Serum markers, obesity and prostate cancer risk: results from the prostate cancer prevention trial

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Abstract

Molecular mechanisms linking obesity to prostate cancer involve steroid hormone and insulin/insulin-like growth factor 1 (IGF1) pathways. We investigated the association of circulating serum markers (e.g. androgens and IGFs/IGFBPs) with BMI and in modifying the association of obesity with prostate cancer risk. Data and specimens for this nested case–control study are from the Prostate Cancer Prevention Trial, a randomized, placebo-controlled trial of finasteride for prostate cancer prevention. Presence or absence of cancer was determined by prostate biopsy. Serum samples were assayed for sex steroid hormone concentrations and IGF1 axis analytes. Logistic regression estimated odds ratio and 95% CIs for risk of overall, low-grade (Gleason 2–6), and high-grade (Gleason 7–10) cancers. We found significant associations between BMI with serum steroids and IGFs/IGFBPs; the IGF1 axis was significantly associated with several serum steroids. Serum steroid levels did not affect the association of BMI with prostate cancer risk; however, IGFBP2 and IGFs modified the association of obesity with low- and high-grade disease. While serum steroids and IGFs/IGFBPs are associated with BMI, only the IGF1 axis contributed to obesity-related prostate cancer risk. Understanding the biological mechanisms linking obesity to prostate cancer risk as it relates to circulating serum markers will aid in developing effective prostate cancer prevention strategies and treatments.

Key Words

- obesity
- BMI
- sex steroids
- insulin/insulin-like growth factor-1
- prostate cancer risk

Introduction

Prostate cancer is the most common non-cutaneous malignancy and the second leading cause of cancer deaths among men in the United States (US), with approximately 248,530 new cases and about 34,130 men expected to die of the disease in 2021 (Siegel *et al.* 2021). The prevalence of obesity (BMI >30 kg/m^2) in the US adult male population is 36.6% (Hales *et al.* 2018). Obesity and related metabolic alterations have been implicated in the risk of cancer (Nimptsch & Pischon 2016). While the link of obesity to overall prostate cancer risk is controversial, studies have consistently shown a strong association of obesity to increased risk of aggressive disease (Gong *et al.*

2006, Vidal *et al.* 2014, Barrington *et al.* 2015, Guerrios-Rivera *et al.* 2017, Perez-Cornago *et al.* 2017).

Molecular mechanisms that explain the link between obesity and prostate cancer have not been elucidated. Biological mechanisms hypothesized to underlie the relationship between the two may involve crosstalk among hormonal pathways that include sex steroid hormones and the insulin/insulin-like growth factor 1 (IGF1) axis, specifically adiposity-related changes in metabolism and endogenous hormone levels (Hsing *et al.* 2007, Kaaks & Stattin 2010, De Pergola & Silvestris 2013, Boibessot & Toren 2018). Notably, the androgen and IGF1 pathways are known to play critical roles in prostate cancer development (Nimptsch & Pischon 2016, Holly *et al.* 2020).

Using data from the Prostate Cancer Prevention Trial (PCPT), we previously found obesity is associated with an increased risk of high-grade prostate cancer and a decreased risk of low-grade disease (Gong *et al.* 2006). In the current follow-up study, we investigated the association of serum sex steroid hormone and IGFs and their binding proteins (IGFPBs) with BMI and hypothesized that these circulating serum markers modify the association of obesity with prostate cancer risk. We first examined the relationship between obesity and serum markers and then determined their effects on modulating obesity-related prostate cancer risk. Our findings suggest that serum steroids and IGFs/IGFBPs are associated with BMI and found that only the IGF1 axis (IGFBP2 and IGFs) modified the association of BMI with low- and high-grade disease.

Methods

Participant and study description

All data for this study originated from the PCPT (SWOG-S9217); details of the trial and participant characteristics have been described previously (Feigl *et al.* 1995, Thompson *et al.* 2003). Briefly, 18,880 eligible men age 55 years and older with a normal digital rectal exam (DRE), prostate-specific antigen (PSA) level of 3 ng/mL or below, and no history of prostate cancer or other clinically significant co-morbid conditions that would have precluded successful completion of the study protocol were randomized to receive either finasteride (5 mg/day) or placebo daily for 7 years. During the trial, 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. At the conclusion of the trial, those men not previously diagnosed with prostate cancer were offered an end-of-study biopsy. Details regarding age, race/ethnicity, family history, smoking, alcohol, and physical activity habits (type, frequency, duration, pace, and intensity), and dietary consumptions were collected at baseline using self-administered questionnaires (Neuhouser *et al.* 1999, Neuhouser *et al.* 2001). Clinic staff measured height and weight at randomization and BMI was calculated as weight (kg) divided by height^2 (m).

The study was performed in accordance with the Declaration of Helsinki and conducted in accordance with the FDA Guidelines on Good Clinical Practice. All men signed informed consent and study procedures were approved by the Institutional Review Boards of the participating 221 study sites (Feigl *et al.* 1995, Thompson *et al.* 2003). The study reported here is part of a large nested case–control study designed to examine multiple hypotheses about prostate cancer risk. Cases were men with biopsy-determined prostate cancer identified either by a for-cause or end-of-study biopsy, and controls were selected from men who completed the end-of-study biopsy procedure and had no evidence of prostate cancer. Controls were frequency-matched to cases based on age, treatment arm, and family history of prostate cancer and were oversampled to include all eligible non-whites.

Sample collection and measurement of serum androgens, SHBG concentrations, and IGFs

Non-fasting blood specimens were collected at baseline and annually thereafter until diagnosis or the end of study. Venous blood was drawn into tubes without anticoagulant, refrigerated, and shipped to a central repository where it was centrifuged, aliquoted, and stored at −70°C. Concentrations of testosterone, sex hormone-binding globulin (SHBG), and 5α-androstane-3α,17β-diol glucuronide (or 3α-androstanediol glucuronide, 3α-dG) were measured from serum for this study in 2008, and a subset of men (313 cases and 346 controls) had serum androstenedione measured in 2009 as part of a different study. For the placebo arm, serum samples were collected at baseline and year 3 and pooled before analysis to better characterize androgen levels and reduce intraindividual variability; alternate years were selected if men were missing a year 3 sample or were diagnosed before year 3, and a single, baseline sample was used if a post-baseline, pre-diagnostic sample was unavailable. For the finasteride arm, all the androgen and SHBG measures were from baseline. Total testosterone, 3α-dG, androstenedione, and SHBG were quantified in serum by highly specific immunoassays as described previously (Kristal *et al.* 2012,

Hoque *et al.* 2015, Price *et al.* 2016). Serum concentrations of estrone (E1) and estradiol (E2) were determined by RIA (Yao *et al.* 2011). Concentrations of IGF1, IGF2, IGFBP2, and IGFBP3 were assayed in the baseline serum samples with a standard ELISA as described previously (Neuhouser *et al.* 2013). Serum steroid hormone and IGF concentrations were available from 1787 cases and 1782 controls; 313 cases and 346 controls with androstenedione.

Statistical methods

We compared baseline demographic and lifestyle characteristics of prostate cancer cases and controls by Student's *t*-test for continuous variables and chi-square test for categorical variables. For ordered categorical variables, a trend *P*-value was calculated based on an ordinal variable corresponding to rank (lowest to highest). Logistic regression was used to calculate odds ratio (ORs) and 95% CIs for risk of total prostate cancer, and polytomous logistic regression was used to calculate ORs and 95% CIs of both low-grade (Gleason 2–6) and high-grade (Gleason 7–10) prostate cancers. The polytomous regression with a generalized logit link permits a model including both low-grade and high-grade cancers as outcomes in the same model, contrasted with no cancer, with no assumption of ordinality in the outcome. Logistic models were stratified by treatment arm (finasteride vs placebo), and also combined arms; combined models were adjusted for the treatment arm. All models were also adjusted for age (continuous), race (white vs nonwhite), and family history of prostate cancer (yes vs no), and adjustments for serum sex steroids and IGFs were added. Trend *P*-values were calculated for main effects of BMI, as well as interaction between BMI and treatment arm and interactions between BMI and serum sex steroids and IGFs, using an ordinal variable corresponding to rank from lowest to the highest category of BMI. Mean concentrations of androgens and IGFs were estimated for each BMI category (normal, <25 kg/m^2; overweight, 25–30 kg/m^2; and obese, ≥30 kg/m^2), and *P*-values were calculated using linear regression, using an ordinal variable corresponding to rank from the lowest category to the highest of BMI. Among controls, mean concentrations of serum steroids and BMI were estimated for each IGF and IGFBP tertile, and trend *P*-values were calculated using linear regression, using an ordinal variable corresponding to rank of IGF tertile, from the lowest category to the highest category. IGF tertiles were calculated based on the observed distribution in the data. All statistical tests were two-sided with statistical significance set at $P < 0.05$ and carried out using SAS statistical software (version 9.4, SAS Corporation, Cary, NC).

Results

Association of serum sex steroids and IGFs/IGFBPs with BMI

Table 1 depicts the demographic and health-related variables of the current PCPT case–control population. Cases were less likely to be diabetic at baseline than controls, but cases and controls were similar with respect to BMI, smoking status, and physical activity, as well as other dietary and lifestyle factors (e.g. consumption of proteins, fat, carbohydrates, fruit, vegetables, calories, and alcohol; data not shown).

We investigated the association of serum steroids and IGFs/IGFBPs with BMI. Table 2 shows the association between BMI and serum sex steroids (testosterone, free testosterone, 3α-dG, estrone, estradiol, SHBG, and androstenedione), separately by treatment arm and combined treatment arms. Serum testosterone, free testosterone, and SHBG have inverse relationships with BMI (all *P*-values < 0.0001). Serum 3a-dG, estrone, and estradiol have a positive, linear association with BMI (all *P*-values < 0.0001). Androstenedione did not appear to have any association with BMI. Table 2 also shows significant associations between BMI and serum IGF2 and IGFBP2. In particular, serum concentrations of IGF2 increased with increasing BMI (*P*-value < 0.01), while IGFBP2 significantly decreased with increasing BMI (*P*-value < 0.0001). IGF1 and IGFBP3 did not have any association with BMI. When stratified by treatment arm, the associations are similar. Our findings demonstrate significant associations between BMI and serum steroids or IGFs/IGFBPs.

Association between serum sex steroids and IGFs/IGFBPs

We next determined the association between IGFs/IGFBPs and serum steroids. Table 3 gives mean values of serum steroids by tertiles of serum IGF1, IGF2, IGFBP2, and IGFBP3 in the controls. Serum concentrations of testosterone, free testosterone, and SHBG increase significantly, and levels of 3α-dG and estrone decrease, with increasing concentrations of IGFBP2. There was evidence of significant associations of IGF1, IGF2, and IGFBP3 with several serum steroids. SHBG has associations with all IGFs, while androstenedione did not appear to have any association with any of the IGFs. Testosterone and 3α-DG were significantly associated with IGF2, IGFBP2, and IGFBP3. Free testosterone was significantly associated with increasing concentrations of IGF1 and IGFBP2. In the finasteride treatment arm, we observed a similar association of serum steroids (testosterone and SHBG) with serum IGFs (Supplementary

Table 1 Baseline demographics of trial participants.

	Case (*n* = 1787)	**Control** (*n* = 1782)	**All** (*n* = 3569)	***P*-value**[a]
Age, mean (s.d.)[b]	63.7 (5.5)	63.6 (5.5)	63.6 (5.5)	NA[b]
Race, *n* (%)[b]				NA[b]
Non-hispanic white	1658 (92.8)	1415 (79.4)	3073 (86.1)	
Minority	129 (7.2)	367 (20.6)	496 (13.9)	
BMI, *n* (%)				0.07
Normal	498 (27.9)	444 (24.9)	942 (26.4)	
Overweight	915 (51.2)	944 (53.0)	1859 (52.1)	
Obese	374 (20.9)	394 (22.1)	768 (21.5)	
Smoking status, *n* (%)				0.55
Never	636 (35.6)	610 (34.2)	1246 (34.9)	
Former	124 (6.9)	137 (7.7)	261 (7.3)	
Current	1027 (57.5)	1035 (58.1)	2062 (57.8)	
Physical activity, *n* (%)				0.56
Sedentary	306 (17.2)	311 (17.5)	617 (17.4)	
Light	740 (41.6)	734 (41.4)	1474 (41.5)	
Moderate	586 (32.9)	543 (30.6)	1129 (31.8)	
Active	148 (8.3)	186 (10.5)	334 (9.4)	
Treatment arm, *n* (%)[b]				NA[b]
Finasteride	755 (42.2)	757 (42.5)	1512 (42.4)	
Placebo	1032 (57.8)	1025 (57.5)	2057 (57.6)	
Diabetes, *n* (%)	84 (4.7)	131 (7.4)	215 (6.0)	<0.001
Family history of prostate cancer, n (%)[b]	380 (21.3)	377 (21.2)	757 (21.2)	NA[b]

[a]*P*-values comparing cases to controls were calculated using *t*-tests for continuous variables and chi-square tests for categorical variables. For ordered categorical variables, linear regression was used to calculate a trend *P* -value, using an ordinal variable corresponding to rank from the lowest category to the highest. [b]*P*-values were not included due to controls being frequency-matched to cases based on age, treatment arm, and family history and were oversampled to include all eligible non-whites.

Table 1, see section on supplementary materials given at the end of this article). Thus, we found significant associations between IGFs/IGFBPs with several serum steroids.

Association between obesity and prostate cancer risk modified by sex steroid hormones and IGFs/IGFPBs

Table 4 examines the association between obesity and total low-grade and high-grade prostate cancer risk stratified by PCPT treatment arm (placebo or finasteride) and factoring in several covariates (e.g. age, race, family history, treatment arm, serum steroids, and IGFs/IGFBP2) to determine their effect on modifying risk. BMI did not have any significant association with total prostate cancer risk. However, when cancer was stratified by grade, risk of low-grade (Gleason 2–6) cancer decreased with increasing BMI (OR (95% CI) for obese participants 0.66 (0.50–0.88), *P*-trend = 0.003) in the placebo arm. Risk of high-grade (Gleason 7–10) cancer was associated with increasing BMI when treatment arms were combined (OR (95% CI) for obese participants 1.34 (1.00–1.79), *P*-trend = 0.05). Results when high-grade cancer was restricted to Gleason sum 8 to 10 demonstrated further increased risk with increasing BMI (OR (95% CI) for obese participants 1.69 (1.00–2.85), *P*-trend = 0.05, data not shown).

When serum steroids were included as an adjustment factor in the risk model, the associations remained the same, suggesting that any association that BMI had with prostate cancer was likely not mediated by serum steroid levels. However, when adjusting for confounders IGFBP2 and IGFs, the risk of high-grade (Gleason 7–10) cancer increasing with increasing BMI in the combined treatment arms became significant (IGFBP2: OR (95% CI) for obese participants 1.48 (1.08–2.04), *P*-trend = 0.01; IGFs: OR (95% CI) 1.47 (1.07–2.02), *P*-trend = 0.02). Alternatively, the association of risk of low-grade cancer decreasing with increasing BMI was no longer significant, suggesting IGFBP2 and IGFs may modify the association of BMI with low- and high-grade prostate cancer. However, when evaluated by separate treatment arms (placebo vs finasteride), IGFBP2 and IGFs had no effects on risk, perhaps due to a smaller sample size vs the increase in number of cases by combining the treatment arms. Therefore, while serum steroid levels did not affect the association of BMI with prostate cancer risk, IGFBP2 and IGFs modified the association of BMI with low- and high-grade disease.

Discussion

Obesity is a pandemic of increasing proportion and a risk factor for prostate cancer. The link between obesity and prostate cancer is complex, with inconsistent

Table 2 Association between mean concentrations[a] of serum steroids and IGFs with BMI in cases and controls.

	Normal (<25 kg/m²)	**Overweight** (25–30 kg/m²)	**Obese** (≥30 kg/m²)	***P*-value[b]**
Combined treatment arms				
Count	942	1859	768	
Testosterone, ng/dL	428.6 (146.0)	380.0 (130.4)	330.1 (112.5)	<0.0001
Free testosterone, pg/mL	9.1 (2.7)	8.6 (2.6)	7.9 (2.4)	<0.0001
3a-DG, ng/mL	6.0 (4.2)	6.8 (4.8)	7.0 (4.5)	<0.0001
Estrone, pg/mL	44.3 (14.4)	45.1 (14.6)	49.7 (16.5)	<0.0001
Estradiol, pg/mL	33.4 (10.3)	33.9 (10.8)	35.5 (10.6)	<0.0001
SHBG, nmol/L	45.1 (18.1)	38.3 (14.7)	33.1 (12.9)	<0.0001
Androstenedione[c], ng/mL	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	0.09
IGF1, ng/mL	211.6 (60.6)	213.4 (64.0)	207.0 (72.3)	0.19
IGF2, ng/mL	1707.9 (400.1)	1758.5 (423.1)	1770.2 (502.9)	0.002
IGFBP2, ng/mL	723.7 (358.4)	504.6 (270.7)	370.0 (201.7)	<0.0001
IGFBP3, ng/mL	4004.8 (907.8)	4083.8 (946.1)	4067.1 (1115.2)	0.16
Finasteride				
Count	399	766	347	
Testosterone, ng/dL	430.1 (146.0)	379.1 (135.6)	326.9 (113.9)	<0.0001
Free testosterone, pg/mL	9.2 (2.8)	8.7 (2.7)	8.0 (2.6)	<0.0001
3a-DG, ng/mL	6.3 (4.7)	6.8 (5.1)	6.9 (4.4)	0.08
Estrone, pg/mL	45.3 (15.1)	45.8 (15.6)	50.1 (16.2)	<0.0001
Estradiol, pg/mL	33.9 (10.4)	34.4 (12.4)	35.5 (10.8)	0.07
SHBG, nmol/L	45.2 (19.2)	37.9 (15.3)	31.9 (11.7)	<0.0001
Androstenedione[c], ng/mL	0.7 (0.3)	0.6 (0.2)	0.6 (0.2)	0.15
IGF1, ng/mL	210.9 (62.9)	214.0 (63.5)	211.7 (73.3)	0.84
IGF2, ng/mL	1705.0 (412.3)	1745.3 (429.4)	1785.2 (475.1)	0.01
IGFBP2, ng/mL	718.9 (331.0)	510.7 (273.1)	367.1 (211.5)	<0.0001
IGFBP3, ng/mL	4001.2 (948.4)	4059.4 (948.6)	4107.1 (1071.4)	0.14
Placebo				
Count	543	1093	421	
Testosterone, ng/dL	427.6 (146.1)	380.7 (126.7)	332.8 (111.4)	<0.0001
Free testosterone, pg/mL	9.0 (2.6)	8.6 (2.5)	7.9 (2.2)	<0.0001
3a-DG, ng/mL	5.9 (3.8)	6.8 (4.6)	7.2 (4.6)	<0.0001
Estrone, pg/mL	43.5 (13.8)	44.6 (13.8)	49.3 (16.8)	<0.0001
Estradiol, pg/mL	33.0 (10.3)	33.6 (9.6)	35.6 (10.5)	<0.01
SHBG, nmol/L	44.9 (17.4)	38.6 (14.3)	34.1 (13.8)	<0.0001
Androstenedione[c], ng/mL	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	0.29
IGF1, ng/mL	212.1 (58.9)	212.9 (64.4)	203.1 (71.3)	0.05
IGF2, ng/mL	1710.0 (391.2)	1767.8 (418.6)	1757.8 (525.0)	0.06
IGFBP2, ng/mL	727.3 (377.6)	500.4 (269.0)	372.5 (193.5)	<0.0001
IGFBP3, ng/mL	4007.5 (877.7)	4100.8 (944.5)	4033.8 (1150.6)	0.55

[a]Serum steroids and IGFs concentrations reported as mean (S.D.); [b] Linear regression was used to calculate a trend *P*-value, using an ordinal variable corresponding to rank from the lowest category to the highest of BMI; [c]Counts for androstenedione concentrations are lower due to the subset of men with available serum data (Normal–Overweight–Obese: combined treatment arm (184–338–137); finasteride (69–142–69); placebo (115–196–68)). No adjustments for multiple testing have been done.

results observed across studies that depend on the anthropometric indicators used to characterize obesity. Many studies including several meta-analyses evaluating the association of BMI with prostate cancer have reported null (Harding *et al.* 2015) or weak results (MacInnis & English 2006, Renehan *et al.* 2008) as well as positive associations between BMI and aggressive disease (Gong *et al.* 2006, Discacciati *et al.* 2012, Fang *et al.* 2018). Other studies have examined whether obesity plays a role in the racial disparity of prostate cancer incidence. While blacks had a significantly increased risk of prostate cancer incidence, BMI, however, was not found to be a significant mediator (Akinyemiju *et al.* 2018). In a separate study, obesity was strongly associated with an increased risk of prostate cancer among black compared to white men in the SELECT trial (Barrington *et al.* 2015), which might reflect a difference in the biological effects of obesity on inflammation or insulin secretion between racial groups. However, a recent re-analysis of the trial data after taking into account differential biopsy assessment, which may affect prostate cancer diagnosis and subsequent cancer risk factors, changed the previously reported positive association between BMI and prostate cancer in black men to null (Tangen *et al.* 2019). Furthermore, the association of

Table 3 Association of serum steroids with IGFs among controls.

	Count	**Testosterone** (ng/dL)	**Free testosterone** (pg/mL)	**3a-DG** (ng/mL)	**Estrone** (pg/mL)	**Estradiol** (pg/mL)	**SHBG** (nmol/L)	**Androstenedione** (ng/mL)
IGF1, ng/mL								
<181	590	388.2 (143.6)	8.5 (2.7)	6.9 (5.0)	45.7 (17.0)	34.5 (11.8)	42.0 (16.9)	0.6 (0.2)
181 to <231	591	383.4 (144.6)	8.6 (2.7)	6.5 (3.7)	45.6 (14.3)	34.2 (10.4)	39.1 (17.0)	0.6 (0.2)
≥231	593	377.5 (123.0)	8.9 (2.6)	6.5 (3.8)	45.2 (14.2)	33.7 (12.0)	35.7 (12.7)	0.6 (0.2)
P -value[a]		0.18	0.006	0.15	0.57	0.19	<0.0001	0.23
IGF2, ng/mL								
<1543	590	407.1 (155.1)	8.7 (2.8)	6.4 (4.2)	44.8 (15.6)	35.1 (11.9)	43.9 (18.7)	0.6 (0.2)
1543–<1903	592	387.3 (129.3)	8.7 (2.6)	6.4 (3.7)	45.5 (14.7)	34.3 (12.2)	39.4 (14.3)	0.6 (0.2)
≥1903	592	354.9 (120.7)	8.5 (2.6)	7.1 (4.6)	46.1 (15.4)	33.0 (10.0)	33.5 (12.2)	0.6 (0.2)
P -value[a]		<0.0001	0.36	0.001	0.14	0.001	<0.0001	0.09
IGFBP2, ng/mL								
<343	590	332.4 (121.2)	8.2 (2.6)	6.9 (4.2)	46.9 (16.2)	33.1 (9.9)	31.3 (12.2)	0.6 (0.2)
343–<563	591	380.1 (123.9)	8.7 (2.6)	6.9 (4.2)	45.8 (15.4)	35.0 (13.2)	38.3 (14.7)	0.6 (0.2)
≥563	593	436.3 (145.6)	9.1 (2.7)	6.2 (4.1)	43.7 (13.8)	34.3 (10.9)	47.1 (16.3)	0.6 (0.2)
P -value[a]		<0.0001	<0.0001	0.004	0.0003	0.07	<0.0001	0.20
IGFBP3, ng/mL								
<3601	590	404.7 (156.5)	8.7 (2.8)	6.5 (4.5)	45.0 (15.8)	34.8 (11.8)	43.5 (18.7)	0.6 (0.2)
3601–<4424	591	381.1 (124.0)	8.6 (2.5)	6.2 (3.5)	45.6 (15.0)	34.4 (12.2)	39.2 (13.7)	0.6 (0.2)
≥4424	593	363.5 (126.5)	8.7 (2.7)	7.2 (4.5)	45.8 (14.9)	33.2 (10.1)	34.1 (13.3)	0.6 (0.2)
P -value[a]		<0.0001	0.87	0.005	0.36	0.02	<0.0001	0.14

[a]Linear regression was used to calculate a trend *P* -value, using an ordinal variable corresponding to rank from the lowest category to the highest of IGF.
This table includes controls only. No adjustments for multiple testing have been made.

Table 4 Association of obesity with prostate cancer risk (BMI vs total, low, high grade) adjusted for covariates.

		All prostate cancer		**Low grade** (Gleason < 7)		**High grade** (Gleason ≥ 7)	
	***n* ctl**	*n* case	OR (95% CI)	*n* case	OR (95% CI)	*n* case	OR (95% CI)
Combined treatment							
Adjusted for age, race, family history of prostate cancer, and treatment arm[a]							
Normal (<25 kg/m^2)	444	498	Ref	363	Ref	115	Ref
Overweight (25–30 kg/m^2)	944	915	0.86 (0.74–1.01)	628	0.81 (0.68–0.97)	247	1.03 (0.80–1.32)
Obese (≥30 kg/m^2)	394	374	0.89 (0.73–1.08)	231	0.75 (0.60–0.93)	126	1.34 (1.00–1.79)
P-trend			0.21		0.01		0.05
P-interaction[e]			0.10		0.21		0.85
Adjusted for age, race, family history, treatment arm, and serum steroids[b]							
Normal (<25 kg/m^2)	442	492	Ref	359	Ref	113	Ref
Overweight (25–30 kg/m^2)	940	909	0.86 (0.73–1.02)	623	0.82 (0.68–0.98)	246	1.01 (0.78–1.30)
Obese (≥30 kg/m^2)	393	371	0.88 (0.72–1.08)	230	0.76 (0.61–0.96)	125	1.27 (0.93–1.73)
P-trend			0.20		0.02		0.14
P-interaction[e]			0.08		0.18		0.92
Adjusted for age, race, family history, treatment arm, and IGFBP2[c]							
Normal (<25 kg/m^2)	442	497	Ref	362	Ref	115	Ref
Overweight (25–30 kg/m^2)	941	910	0.92 (0.78–1.09)	625	0.88 (0.73–1.05)	245	1.09 (0.83–1.42)
Obese (≥30 kg/m^2)	391	374	1.00 (0.81–1.24)	231	0.85 (0.67–1.08)	126	1.48 (1.08–2.04)
P-trend			0.99		0.16		0.01
P-interaction[e]			0.12		0.24		0.81
Adjusted for age, race, family history, treatment arm, and IGFs[d]							
Normal (<25 kg/m^2)	442	497	Ref	362	Ref	115	Ref
Overweight (25–30 kg/m^2)	941	910	0.93 (0.79–1.10)	625	0.88 (0.73–1.06)	245	1.08 (0.83–1.41)
Obese (≥30 kg/m^2)	391	374	1.01 (0.82–1.26)	231	0.87 (0.68–1.10)	126	1.47 (1.07–2.02)
P-trend			0.93		0.21		0.02
P-interaction[e]			0.12		0.25		0.82
Finasteride Arm							
Adjusted for age, race, and family history of prostate cancer[a]							
Normal (<25 kg/m^2)	202	197	Ref	125	Ref	66	Ref
Overweight (25–30 kg/m^2)	383	383	0.97 (0.75–1.24)	227	0.89 (0.67–1.19)	141	1.08 (0.76–1.52)
Obese (≥30 kg/m^2)	172	175	1.08 (0.80–1.46)	94	0.88 (0.62–1.25)	69	1.33 (0.89–2.00)
P-trend			0.65		0.46		0.17
Adjusted for age, race, family history, and serum steroids[b]							
Normal (<25 kg/m^2)	201	191	Ref	121	Ref	64	Ref
Overweight (25–30 kg/m^2)	379	378	0.98 (0.76–1.27)	222	0.91 (0.68–1.23)	141	1.09 (0.76–1.55)
Obese (≥30 kg/m^2)	171	172	1.08 (0.79–1.49)	93	0.92 (0.63–1.33)	68	1.29 (0.84–1.98)
P-trend			0.64		0.62		0.25
Adjusted for age, race, family history, and IGFBP2							
Normal (<25 kg/m^2)	201	197	Ref	125	Ref	66	Ref
Overweight (25–30 kg/m^2)	382	379	1.04 (0.80–1.36)	225	0.97 (0.72–1.31)	139	1.17 (0.81–1.68)
Obese (≥30 kg/m^2)	172	175	1.24 (0.89–1.73)	94	1.02 (0.70–1.50)	69	1.57 (1.01–2.44)
P-trend			0.20		0.92		0.05
Adjusted for age, race, family history, and IGFs							
Normal (<25 kg/m^2)	201	197	Ref	125	Ref	66	Ref
Overweight (25–30 kg/m^2)	382	379	1.05 (0.80–1.37)	225	0.98 (0.72–1.33)	139	1.16 (0.81–1.67)
Obese (≥30 kg/m^2)	172	175	1.24 (0.89–1.73)	94	1.04 (0.71–1.52)	69	1.54 (0.99–2.40)
P-trend			0.20		0.86		0.06

Table 4 Continued.

	n ctl	All prostate cancer		Low grade (Gleason < 7)		High grade (Gleason ≥ 7)	
		n case	OR (95% CI)	*n* case	OR (95% CI)	*n* case	OR (95% CI)
Placebo arm							
Adjusted for age, race, and family history of prostate cancer[a]							
Normal (<25 kg/m^2)	242	301	Ref	238	Ref	49	Ref
Overweight (25–30 kg/m^2)	561	532	0.78 (0.64–0.97)	401	0.75 (0.60–0.94)	106	0.95 (0.66–1.38)
Obese (≥30 kg/m^2)	222	199	0.76 (0.59–0.99)	137	0.66 (0.50–0.88)	57	1.35 (0.88–2.06)
P-trend			0.03		0.003		0.17
Adjusted for age, race, family history, and serum steroids[b]							
Normal (<25 kg/m^2)	241	301	Ref	238	Ref	49	Ref
Overweight (25–30 kg/m^2)	561	531	0.77 (0.62–0.95)	401	0.75 (0.60–0.94)	105	0.89 (0.61–1.31)
Obese (≥30 kg/m^2)	222	199	0.75 (0.57–0.98)	137	0.67 (0.50–0.90)	57	1.24 (0.79–1.94)
P-trend			0.03		0.01		0.33
Adjusted for age, race, family history, and IGFBP2							
Normal (<25 kg/m^2)	241	300	Ref	237	Ref	49	Ref
Overweight (25–30 kg/m^2)	559	531	0.83 (0.67–1.04)	400	0.81 (0.64–1.02)	106	0.97 (0.66–1.44)
Obese (≥30 kg/m^2)	219	199	0.85 (0.64–1.12)	137	0.75 (0.55–1.01)	57	1.40 (0.88–2.23)
P-trend			0.22		0.06		0.14
Adjusted for age, race, family history, and IGFs							
Normal (<25 kg/m^2)	241	300	Ref	237	Ref	49	Ref
Overweight (25–30 kg/m^2)	559	531	0.84 (0.67–1.05)	400	0.82 (0.64–1.03)	106	0.98 (0.66–1.45)
Obese (≥30 kg/m^2)	219	199	0.86 (0.65–1.15)	137	0.76 (0.56–1.04)	57	1.41 (0.88–2.25)
P-trend			0.28		0.08		0.14

[a]Adjusted for age (continuous) and race (white vs non-white). Combined models were also adjusted for treatment arm; [b]Adjusted for the above factors, as well as serum testosterone, SHBG, and 3a-DG. *P*-value testing interaction between BMI and serum steroids is 0.29. [c]*P*-value testing interaction between BMI and IGFBP2 is 0.71. [d]IGFs include IGF1, IGF2, IGFBP2, and IGFBP3. *P*-value testing interactions between BMI and IGFs is 0.97. [e]*P*-value tests the interaction between treatment arm and BMI.

No adjustments for multiple testing have been made. Odds ratios for low- and high-grade cancer were calculated using polytomous logistic regression, with no assumption of ordinality in the outcome.

BMI with prostate cancer was generally stronger in studies that reported mortality rather than incidence (Zhong *et al.* 2016, Fang *et al.* 2018, Jochems *et al.* 2020). Future studies are warranted to investigate the role of high BMI in increased mortality among patients with prostate cancer including our PCPT population.

Biological mechanisms that explain the apparent link between obesity and prostate cancer have not been fully elucidated. Several mechanisms have been proposed to explain the association between obesity and prostate cancer, which include inter-related pathways that involve altered sex steroid hormones, insulin/IGF1 axis, and adipokine signaling caused by inflammation. We undertook the current study to understand the association between circulating serum markers (e.g. sex serum steroid, serum IGFs/IGFBPs) and obesity with prostate cancer risk. The impact of these serum markers on obesity-related prostate cancer risk may play a critical role in prostate carcinogenesis and disease progression.

We identified significant associations between BMI with serum steroids and IGFs/IGFBPs. Our results showed obese men having lower concentrations of serum testosterone, free testosterone, and SHBG and higher levels of serum 3a-dG, estrone, and estradiol. Serum SHBG, a carrier protein that binds circulating sex steroid hormones and reduces their availability to tissues, correlates inversely with BMI due mostly to increases in serum insulin, which inhibits hepatic SHBG synthesis (Kaaks *et al.* 2000, Kaaks & Stattin 2010). Obesity is associated with a lower concentration of free testosterone, resulting in the growth of aggressive prostate tumors (Allott *et al.* 2013) and men with prostate cancer who have low testosterone tend toward a more aggressive phenotype. Our data are consistent with a recent international collaboration that combined data from over 12,300 men from 25 studies that found BMI was strongly associated with concentrations of all the sex hormones and SHBG (Watts *et al.* 2017). We also found significant associations between BMI and serum IGF2 and IGFBP2. Specifically, obese men tended to have higher

serum concentrations of IGF2 and lower concentrations of IGFBP2. Moreover, we found significant associations between IGFs/IGFBPs with several serum steroids (Table 3).

We next investigated whether sex steroid hormones and IGFs/IGFPBs are involved in modifying the association between obesity and prostate cancer risk since we previously found that BMI increased the risk of high-grade disease but decreased the risk of low-grade disease in PCPT (Gong *et al.* 2006). We showed that serum steroid levels did not modify the association of BMI with prostate cancer risk. This result is not surprising since circulating sex steroid hormones were not associated with the risk of prostate cancer in our PCPT studies (Yao *et al.* 2011, Kristal *et al.* 2012, Schenk *et al.* 2016) as well as others (Endogenous *et al.* 2008).

Our results revealed that the association between BMI and low- and high-grade prostate cancer may be modified by the IGF axis, specifically IGFBP2 and IGFs. We previously showed that only high serum IGFBP2 was a risk factor for low-grade disease, which was attenuated for men on finasteride (Neuhouser *et al.* 2013). In the current study, after adjusting for IGFs and IGFBP2, the association of obesity with risk reduction of low-grade disease diminished, while the risk of high-grade (Gleason 7–10) prostate cancer was increased. IGFs have mitogenic and anti-apoptotic effects and the IGF1 axis (comprised of IGF1, IGF2, insulin, and their respective receptors, as well as binding proteins) regulates many physiological processes. This axis has been implicated in playing an important role in tumor development and progression. IGF1 and IGF2 are responsible for cellular growth, and IGFBPs regulate the bioactivity of IGFs for binding of their receptors (Clemmons 1997). Obese men have higher levels of insulin and IGFs (Giovannucci & Michaud 2007). Obesity and hyperinsulinemia are associated with not only alterations in sex steroids and adipocytokines but also with decreased concentrations of IGFBPs resulting in increased circulating levels of bioactive IGF1, which in turn elevate circulating growth factors (Renehan *et al.* 2006). Studies have found that circulating IGFs and binding proteins may be associated with prostate cancer development or progression as well as increased risk of advanced prostate cancer (Roddam *et al.* 2008). In epidemiological studies, plasma IGF1 levels were positively associated with risk of total prostate cancer, and plasma fasting IGFBP1 was strongly inversely associated with low- and intermediate-grade but not high-grade prostate cancer in the Health Professionals Follow-up Study (Cao *et al.* 2015). BMI was associated with IGFBP1 but not IGF1 (Cao *et al.* 2015). Further research would be needed to better understand the relationship between these proteins and prostate cancer.

There are strengths and limitations to our study. The PCPT was a large placebo-controlled randomized trial that used prostate biopsies to verify absence or presence of cancer; thus, the control group all had confirmed negative prostate biopsies, largely eliminating the possibility that controls may have had undiagnosed or undetected disease. Additional strengths included the use of a central pathology laboratory for uniform adjudication of all cases (including adjudication of Gleason grade), highly sensitive and specific assays for quantitating circulating serum steroids and IGFs, and the large sample size of our patient population. Our observational study was limited in that single time point measurement of biomarkers (e.g. serum steroids, SHBG, IGFs, IGFBPs) may not reflect long-term circulating levels, and laboratory measurements were performed on non-fasting blood samples, which may affect IGF levels. Levels of circulating biomarkers may be affected by genetic and lifestyle factors, which may modify the serum concentrations of these biomarkers. Men on this trial underwent 6-core biopsy so there was a possibility that prostate cancer detection may be missed. Limitations of sample size by disease grade may have precluded detection of stronger interactions between obesity, circulating biomarkers, and treatment arm and increased the possibility of spurious associations as a result of multiple comparisons. This analysis included largely white participants; however, this minimized concerns of selection bias or population stratification.

In conclusion, our previous study found an association between BMI and an increased the risk of high-grade disease and a decreased the risk of low-grade disease (Gong *et al.* 2006). The current follow-up study reveals that circulating serum biomarkers along the IGF1 axis, specifically IGFBP2 and IGFs, may modify the association of obesity with prostate cancer risk. Future studies are warranted to delineate the relationship between obesity and circulating serum biomarkers and to elucidate the biological mechanism involved in driving prostate cancer progression. This is important as a thorough understanding of these mechanisms may be valuable in the development of effective prostate cancer prevention strategies and treatments. More research is necessary to ascertain the roles of these potential modifying factors in obesity-related prostate cancer risk.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/ERC-21-0107.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

Conception and study design (I M T, W D F), data acquisition and analysis (C H C, C T, D K P, P J G, M L N, M P), drafted manuscript (C H C, C T), revised and approved final manuscript (all authors).

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