Insulin-Like Growth Factor-I, Insulin-Like Growth Factor Binding Protein-3 and Risk of Benign Prostate Hyperplasia in the Prostate Cancer Prevention Trial

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BACKGROUND. We investigated whether peptides involved in cellular proliferation and apoptosis, [insulin-like growth factor I (IGFI) and its major binding protein (insulin-like growth factor binding protein 3)], predicted risk of benign prostate hyperplasia (BPH).

METHODS. We conducted a nested-case–control study in the placebo arm of the prostate cancer prevention trial (PCPT). Cases (n = 727) were men with surgical or medical treatment for BPH; two or more IPSS scores >14; or two scores of at least five points over baseline one of which was ≥12. Controls (n = 727) were frequency matched by age to cases, reported no BPH treatment, and no IPSS score >8. Cases and controls remained on the PCPT placebo and were followed closely until their 7-year PCPT anniversary. Baseline serum was analyzed for IGFI and IGFBP3. Unconditional logistic regression and polytomous regression estimated the multivariate-adjusted odds ratio (OR) for BPH risk.

RESULTS. IGFBP3 was inversely and the IGFI:IGFBP3 ratio was positively associated with BPH risk, but findings were statistically significant only for men with severe symptoms (OR = 0.60, 95% CI = 0.40–0.90 for the fifth vs. first quintile of IGFBP3, *P*-trend = 0.01). Associations did not differ by age (<65 or ≥65 years), and there was a suggestion that the IGFI:IGFBP3 – BPH risk association may be stronger among overweight men.

CONCLUSIONS. A high IGFI:IGFBP3 ratio was associated with increased BPH risk, and high serum IGFBP3 was associated with decreased BPH risk among men with severe symptoms. These results confirm findings from other recent studies.

KEY WORDS: **prostatic hyperplasia; insulin-like growth factors; insulin-like growth factor binding proteins; case–control studies**

INTRODUCTION

Benign Prostate Hyperplasia (BPH) is one of the most common medical conditions in aging men [1,2]. The pathogenesis of BPH is poorly understood, though it likely results from an imbalance of hormonal and other growth-regulatory factors such as insulin-like growth factors (IGFs), leading to cellular proliferation

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primarily in the stromal, and to a lesser extent in the epithelial regions of the prostate [3]. The hyperplasia leads to a constellation of lower urinary tract symptoms including urgency, weak stream, frequency, and nocturia [2–4]. These clinical symptoms can severely limit activities of daily living and lead to diminished quality of life. Research to understand the etiology of BPH may lead to more effective treatments as well as preventive strategies that could improve the health and well-being for millions of men.

IGFs and their binding proteins (IGFBPs) may play an important role in understanding the etiology of prostate disease, including BPH. IGFs are molecules that act as both hormones and growth factors and they exhibit autocrine, paracrine and endocrine capabilities [5–7]. IGFs are synthesized in the liver and peripheral tissues (including the prostate) and circulate bound to one of six insulin-like growth factor binding proteins (IGFBPs), principally IGFBP3. Circulating concentrations of IGFs and IGFBPs are influenced by nutritional factors, exogenous and endogenous hormones and genetic characteristics [6,7]. Of particular interest is that energy restriction is associated with lower IGFI and energy excess (and thus obesity) is associated with IGFI excess [6,8]. IGFs and IGFBPs are directly involved in both cellular proliferation and apoptosis [7,9]. For example, IGFI induces cyclin D1 production, which stimulates progression of the cell cycle from G1 to S phase, thereby increasing DNA synthesis and cellular proliferation [7,9]. IGFI is a ligand for IGFIR, which is a tyrosine kinase cell-surface receptor. Downstream signaling from the IGFIR includes the PI3K-AKT-TOR and RAF-MAPK pathways [7]. Several in vitro studies demonstrate the importance of the IGF axis in cellular growth in the human prostate. IGFI and to a lesser extent IGFII stimulate growth of prostate epithelial cells in primary culture, and this growth is modulated by the IGFI receptor and the IGFBPs [10]. IGFI has mitogenic effects in the prostate, while IGFBP3 is growth inhibitory due to its ability to regulate availability of the IGFs, other growth factors and steroid hormones [7]. In addition to its important role in regulating the bioavailability and signaling capacity of IGFI, IGFBP3 has independent actions that are growth-inhibitory and pro-apoptotic [7]. IGFBP3 is also known to inhibit angiogenesis via decreasing vascular endothelial growth factor (VEGF) [11].

There is variable secretion of IGFBPs across the different zones of the prostate and between normal and hyperplastic tissue [12], with particularly low secretion of IGFBP3 in transition zone stromal cells in BPH tissue. These low levels of IGFBP3 in BPH tissues would favor hyperplastic growth, and may play a role in the development of BPH. Other lines of evidence also support the importance of the IGF axis in BPH. Acromegalic patients, who have very high levels of IGF1 (along with low levels of testosterone and DHT) have enlarged prostates and high rates of BPH [13–15]. Treatment to suppress IGFI in acromegalic patients decreases prostate volume and urinary symptomology [13–15].

Only a few published studies have examined whether IGF axis analytes are associated with risk of BPH. Chokkalingham et al. [16] conducted a case–control study in China and reported that compared to men in the lowest tertile of serum IGF1, the odds ratio (OR) for BPH for those men in the highest tertile of IFG1 was 2.80 (95% CI, 1.60–4.92). Serum concentrations of IGFBP3 were associated with an inverse risk of BPH in the same men (OR = 0.40, 95% CI, 0.23–0.69) [16]. More recently, Rohrmann et al. [17] reported results from the National Health and Nutrition Examination Survey III (NHANES). IFG1 was associated with a non-statistically significant increased risk of lower urinary tract symptoms (OR = 3.20, 95% CI, 0.89–11.4) while IGFBP3 was associated with a significant reduction in risk (OR = 0.25, 95% CI, 0.08–0.81). Roberts et al. [18] found no association of IGF1 with BPH, but a suggestive inverse association with IGFBP3. The present study investigates whether high serum IGFI or low serum IGFBP3 is associated with risk of BPH among men participating in the prostate cancer prevention trial (PCPT).

METHODS

Study Population

Data are from the placebo arm of the PCPT, a double-blind, placebo-controlled randomized trial testing whether a 5-α-reductase inhibitor, finasteride (Proscar®), could reduce the 7-year period prevalence of prostate cancer. Details of the design and overall study findings are published [19]. Briefly, 18,882 men aged 55 years and older who had a normal digital rectal exam (DRE) and a prostate-specific antigen (PSA) level less than or equal to 3 ng/ml, as well as no prior history of prostate cancer, and no severe BPH [defined as an International Prostate Symptom Score (IPSS) of 19 or lower] [4], were randomized to receive a daily dose of 5 mg finasteride or placebo. Men received careful medical monitoring during the trial via twice yearly clinic visits and between-visit telephone calls. All men with a DRE suspicious for prostate cancer or a PSA $\geq$ 4.0 ng/ml during these clinic visits were referred for a prostate biopsy, but continued trial participation if the biopsy was negative. All prostate cancer free study participants were asked to undergo a prostate biopsy at 7 years post-randomization [19]. The Institutional Review Board of the Fred Hutchinson

Cancer Research Center, which serves as the statistical center for the PCPT and the Institutional Review Board for each participating clinic site approved of all study procedures and all participants signed written informed consent.

Participants for this nested case–control study were drawn from the 9,457 men randomized to the placebo arm of the PCPT. We restricted the analyses to the placebo arm since finasteride is an effective treatment for BPH [20]. Exclusion criteria for these analyses included men who, at baseline, had previous medical or surgical treatment for BPH (n = 701), a self-reported history of BPH (n = 1,904), or had significant lower urinary tract symptoms [defined as a score of greater than 7 on the IPSS] (n = 1,820). In addition, men using steroid hormones at any time during the study (n = 61) were excluded, leaving 4,971 men eligible for this study.

Definition of BPH and Selection of Cases and Controls

Cases. Cases were men who experienced at least one BPH defining event during the PCPT. BPH events were defined hierarchically by (1) self-reports of medical or surgical procedures and (2) annual self-assessments of lower urinary tract symptoms as assessed by the IPSS [4,21]. This hierarchical approach facilitated a single diagnosis code in the dataset and ensured no double counting of events.

We defined two categories of BPH: (1) ''clinical BPH'' and (2) ''symptomatic progressive BPH.'' Clinical BPH was based on medical/surgical treatment or sustained, significant clinical presentation. Clinical BPH events included trans-uretheral resection of the prostate (TURP), balloon dilation or laser prostatectomy, or reported use of doxazosin, tamsulosin, terazosin, or finasteride medications, or two or more post-randomization IPSS scores >14. Symptomatic progressive BPH was defined as two increases in the IPSS symptom score of at least five points over baseline, with at least one score ≥12. Transient elevations in symptom scores (i.e., a single, isolated elevation of less than five points at one point in time) were not included as BPH events. The entire case group consisted of both clinical BPH cases (n = 427) and symptomatic progressive BPH (n = 300) yielded a sample size of 727 men.

Controls. Controls were drawn from the 1,497 men who, during 7 years of observation, had no more than two missing IPSS scores, no single IPSS greater than eight and no surgical or medical treatment for BPH. These criteria deliberately excluded men with mild to moderate symptoms and yielded a control group with a definitive absence of BPH symptoms and were taking blinded study drug until the end of 7 years. From this sample, we selected all men aged 70 years and over and all non-Caucasian men, in order to maximize power when examining these subgroups. Remaining controls were randomly selected to yield a total control sample (n = 727) that was frequency matched to the age distribution (in 5-year age groups) of cases.

Blood Collection, Processing and Laboratory Analysis

Nonfasting blood specimens were collected at screening (approximately 3 months prior to randomization) and at each annual PCPT visit. Bloods were collected in a 7 ml vacutainer tube without anticoagulant, containing a gel to separate serum from clot after centrifugation. Serum was then removed and the sample frozen as quickly as possible (within 2–4 hr) after separation. Samples were generally sent by overnight courier to Esoterix (Calabasas, CA) within 24 hr of collection but some were stored for up to 7 days at −20°C before shipment [22]. When received, blood specimens were stored at −70°C until analysis. A standard protocol was used to ship specimens from the biorepository to the analytic lab. All specimens were transported on dry ice to the analytic laboratory and were received by next day delivery via air courier. The specimens used for this report are from the screening (baseline) blood draw.

Serum concentrations of IGFI and IGFBP3 were assayed in the laboratory of Dr. Michael Pollak at McGill University, Montreal, Canada. This laboratory uses custom production lots of kits obtained from Diagnostic System Limited (DSL, Webster, TX) to perform enzyme-linked immunosorbent assays (ELISAs). Laboratory personnel were blinded as to which samples were cases and controls. All assays were run in duplicate and the mean of the two measures was used in analysis. The CV% for the duplicate measures were 3.6% and 4.9% for IGFI and IGFBP3, respectively.

Demographic, Health History and Lifestyle Data

Data on race/ethnicity, age, education, health-related behaviors such as smoking and physical activity were collected in PCPT at baseline using self-administered questionnaires. Anthropometry data (height, weight and circumferences of the waist, hip, and abdomen) were collected at 1-year post-baseline by trained clinic staff using standard procedures [23]. Body mass index was calculated as weight (kg) divided by height (m^2). Participants were classified as being normal weight (BMI = 18.5–24.9), overweight (BMI = 25.0–29.9), or obese (BMI ≥ 30.0) according to the Expert Panel on the Identification, Evaluation and

Treatment of Overweight and Obesity in Adults [24]. Extensive medical history data were collected at baseline and updated at the follow-up clinic visits and telephone calls that were part of the study protocol.

Statistical Analyses

Descriptive statistics were used to characterize the study sample. Plasma concentrations of IGFI, IGFBP3 and the IGFI:IGFBP3 molar ratio were categorized into quintiles based on the distribution in the controls. We first used unconditional logistic regression to estimate the odds ratios (OR) and their 95% Confidence Intervals for risk of BPH. We then used polytomous logistic regression to calculate the ORs for clinical BPH and symptomatic progression BPH versus controls. All models were adjusted for age, body mass index and race and only these adjusted results are presented since unadjusted (raw) results can appear to show associations that are actually attributable to confounding. Tests for linear trend across the quintiles was performed by using an ordinal variable corresponding to rank from lowest to highest category, as described by Breslow and Day [25]. We also conducted these analyses stratified by age and body mass index. Twenty-three (3.2%) cases and 18 (2.5%) controls were missing baseline serum specimens, leaving 704 cases and 709 controls available for analysis. All P values were two-sided and considered statistically significant at $P < 0.05$. Statistical analyses were conducted using SAS (version 9.1 Cary, NC).

RESULTS

Table I gives the distributions of demographic and lifestyle characteristics of all cases (n = 704) and controls (n = 709). The mean age for both cases and controls was 63 years. Both cases and controls were overweight, but there were no overall differences in the distributions of normal weight, overweight and obese between cases and controls. Most men reported light or moderate physical activity, and there were no differences in activity levels between cases and controls. There were no differences in distributions of

TABLE I. Demographic and Lifestyle Characteristics of Men With and Without Benign Prostate Hyperplasia in the Prostate Cancer PreventionTrial (PCPT)*

	Benign prostatic hyperplasia (BPH)		
	Cases (n = 704)	BPH controls (n = 709)	*P*
Age (year)			
Mean (SD)	63.4 (5.6)	63.3 (5.4)	0.53[a]
55–59, n (%)	212 (49.9)	213 (50.1)	0.98[b]
60–64, n (%)	199 (50.1)	198 (49.9)	
65–69, n (%)	187 (50.1)	186 (49.9)	
≥70, n (%)	106 (48.6)	112 (51.4)	
BMI (kg/m^2)			
Mean (SD)	27.8 (4.0)	27.4 (4.1)	0.04[a]
Normal (18.5–24.9), n (%)	163 (45.0)	199 (55.0)	0.11[b]
Overweight (25.0–29.9), n (%)	366 (50.5)	358 (49.5)	
Obese (≥30.0), n (%)	163 (52.6)	147 (47.4)	
Race/ethnicity			
White, n (%)	653 (49.8)	657 (50.2)	0.95[b]
Other, n (%)	51 (49.5)	52 (50.5)	
Physical activity			
Met hr/day (mean, SD)	1.87 (2.5)	2.02 (2.5)	0.26[a]
Sedentary, n (%)	113 (52.3)	103 (47.7)	0.25[b]
Light, n (%)	315 (51.6)	295 (48.4)	
Moderate, n (%)	199 (45.9)	235 (54.1)	
Very active, n (%)	74 (50.0)	74 (50.0)	
Smoking history			
Current, n (%)	53 (55.8)	42 (44.2)	0.42[b]
Former, n (%)	414 (49.8)	417 (50.2)	
Never, n (%)	234 (48.5)	249 (51.6)	

[a]From *t*-test.
[b]From chi-square test.
*All men in this study were in the placebo arm of the PCPT.

race/ethnicity or smoking history between cases and controls. The unadjusted mean concentrations of IGFI were 234.4 and 234.8 ng/ml and for IGFBP3 concentrations were 4,205 and 4,303 ng/ml for cases and controls and controls, respectively (data not shown).

Of the 707 BPH cases in this study, most were classified based on IPSS scores, (55.7%) or medical treatment (39.5%; Table II). Those classified by IPSS score included (1) two or more post-randomization scores >14 (n = 103); or (2) two or more increases of at least five points over the baseline IPSS score (n = 291). Only 4.8% of cases reported surgical treatment. Well over half of cases (58.4%) were classified as clinical BPH, defined as all cases except those cases whose only diagnosis was two or more IPSS scores greater than five points above baseline.

Table III gives associations of serum concentrations of IGFI, IGFBP3 and the IGF1:IGFBP3 molar ratio with risk of BPH. These results suggest an inverse association with IGFBP3, but were only statistically significant for clinical BPH. The multivariate-adjusted odds of BPH was OR = 0.60 (95% CI = 0.40–0.90, *P*-trend = 0.01) for the fifth versus first quintile of IGFBP3. While there was no association of IGFI with risk of BPH, regardless of classification (total BPH, clinical BPH or symptomatic progression BPH), we observed a suggestion of an increased risk when we modeled the IGFI:IGFBP3 molar ratio. For total BPH and clinical BPH, a higher versus lower IGFI: IGFBP3 ratio was associated with increased BPH risk. However, while the *P*-value for trend was statistically significant for clinical BPH ($P = 0.02$) there is some inconsistency in the point estimates across the quintiles and all but one point estimate's 95% confidence interval included the null value of 1.0. Therefore, these results must be interpreted cautiously. There were no associations of any of the IGF measures with risk of Symptomatic Progression BPH.

TABLE II. Definitions of BPH Events in the Prostate Cancer Prevention Trial (n = 704)

BPH events[a]	n (%)
Surgical treatment of BPH	32 (4.6)[c]
Medical (drug) treatment of BPH	278 (39.5)[c]
Two or more International Prostate Symptom Scores[b] (IPSS) ≥ 14	103 (14.6)[c]
Two or more IPSS ≥ 5 points above baseline score	291 (41.3)

[a]Events were selected hierarchically in the order listed.
[b]International Prostate Symptom Score's range from 0 to 30, with 0–7 indicating mildly symptomatic, 8–19 moderately symptomatic; and 20–35 severely symptomatic.
[c]Included in definition of ''clinical BPH.''

Table IV gives associations of serum IGFI, IGFBP3 and IGFI: IGFBP3 molar ratio, stratified by age, since age is a very strong risk factor for BPH, and statistical adjustments may not completely remove any confounding [26]. For these analyses, we focus on men with clinical BPH and our two strata were 55–64 years and ≥65 years. In general, IGFBP3 was protective for both age strata. For younger men, comparing the highest to lowest quintile of IGFBP3 there was a reduced risk of clinical BPH (OR = 0.63, 95% CI 0.38–1.03 *P*-trend = 0.03). For older men, the fifth versus first quintile of IGFBP3 was associated with a reduced risk of clinical BPH (OR = 0.43, 95% CI = 0.21–0.89, *P*-trend = 0.13). None of the other IGF analytes varied by any clear or consistent pattern across the two age strata.

Additional analyses were conducted to investigate whether the association of any IGF-axis analytes with BPH risk differed according to body mass index (Table V). Neither IGFI, IGFBP3 nor the IGFI:IGFBP3 molar ratio was associated with BPH among normal weight men (BMI = 18.0–24.9). There was only modest evidence that associations of IGF-axis analytes differed across the BMI strata. For men who were overweight (BMI = 25.0–29.9), there was a nearly doubling in risk of BPH for overweight men in the fourth compared to first quintile of IGFI (OR = 1.90, 95% CI 1.11–3.25), but the test for trend was not statistically significant ($P = 0.13$). For IGFBP3, there was an inverse association; compared to overweight men in the lowest quintile those in higher quintiles had a lower risk, but the point estimates for each quintile are similar in magnitude to the normal weight men. Further, while the test for trend among for IGFBP3 among overweight men was statistically significant ($P = 0.03$), none of the point estimates were statistically significant. Similarly, a higher compared to a lower IGFI:IGFBP3 molar ratio was associated with a near twofold increased risk of BPH for overweight men (OR = 1.95, 955 CI, 1.12-3.38, *P*-trend <0.001). Among men who were obese, there were no meaningful results for any of the IGF-axis related analytes with risk of BPH. The only statistically significant finding was a protective association for higher vs. lower IGFBP3 (OR = 0.24, 95% CI = 0.09–0.68). However, the number of cases in the 5th quintile was quite small (n = 6), so these results must be interpreted with caution. To further examine these associations of BMI with BPH risk, we used multiplicative interaction terms to assess whether or not BMI was an effect modifier of BPH risk. However, none of the *P* values for interaction were statistically significant; the *P* values for interaction were 0.46, 0.82 and 0.43 for BMI*IGFI, BMI*IGFBP3, and BMI*IGFI:IGFBP3, respectively (data not shown).

TABLE III. Associations of IGFI, IGFBP3 and IGFI:IGFBP3 With Risk of BPH in the PCPT

	n		All BPH[a]		Clinical BPH[a]		Symptomatic progression BPH[a]	
	Case (n = 704)	Control (n = 709)	OR (95% CI)[b]	OR (95% CI)[c]	No. of cases	OR (95% CI)[d]	No. cases	OR (95% CI)[d]
IGF1 (ng/ml)								
Q1 <172.7	156	142	1.00	1.00	88	1.0	68	1.0
Q2 172.7 <209.5	122	142	0.78 (0.57–1.10)	0.79 (0.56–1.10)	78	0.89 (0.60–1.31)	44	0.66 (0.42–1.03)
Q3 209.5 to <242.7	124	142	0.80 (0.57–1.12)	0.82 (0.59–1.15)	72	0.85 (0.57–1.26)	52	0.79 (0.51–1.22)
Q4 242.7 <295.9	166	141	1.09 (0.79–1.50)	1.14 (0.82–1.58)	103	1.27 (0.87–1.85)	63	0.98 (0.64–1.50)
Q5 ≥ 295.9	136	142	0.89 (0.64–1.24)	0.93 (0.66–1.30)	72	0.88 (0.59–1.31)	64	0.99 (0.65–1.52)
P-trend			0.84	0.56		0.75		0.49
IGFBP3 (ng/ml)								
Q1 <3508.8	161	141	1.00	1.00	104	1.0	57	1.0
Q2 3508.8 <4070.3	160	142	0.99 (0.72–1.37)	1.04 (0.75–1.45)	101	1.03 (0.72–1.50)	59	1.06 (0.68–1.65)
Q3 4070.3 to <4491.8	112	142	0.70 (0.50–0.97)	0.74 (0.53–1.05)	64	**0.66 (0.45–0.98)**	48	0.89 (0.57–1.41)
Q4 4491.8 <5040.5	150	142	0.93 (0.67–1.29)	0.98 (0.70–1.36)	85	0.87 (0.60–1.27)	65	1.17 (0.76–1.81)
Q5 ≥ 5040.5	121	142	0.75 (0.54–1.05)	0.77 (0.55–1.08)	59	**0.60 (0.40–0.90)**	62	1.08 (0.70–1.68)
P-trend			0.10	0.13		**0.01**		0.61
IGF1: IGFBP3 molar ratio								
Q1 <.044	136	142	1.00	1.00	72	1.0	64	1.0
Q2 .044 to <0.050	118	142	0.87 (0.62–1.22)	0.85 (0.61–1.20)	59	0.83 (0.55–1.26)	59	0.88 (0.57–1.36)
Q3 0.050 to <0.057	154	141	1.14 (0.82–1.58)	1.19 (0.85–1.65)	103	**1.50 (1.02–2.20)**	51	0.82 (0.53–1.27)
Q4 0.057 to <0.64	133	142	0.99 (0.71–1.38)	1.06 (0.75–1.49)	83	1.25 (0.84–1.86)	50	0.82 (0.53–1.29)
Q5 ≥ 0.64	163	142	1.21 (0.87–1.67)	1.25 (0.90–1.74)	96	1.39 (0.94–2.05)	67	1.10 (0.72–1.68)
P-trend			0.18	0.08		**0.02**		0.73

Quartile 1 is the referent for all models.
[a]The models for ''all BPH'' include all cases; the models for ''clinical BPH'' and ''symptomatic progression BPH'' are models for the two subtypes of BPH.
[b]Adjusted for age at baseline and race.
[c]Adjusted for age at baseline, race and BMI.
[d]Polytomous logistic regression adjusting for age at baseline, race and BMI.

TABLE IV. Associations of IGFI, IGFBP3 and IGFI:IGFBP3 with Risk of Clinical BPH, Stratified by Age in the PCPT

	Age 55–64 years				Age 65+ years		
	Clinical case (n = 244)	Control (n = 409)	OR (95% CI)[a]		Clinical case (n = 164)	Control (n = 295)	OR (95% CI)[a]
IGF1 (ng/ml)							
Q1 <182.5	56	83	1.00	Q1 <156.3	28	58	1.00
Q2 182.5 to <217.0	38	82	0.69 (0.41–1.16)	Q2 156.3 to <197.7	41	60	1.49 (0.81–2.74)
Q3 217.0 to <252.4	45	82	0.83 (0.51–1.37)	Q3 197.7 to <232.8	31	59	1.18 (0.62–2.22)
Q4 252.4 to <304.9	57	80	1.08 (0.66–1.74)	Q4 232.8 to <283.5	36	60	2.29 (0.69–2.24)
Q5 ≥ 304.9	48	82	0.89 (0.54–1.46)	Q5 ≥ 283.5	28	58	1.06 (0.56–2.03)
P-trend			*0.76*				*0.93*
IGFBP3 (ng/ml)							
Q1 <3685.4	68	83	1.00	Q1 <3363.3	35	59	1.00
Q2 3685.4 to <4199.8	46	81	0.71 (0.43–1.15)	Q2 3363.3 to <3838.1	40	59	1.27 (0.70–2.29)
Q3 4199.8 to <4653.3	52	81	0.79 (0.49–1.27)	Q3 3838.1 to <4324.9	29	588	0.96 (0.51–1.79)
Q4 4653.3 to <5076.6	36	82	**0.54 (0.33–0.90)**	Q4 4324.9 to <5001.8	46	60	1.36 (0.77–2.42)
Q5 ≥ 5076.6	42	82	0.63 (0.38–1.03)	Q5 ≥ 5001.8	14	59	**0.43 (0.21–0.89)**
P-trend			***0.03***				*0.13*
IGF1: IGFBP3 molar ratio							
Q1 <.045	47	82	1.00	Q1 <0.043	24	59	1.00
Q2 .045 to <0.051	31	82	0.67 (0.39–1.15)	Q2 0.43 to <0.051	35	60	1.43 (0.76–2.71)
Q3 .051 to <0.058	60	83	1.32 (0.80–2.16)	Q3 0.51 to <0.056	38	59	1.63 (0.87–3.07)
Q4 .058 to <0.065	47	81	1.06 (064–1.78)	Q4 .056 to <0.063	33	58	1.43 (0.75–2.73)
Q5 ≥ 0.065	59	81	1.32 (0.81–2.18)	Q5 ≥ 0.63	34	59	1.40 (0.74–2.66)
P trend			*0.10*				*0.39*

[a]Adjusted for BMI and race. Quartile 1 is the referent for all models.

DISCUSSION

In this nested case–control study of 1,454 men enrolled in the placebo arm of the PCPT, we found that the IGFI:IGFBP3 molar ratio was positively associated with risk of clinical BPH, while IGFBP3 was inversely associated with clinical BPH risk. Further, we observed modest associations between body mass index and IGF analytes in relation to BPH risk. Overweight men in the highest quintile of IGFI:IGFBP3 molar ratio had a near doubling in risk of clinical BPH compared to those in the lowest quintile.

While numerous studies have confirmed the strong association between elevated IGFI and BPH among acromegalic patients [27], very few studies of IGFs and BPH risk have been conducted in otherwise healthy men. In a Swedish case–control study (50 BPH cases and 38 controls), there were no statistically significant associations of either IGFI or IGFBP3 with BPH risk [28], and the magnitudes and directions of association were similar to the results we reported here. A very small Turkish study (n = 45 BPH cases and n = 53 prostate cancer cases) measured IGFI and IGFBP3 but the study included no disease-free controls so relative comparisons are not possible [29]. A case–control study in China reported a statistically significant threefold increased risk of BPH associated with higher IGFI [16].

Some of our obesity-related observations, albeit modest, are worthy of further consideration. IGFI synthesis is regulated by other hormones and peptides, including insulin and growth hormone [13,27,30]. Hyperinsulinemia is a well-known consequence of obesity so a more pronounced association of IGFI with

TABLE V. Associations of IGFI, IGFBP3 and IGFI:IGFBP3 With Risk of Clinical BPH, Stratified by Body Mass Index (BMI) in the PCPT

	Normal weight (BMI 18.0–24.9)				Overweight (BMI 25.0–29.9)				Obese (BMI ≥ 30.0)		
	Case[a] (n = 97)	Control (n = 206)	OR (95% CI)[b]		Case[a] (n = 223)	Control (n = 365)	OR (95% CI)[b]		Case[a] (n = 102)	Control (n = 151)	OR (95% CI)[b]
IGF1 (ng/ml)											
Q1 <187.0	21	40	1.00	Q1 <165.6	34	72	1.00	Q1 <170.4	32	29	1.00
Q2 187.0 to <214.3	14	40	0.69 (0.41–1.16)	Q2 165.6 to <209.5	43	72	1.29 (0.74–2.25)	Q2 170.4 to <203.1	13	30	0.44 (0.19–1.02)
Q3 214.3–246.7	23	40	1.08 (0.52–2.26)	Q3 209.5 to <242.9	36	71	1.11 (–.62–1.97)	Q3 203.1 to <236.4	17	30	0.56 (0.25–1.24)
Q4 246.7 to <297.5	18	40	0.83 (0.38–1.80)	Q4 242.9 to <299.8	62	72	**1.90 (1.11–3.25)**	Q4 236.4 to <284.2	19	29	0.65 (0.30–1.42)
Q5 ≥ 297.5	17	39	0.80 (0.37–1.77)	Q5 ≥ 299.8	41	71	1.29 (0.73–2.28)	Q5 ≥ 284.2	17	29	0.55 (0.25–1.05)
P-trend			*0.75*	*P-trend*			*0.13*	*P-trend*			*0.28*
IGFBP3 (ng/ml)											
Q1 <3618.7	25	40	1.00	Q1<3490.5	52	72	1.00	Q1 <3479.0	28	30	1.00
Q2 3618.7 to <4064.2	24	40	0.94 (0.46–1.93)	Q2 3490.0 to <4133.8	54	72	1.05 (0.63–1.74)	Q2 3479.0 to <4043.4	19	29	0.75 (0.34–1.66)
Q3 4064.2 to <4425.2	13	40	0.51 (0.23–1.14)	Q3 4133.8 to <4591.5	45	71	0.89 (0.53–1.50)	Q3 4043.4 to <4482.9	13	30	0.47 (0.20–1.11)
Q4 4425.2 to <4957.3	15	40	0.57 (0.26–1.26)	Q4 4591.5 to <5068.9	35	72	0.69 (0.40–1.19)	Q4 4482.9 to <5210.5	32	28	1.26 (0.60–2.64)
Q5 ≥ 4957.3	17	39	0.68 (0.32–1.46)	Q5 ≥ 5068.9	30	71	0.60 (0.34–1.05)	Q5 ≥ 5210.5	6	30	**0.24 (0.09–0.68)**
P-trend			*0.14*	*P-trend*			***0.03***	*P-trend*			*0.15*
IGF1: IGFBP3 molar ratio											
Q1 <0.046	18	40	1.00	Q1 <0.043	30	72	1.00	Q1 <0.042	20	30	1.00
Q2 .046 to <0.053	17	40	0.93 (0.42–2.07)	Q2 .043 to <0.049	23	72	0.75 (0.40–1.42)	Q2 .042 to <0.049	28	29	1.51 (0.69–3.29)
Q3 .053 to <0.059	24	39	1.34 (0.63–2.85)	Q3 .049 to <0.056	54	71	**1.81 (1.04–3.16)**	Q3 .049–0.056	21	29	1.15 (0.51–2.59)
Q4 .059 to <0.065	18	41	0.95 (0.43–2.10)	Q4 .056 to <0.064	52	72	**1.76 (1.01–3.07)**	Q4 .056 to <0.064	12	29	0.64 (0.26–1.55)
Q5 ≥ 0.065	17	39	0.94 (0.42–2.13)	Q5 ≥ 0.064	57	71	**1.95 (1.12–3.38)**	Q5 ≥ 0.064	17	30	0.84 (0.34–1.94)
P-trend			*0.92*	*P-trend*			**0.001**	*P-trend*			*0.22*

Quartile 1 is referent for all models.
[a]Restricted to clinical cases only.
[b]Adjusted for age and race.

BPH risk among overweight men is plausible and completely consistent with our previous report that obesity, particularly abdominal obesity, was a strong risk factor for BPH [26]. Another recent study has also shown that hyperinsulinemia was an independent risk factor for BPH, even among non-diabetic men [31], another found no association [32], while a third study reported that IGFI was lower among diabetics and only modestly associated with C-peptide (used as a surrogate of insulin) [33]. Taken together, one might conclude that the associations of obesity with biomarkers of risk, such as IGFI, and subsequent risk of disease is complex and not completely understood. It is possible that the obesity-BPH risk mechanism is via an alternate pathway than insulin resistance or the IGF-pathways. Obesity is a complex disorder; it is well known that persons who are obese have unfavorable metabolic profiles, with higher circulating concentrations of adipokines, proinflammatory cytokines and growth factors. We acknowledge that our results for IGF1 and the IGF:IGFBP3 molar ratio by BMI categories, especially overweight, are modest. However, because IGFI can be modified by diet, physical activity and various pharmaceuticals, further research to understand these relationships may have implications for treatment and prevention.

There are several strengths to this study. In this large randomized, controlled clinical trial, there was careful assessment of prostate-related disease in all participants at baseline and throughout the trial, including cancer screening (serum prostate specific antigen and DRE) and lower urinary tract symptom assessments completed annually, and interviews on prostate disease-related diagnoses, surgical treatments and prescription drug use completed quarterly [19]. All anthropometry measures were collected by trained staff using a uniform protocol, eliminating the possibility of inaccurate height and weight from self-report. The ELISA kits used for the analyses of IGF1 and IGFBP3 were obtained from custom production lots from the manufacturer; this reduces any between lot performance and unexplained variability of the assay (the CV% for the blinded duplicates was 3.6% and 4.9% for IGF1 and IGFBP3, respectively). There are also limitations. All information used to define BPH endpoints was based on self-report, including medical and surgical treatment and lower urinary tract symptoms. We used specific interviewer-administered probes to collect treatment information every 3 months during the PCPT but did not have access to medical records to confirm responses. We also used a standardized and well validated self-administered questionnaire to collect urinary-related symptom data on an annual basis, but reporting of symptoms is highly subjective and may differ across race, ethnic and socioeconomic groups. Men in this study were part of an on-going clinical trial and may not be representative of the general population of U.S. men. Finally, the study sample consisted primarily of non-Hispanic white men, so we were unable to examine whether or not the observed associations differed by race/ethnicity.

In conclusion, BPH is a wide-spread clinical problem that seriously affects the quality of life of millions of American men. IGFI and IGFBP3 appear to be associated with BPH risk. Circulating concentrations of these two peptides are modified by genetics, as well as by diet, physical activity and other modifiable lifestyle factors [34–39]. Should continued work in the PCPT, as well as other cohorts, provide further support that lifestyle factors can modify the risk of BPH, then measures to design BPH prevention strategies, or potential targets of drug therapies will help the millions of men who suffer from this disease.

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