.66–1.30)	1.24 (0.88–1.76)	1.02 (0.73–1.43)	0.55
No. of cases	134	142	157	160	
Gleason 2–6	1.0 (ref.)	0.92 (0.62–1.37)	1.31 (0.88–1.95)	1.05 (0.71–1.55)	0.45
No. of cases	76	82	97	98	
Gleason 7–10	1.0 (ref.)	0.95 (0.61–1.49)	1.15 (0.72–1.82)	0.96 (0.61–1.51)	0.96
No. of cases	53	56	54	55	
<i>P</i> values for interaction tests (treatment × IGF1) were 0.87 (all cancers), 0.90 (Gleason 2–6), and 0.87 (Gleason 7–10)					
	Serum IGF2 (ng/mL) ^a				<i>P</i> _{trend}
	Q1 <1,448.3 ng/mL	Q2 1,448.3 to <1,722.3 ng/mL	Q3 1,722.3 to <1,999.7 ng/mL	Q4 ≥1,999.7 ng/mL	
	Placebo				
All cases	1.0 (ref.)	1.23 (0.92–1.63)	1.22 (0.92–1.63)	1.13 (0.84–1.52)	0.46
No. of cases	167	214	230	202	
Gleason 2–6	1.0 (ref.)	1.19 (0.87–1.62)	1.21 (0.89–1.65)	1.13 (0.82–1.56)	0.48
No. of cases	125	160	177	158	
Gleason 7–10	1.0 (ref.)	1.27 (0.78–2.07)	1.18 (0.72–1.92)	1.08 (0.65–1.81)	0.85
No. of cases	37	44	44	37	
Finasteride					
All cases	1.0 (ref.)	0.99 (0.71–1.40)	1.14 (0.81–1.59)	1.02 (0.73–1.44)	0.70
No. of cases	132	144	164	153	
Gleason 2–6	1.0 (ref.)	1.19 (0.80–1.77)	1.29 (0.87–1.91)	1.13 (0.76–1.69)	0.52
No. of cases	70	92	99	92	
Gleason 7–10	1.0 (ref.)	0.80 (0.51–1.27)	1.01 (0.65–1.57)	0.93 (0.59–1.47)	0.99
No. of cases	55	48	60	55	
<i>P</i> values for interaction tests (treatment × IGF2) were 0.87 (all cancers), 0.90 (Gleason 2–6), and 0.95 (Gleason 7–10)					
	Serum IGFBP3 (ng/mL) ^b				<i>P</i> _{trend}
	Q1 <3,418.2 ng/mL	Q2 3,418.2 to <3,997.7 ng/mL	Q3 3,997.7 to <4,644.2 ng/mL	Q4 ≥4,644 ng/mL	
	Placebo				
All cases	1.0 (ref.)	1.03 (0.76–1.38)	1.12 (0.82–1.54)	1.02 (0.71–1.47)	0.77
No. of cases	174	197	226	216	
Gleason 2–6	1.0 (ref.)	1.01 (0.73–1.39)	1.08 (0.77–1.51)	0.99 (0.67–1.46)	0.95
No. cases	129	150	172	169	
Gleason 7–10	1.0 (ref.)	1.01 (0.60–1.68)	1.30 (0.77–2.22)	1.10 (0.59–2.05)	0.56
No. of cases	39	37	47	39	

(Continued on the following page)

Table 3. Associations between serum IGF1, IGF2, IGFBP3, IGF1:IGFBP3 with risk of total and high-grade prostate cancer by treatment arm in the PCPT (Cont'd)

	Serum IGFBP3 (ng/mL) ^b				
	Q1 <3,418.2 ng/mL	Q2 3,418.2 to <3,997.7 ng/mL	Q3 3,997.7 to <4,644.2 ng/mL	Q4 ≥4,644 ng/mL	
Finasteride					
All cases	1.0 (ref.)	0.86 (0.60–1.23)	1.22 (0.83–1.78)	1.23 (0.79–1.91)	0.16
No. of cases	134	130	170	159	
Gleason 2–6	1.0 (ref.)	0.91 (0.60–1.38)	1.34 (0.87–2.08)	1.30 (0.78–2.17)	0.14
No. of cases	75	78	105	95	
Gleason 7–10	1.0 (ref.)	0.82 (0.50–1.32)	1.08 (0.65–1.80)	1.30 (0.72–2.34)	0.25
No. of cases	54	47	57	60	
<i>P</i> values for interaction tests (treatment × IGFBP3) were 0.98 (all cancers), 0.89 (Gleason 2–6), and 0.92 (Gleason 7–10)					
	Serum IGFBP2 (ng/mL) ^c				
	Q1 <318.2 ng/mL	Q2 318.2 to <466.9 ng/mL	Q3 466.9 to <675.9 ng/mL	Q4 ≥675.9 ng/mL	
Placebo					
All cases	1.0 (ref.)	1.20 (0.90–1.61)	1.33 (0.98–1.81)	1.48 (1.06–2.06)	0.02
No. of cases	169	212	205	227	
Gleason 2–6	1.0 (ref.)	1.21 (0.88–1.66)	1.40 (1.00–1.96)	1.55 (1.08–2.22)	0.01
No. of cases	123	158	162	177	
Gleason 7–10	1.0 (ref.)	1.42 (0.88–2.31)	1.19 (0.70–2.04)	1.40 (0.79–2.49)	0.40
No. of cases	37	50	35	40	
Finasteride					
All cases	1.0 (ref.)	1.16 (0.81–1.67)	0.89 (0.61–1.30)	1.16 (0.77–1.73)	0.77
No. of cases	124	149	147	173	
Gleason 2–6	1.0 (ref.)	1.09 (0.73–1.65)	0.76 (0.49–1.18)	1.16 (0.73–1.84)	0.81
No. of cases	77	88	79	109	
Gleason 7–10	1.0 (ref.)	1.35 (0.82–2.20)	1.19 (0.71–1.98)	1.25 (0.72–2.17)	0.60
No. of cases	41	56	62	59	
<i>P</i> values for interaction tests (treatment × IGFBP2) were 0.64 (all cancers), 0.46 (Gleason 2–6), and 0.47 (Gleason 7–10)					
	IGF1:IGFBP3 ^a				
	Q1 <0.045 ng/mL	Q2 0.045 to <0.052 ng/mL	Q3 0.052 to < 0.059 ng/mL	Q4 ≥0.059 ng/mL	
Placebo					
All cases	1.0 (ref.)	0.92 (0.70–1.22)	0.89 (0.67–1.17)	1.07 (0.80–1.42)	0.77
No. of cases	202	206	204	201	
Gleason 2–6	1.0 (ref.)	0.81 (0.60–1.10)	0.85 (0.63–1.15)	1.11 (0.82–1.50)	0.48
No. of cases	157	143	156	164	
Gleason 7–10	1.0 (ref.)	1.53 (0.96–2.43)	1.08 (0.66–1.78)	0.93 (0.54–1.59)	0.49
No. of cases	35	57	41	29	
Finasteride					
All cases	1.0 (ref.)	0.98 (0.70–1.38)	1.10 (0.79–1.55)	0.87 (0.62–1.20)	0.51
No. of cases	149	140	151	153	
Gleason 2–6	1.0 (ref.)	0.95 (0.64–1.41)	1.18 (0.81–1.73)	0.83 (0.57–1.21)	0.53
No. of cases	87	81	97	88	
Gleason 7–10	1.0 (ref.)	0.95 (0.61–1.49)	0.96 (0.61–1.51)	0.81 (0.52–1.26)	0.37
No. of cases	60	53	50	55	
<i>P</i> values for interaction tests (treatment × IGF1:IGFBP3) were 0.46 (all cancers), 0.36 (Gleason 2–6), and 0.96 (Gleason 7–10)					

^aAdjusted for age, race (white vs. non-White), family history of first-degree relative with prostate cancer, BMI, dietary protein intake, and pack-years of smoking.

^bAlso adjusted for serum IGF1.

^cAlso adjusted for serum IGF2.

serum IGF1, IGF2, IGFBP3 nor the IGF1:IGFBP3 ratio were associated with prostate cancer risk. The null findings were consistent for total cancer, low-grade, and high-grade prostate cancers and across both PCPT study arms. Only serum IGFBP2 was associated with a modest, but significant, increased risk of total (OR = 1.48) and low-grade (OR = 1.55) prostate cancer among placebo-randomized men but not finasteride-randomized men.

To our knowledge, this is the first report implicating serum IGFBP2 in prostate cancer risk. The pooled analysis of 12 cohort studies found no association of serum IGFBP2 with prostate cancer risk, but power was limited to detect associations as only 4 of 12 studies had data on IGFBP2 (15). The PCPT finding that high versus low IGFBP2 is associated with increased prostate cancer risk is somewhat novel and is supported by data from *in vitro* and animal model studies. Meherian-Shai and colleagues used expression profiling of prostate cancer xenografts to show that serum IGFBP2 may be a serum biomarker of PTEN status and activation of the PI3/Akt pathway in prostate cancer (33). In their experiments, these investigators found that elevated IGFBP2 expression was common in PTEN-mutant tumors (33). Because PTEN is a well-known tumor suppressor gene, the finding is potentially important in terms of identifying both the etiology of some prostate cancers as well as confirming a role for molecules in the IGF family and their relationship to activation of the PI3/AKT pathway. IGFBP2 has also been suggested to be a growth factor for DU145 human prostate cells and it may be involved in growth regulation of both normal and neoplastic prostate cells (34). Thus, these PCPT results have may have important biologic relevance.

The lack of an association between circulating IGFI concentrations and prostate cancer risk in the PCPT was unanticipated, given the results of many prior studies as summarized in the 2008 meta-analysis and more recently the results from the large EPIC cohort (14, 15). Assay inaccuracy is an unlikely explanation for the lack of an association in the PCPT, as internal controls were satisfactory and the expected relationships between IGFI concentrations and age and between IGF1 and IGFBP3 concentrations were observed (data not shown). Prior studies of the Physicians' Health Study cohort noted that the IGFI-related risk was greater in the pre-PSA screening era than after PSA screening became common (4, 9). This observation suggested that IGFI-related risk may not operate early in carcinogenesis, but rather that high serum IGFI influenced rate of progression from subclinical to symptomatic disease. Thus, when cases were assessed earlier in the natural history due to PSA screening, the impact of IGFI as a risk factor becomes reduced. Notably, routine PSA screening is not conducted in the countries participating in EPIC where higher versus lower serum IGF1 was associated with a 69% increased risk of prostate cancer (14). We speculate that in the closely monitored PCPT population, IGFI and other IGF analytes did not emerge as prostate cancer risk factors for this reason. Interestingly, however, this does not preclude use of serum IGFI concentration as a predictor

of risk of clinically significant disease, an issue not investigated in PCPT.

We had hypothesized that associations of serum IGF analytes with prostate cancer risk might vary by PCPT treatment arm. Finasteride blocks the conversion of testosterone to the more potent dihydrotestosterone by inhibiting finasteride. While androgens are the primary target of finasteride, evidence suggests cross-talk exists between androgens and IGFs or their signaling pathways (1, 35–37). For example, one recent report showed an increase in steroid hormone synthesis following insulin treatment of prostate cancer cell lines (36). Other data suggest direct interaction may exist between the androgen receptor and the IGF receptor (IGF-IR; ref. 37) offering biologic plausibility to support these findings from the PCPT. Despite the biologic rationale and the modest attenuation of the IGFBP2 ORs in the finasteride arm, we observed no conclusive evidence for an interaction of PCPT treatment arm with IGF analytes in relation to prostate cancer risk.

This study has several strengths. The PCPT was a large placebo-controlled randomized trial. Part of the trial design specified that prostate cancer outcomes would be based on for-cause or end-of-study biopsy results. As such, the control group used in these analyses all had negative prostate biopsies, thus reducing the possibility that controls may have had undiagnosed or undetected disease. Other strengths include the carefully collected data throughout the course of the trial, the central pathology laboratory for uniform adjudication of all cases (including adjudication of Gleason). Limitations should also be noted, including the fact that the PCPT included few minorities. While we oversampled non-White controls to increase power for analyses by race, the power for any race-specific substrata was limited and thus not conducted for this report. In addition, most of the cases were low-grade so power was limited to detect differential associations by tumor grade. Finally, few deaths from prostate cancer have occurred in the PCPT, so we are unable to conduct analyses to examine mortality as an endpoint.

In conclusion, in this nested case-control study from the PCPT, we found that higher versus lower serum IGFBP2 was associated with a 55% increased risk of low-grade prostate cancer cancers. Unlike several previous studies, though, we found no association of any of the other IGF-axis analytes with prostate cancer risk and no effect modification by finasteride.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M.L. Neuhouser, C.M. Tangen, P.J. Goodman, Y. Tao, M.S. Lucia, M. Pollak

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M.L. Neuhouser, E.A. Platz, C. Till, C.M. Tangen, P.J. Goodman, A. Kristal, M.S. Lucia, A. Hoque, A.W. Hsing, M. Pollak

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