Insulin-Like Growth Factors and Risk of Benign Prostatic Hyperplasia

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BACKGROUND. Insulin-like growth factors (IGFs) have potent mitogenic and anti-apoptotic effects on prostate tissue, whereas IGF binding proteins (IGFBPs) inhibit growth of prostatic tissue. The IGF axis has been implicated in prostate cancer risk, but its role in benign prostatic hyperplasia (BPH) is unclear.
METHODS. Plasma levels of IGF-I, IGF-II, IGFBP-1, and IGFBP-3 were determined from the fasting bloods of 206 BPH cases admitted for treatment and 306 randomly selected population controls in Shanghai, China.
RESULTS. Relative to the lowest tertile, men in the highest tertile of IGF-I levels had a significantly elevated risk of BPH (odds ratio [OR] = 2.80, 95% confidence interval [95% CI] = 1.60–4.92; $P_{trend} < 0.001$). Results for IGF-I were more pronounced after adjustment for serum androgens. In contrast, men in the highest IGFBP-3 tertile had a significantly reduced risk (OR = 0.40; 95% CI = 0.23–0.69; $P_{trend} < 0.001$). No associations of BPH with IGF-II and IGFBP-1 were observed.
CONCLUSION. As has been previously observed for prostate cancer, we found that IGF-I and IGFBP-3 are associated with BPH risk in China. Further investigation is needed to elucidate the role of the IGF axis in BPH etiology. *Prostate 52: 98–105, 2002.*
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KEY WORDS: **IGF; growth factors; binding proteins; China; epidemiology**

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a common disorder among older men. Autopsy studies have revealed histologic evidence of BPH in 42% of men aged 51–60 years, rising to 85% among men older than 80 years [1]. In the United States, BPH accounted for an estimated 1.7 million physician visits and 380,000 hospital stays in 1997 [2]. Characterized histologically by nonmalignant proliferation of periurethral transition zone cells, BPH first manifests itself clinically in such symptoms as urinary frequency, urgency, and nocturia [3]. If left untreated, the condition may progress in severity, leading to recurrent bladder infections, bladder calculi, and acute urinary retention.

Insulin-like growth factor I (IGF-I) and IGF-II are peptides functioning as both endocrine hormones and tissue growth factors [4]. Modulating IGF bioactivity

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are six IGF binding proteins (IGFBPs), which bind to IGFs and prevent activation of the type I IGF receptor (IGF1R). Numerous in vivo and in vitro laboratory studies implicate the IGF axis in prostate growth, indicating that both normal and malignant prostate cells express IGFs and IGFBPs [5] and that growth is stimulated by IGFs and inhibited by IGFBPs [6–9]. The role of the IGF axis in BPH is suggested by studies showing that expression of both IGF-II and IGF1R is not only higher in periurethral than in intermediate and subcapsular regions of BPH tissue [10] but also higher in BPH cells than in normal or cancer cells [11]. In addition, in a recent study, men with BPH and increased levels of IGF-I and growth hormone (GH) due to acromegaly regained normal prostate volumes when they achieved GH/IGF-I control [12].

A recent epidemiologic study among Scandinavian men revealed a nonsignificant upward trend in BPH risk associated with increasing circulating IGF-I ($P_{trend} = 0.10$), and a decreasing risk associated with increasing IGFBP-1 ($P_{trend} = 0.10$) [13]. However, a study of Greek men found no association of IGF-I levels with BPH [14]. To further clarify the role of the IGF axis in BPH, we examined whether plasma levels of IGF-I, IGF-II, IGFBP-1, and IGFBP-3 are associated with the risk of BPH in a population-based case-control study in China, where prostate cancer incidence is low but BPH prevalence appears to be similar to that of Western nations [15].

MATERIALS AND METHODS

Study Population

This study was part of a larger population-based, case-control study of prostate disease in Shanghai, China that has been described previously [16,17]. BPH cases were identified as follows: upon the mandatory reporting of each primary prostate cancer case newly diagnosed between 1993 and 1995 to one of the 28 collaborating hospitals in the catchment area of the Shanghai Cancer Registry, the next BPH patient admitted to that hospital for either transurethral resection of the prostate (TURP) or prostatectomy was invited to participate in the study. Based on prostate tissue removed during these procedures, included cases were histologically confirmed to have BPH and found to be negative for prostate cancer. The study was limited to BPH patients who were permanent residents in the 10 districts of urban Shanghai and who had no history of any cancer. Healthy male controls were randomly selected from the household registration records of the 6.5 million permanent residents of Shanghai, China, and were negative for prostate cancer based on digital rectal exam (DRE) and transrectal ultrasound (TRUS).

Data Collection

Using a structured questionnaire administered within 30 days of selection, trained interviewers elicited information on demographic characteristics such as age, marital status, and educational attainment; personal medical history; usual adult dietary patterns; smoking history; alcohol use; and body size. Controls were interviewed at home, whereas BPH cases were interviewed at the hospital. Interviewers also took anthropometric measurements, including height, weight, and circumferences of the waist, hip, and right upper arm. Interview response rates were over 95% among both BPH cases and population controls.

To minimize the influence of possible undiagnosed prostate cancer, BPH cases and population controls with prostate-specific antigen (PSA) levels > 50 ng/ml ($n = 6$ and 4, respectively) were not included in this analysis. To identify potential unrecognized or asymptomatic BPH among the population controls, we elicited information on medical history, conducted a review of medical records and a physical examination (DRE and TRUS), and measured PSA levels in blood. On the basis of this information, 23 controls (7.6%) had a self-reported history of BPH diagnosis, a further 60 controls (19.9%) were found to have BPH during the physical exam, and 27 additional controls (8.9%) had PSA levels over 4 ng/ml, suggesting possible BPH. These subgroups of controls were excluded sequentially in statistical analyses to investigate whether their inclusion affected the results.

Written informed consent was obtained from all study participants. The investigation was approved by the Institutional Review Boards at the U.S. National Cancer Institute (NCI), Bethesda, Maryland, and the Shanghai Cancer Institute, Shanghai, China.

Blood Collection

Cases and controls provided 20 ml of overnight fasting blood for the study. Samples for BPH cases were collected at the hospital before treatment, whereas those for controls were collected at the time of interview. Samples were processed within 3 hr of collection at a central laboratory in Shanghai, and the plasma fractions were stored at -70°C before being shipped frozen to the United States on dry ice.

Laboratory Methods

Laboratory personnel were masked to case-control status. To minimize day-to-day laboratory variation, plasma samples were physically arranged in case-control pairs or triplets such that each assay batch included the same proportion of total cases and controls. Concentrations of IGF-I and IGF-II were

assayed using kits based on enzyme-linked immunosorbent assay (ELISA) preceded by IGFBP removal by means of acid-ethanol extraction (Diagnostic Systems Laboratories [DSL], Webster, TX). Sensitivities of the IGF-I and IGF-II assays are 0.03 ng/ml and 2.4 ng/ml, respectively. Levels of IGFBP-1 and IGFBP-3 were also quantified using ELISA assays from DSL; sensitivities of both assays are 0.04 ng/ml. For all four analytes, each sample was assayed twice, and the mean of the two determinations was used for data analysis. Samples for which the relative difference between the two determinations exceeded 10% were repeated. For quality control purposes, split samples (n = 45) from a single individual were included among the study samples. For IGF-I, IGF-II, IGFBP-1, and IGFBP-3, the coefficients of variation for these split samples were 11.2%, 13.8%, 16.4%, and 17.3%, respectively.

Serum concentrations of testosterone (T), dihydrotestosterone (DHT), 5α-androstane-3α 17β-diol glucuronide (3α-diol G), and sex hormone binding globulin (SHBG) were determined by one of us (F.Z.S.) by using radioimmunoassay. Intra- and interassay coefficients of variation for all analytes ranged from 4 to 8% and 10 to 13%, respectively.

Statistical Analysis

We used pairwise *t*-tests from linear regression models to compare mean age-adjusted levels of IGF-I, IGF-II, IGFBP-1, and IGFBP-3 between BPH cases and controls. We calculated odds ratios (ORs) and corresponding 95% confidence intervals (CIs) to measure effects of IGFs and IGFBPs on BPH risk, by using unconditional logistic regression models to adjust for other potential risk factors, including age, height, weight, body mass index (BMI), waist-to-hip ratio (WHR), T, DHT, 3α-diol G, and SHBG [18]. We also performed a series of regression models to evaluate the effect of eliminating possible undetected BPH cases from the control group. For regression analyses, IGF and IGFBP levels were categorized into tertiles based on their distributions among the controls in each analysis, and tests for linear trend were performed by using these tertile levels as continuous variables. All presented *P* values are two-sided.

RESULTS

The demographic and anthropometric factors of the 200 BPH cases and 302 population controls are shown in Table I. Relative to controls, cases were significantly younger, significantly more likely to be married, and significantly less likely to be smokers. Cases had significantly higher WHRs than controls, indicating greater abdominal obesity. Cases were also more educated, were more obese, consumed more calories, and were less likely to be alcohol users than controls, although these differences were not significant at the 0.05 level.

Cases had significantly higher age-adjusted mean IGF-I levels than controls (Table II, $P < 0.01$). Mean levels of IGFBP-1 and IGFBP-3 were somewhat lower among cases relative to controls, but not significantly

TABLE I. Selected Characteristics of 200 Benign Prostatic Hyperplasia Cases and 302 Population Controls' China

Characteristics	Cases (n = 200)	Controls (n = 302)	*P* value[a]
Age[b] (yr)	69.0 (6.0)	71.9 (7.0)	< 0.001
Height[b] (cm)	167.8 (5.34)	167.5 (5.85)	0.57
Weight[b] (kg)	62.8 (10.2)	61.4 (10.1)	0.13
Body mass index[b] (kg/m^2)	22.3 (3.27)	21.9 (3.26)	0.17
Waist-to-hip ratio[b]	0.90 (0.05)	0.89 (0.06)	< 0.001
Total daily caloric intake[b,c] (kcal)	2436 (595)	2337 (726)	0.09
PSA[d] (ng/ml)	6.75	1.55	
Married[e]	195 (97.5%)	277 (91.7%)	< 0.01
Education ≥ middle school[e]	118 (59.0%)	154 (51.0%)	0.08
Ever used alcohol[e]	71 (35.5%)	130 (43.1%)	0.09
Ever smoked[e]	103 (51.5%)	199 (65.9%)	< 0.01

[a]*t*-test for continuous variables; Mantel-Haenszel chi-squared test for categorical variables.
[b]Mean (standard deviation).
[c]Excluding calories from alcohol intake.
[d]Median values of prostate-specific antigen.
[e]Number (percentage).

TABLE II. Age-Adjusted Means (in ng/ml) of IGF-I, IGF-II, IGFBP-1, and IGFBP-3 by BPH Case/Control Status*

	Cases		Controls		
Analyte	N	Mean (95% CI)	N	Mean (95% CI)	P_{diff}
IGF-I	200	137.1 (126.7–148.4)	302	122.6 (114.1–131.7)	< 0.01
IGF-II	200	449.2 (422.5–477.6)	302	440.7 (416.8–466.1)	0.50
IGFBP-1	198	81.1 (70.8–92.9)	296	87.5 (77.4–98.8)	0.23
IGFBP-3	200	2,703 (2,536–2,882)	301	2,774 (2,617–2,941)	0.38

*IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; BPH, benign prostatic hyperplasia; CI, confidence interval.

so, whereas IGF-II levels did not differ appreciably between the two groups.

ORs for BPH associated with IGF and IGFBP levels are shown in Table III. After adjustment for age, men in the highest tertile of IGF-I had a 1.9-fold increased risk of BPH compared with men in the lowest tertile (OR = 1.89; 95% CI = 1.18–3.03), with a significant trend ($P < 0.01$). After further adjustment for IGFBP-3, risk among men in the highest tertile of IGF-I rose to 2.8-fold compared with men in the lowest tertile (OR = 2.85, 95% CI = 1.61–5.04), with a significant trend ($P_{trend} < 0.001$). IGF-II was not significantly associated with BPH risk after adjustment for age, and a nonsignificant increase in risk was seen after simultaneous adjustment for IGFBP-3 (OR = 1.54, 95% CI = 0.86–2.77).

Plasma levels of IGFBP-3 and IGFBP-1 were not associated with BPH risk after adjustment for age

TABLE III. Odds Ratios and 95% Confidence Intervals for BPH in Relation to Plasma Levels of IGF-I, IGF-II, IGFBP-1, and IGFBP-3*

		Adj for Age[b]	Adj for Age, IGFs[c]	Adj for Age, IGFs, 3α-diol G, SHBG[d]
Tertile of IGFs (ng/ml)	N_1/N_2[a]	OR (95% CI)	OR (95% CI)	OR (95% CI)
IGF-I				
T1 (< 105.9)	43/100	1.00 (–)	1.00 (–)	1.00 (–)
T2 (105.9–< 139.7)	51/101	1.14 (0.69–1.87)	1.43 (0.84–2.43)	1.69 (0.97–2.93)
T3 (≥ 139.7)	105/101	1.89 (1.18–3.03)	2.85 (1.61–5.04)	4.00 (2.17–7.39)
		$P_{trend} < 0.01$	$P_{trend} < 0.001$	$P_{trend} < 0.001$
IGF-II				
T1 (< 372.5)	53/100	1.00 (–)	1.00 (–)	1.00 (–)
T2 (372.5–< 486.5)	61/101	1.01 (0.63–1.62)	1.16 (0.70–1.91)	1.25 (0.75–2.10)
T3 (≥ 486.5)	86/101	1.16 (0.72–1.86)	1.54 (0.86–2.77)	1.72 (0.94–3.15)
		$P_{trend} = 0.52$	$P_{trend} = 0.14$	$P_{trend} = 0.07$
IGFBP-1				
T1 (< 71.07)	81/98	1.00 (–)	1.00 (–)	1.00 (–)
T2 (71.07–< 127.29)	70/99	0.94 (0.61–1.46)	1.04 (0.67–1.62)	0.79 (0.49–1.27)
T3 (≥ 127.29)	47/99	0.72 (0.45–1.15)	0.90 (0.55–1.48)	0.64 (0.37–1.09)
		$P_{trend} = 0.18$	$P_{trend} = 0.72$	$P_{trend} = 0.10$
IGFBP-3				
T1 (< 2,405.7)	65/100	1.00 (–)	1.00 (–)	1.00 (–)
T2 (2,405.7–< 3,052.2)	66/100	0.92 (0.59–1.45)	0.62 (0.38–1.01)	0.62 (0.37–1.03)
T3 (≥ 3,052.2)	69/101	0.81 (0.51–1.28)	0.39 (0.22–0.68)	0.39 (0.22–0.69)
		$P_{trend} = 0.37$	$P_{trend} < 0.001$	$P_{trend} < 0.001$

*BPH, benign prostatic hyperplasia; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; OR, odds ratio; CI, confidence interval; 3α-diol G, 5α-androstane-3α,17β-diol glucuronide; SHBG, sex hormone binding globulin.
[a]N_1 = number of cases; N_2 = number of controls.
[b]Adjusted for age (continuous).
[c]Same as footnote [b] but IGF-I and IGF-II adjusted for IGFBP-3 (continuous); IGFBP-1 and IGFBP-3 adjusted for IGF-I (continuous).
[d]Same as [c], but further adjusted for 3α-diol G (continuous) and SHBG (continuous).

alone. However, after adjustment for both age and IGF-I levels, IGFBP-3 was significantly inversely associated with risk of BPH, with men in the highest tertile having an OR of 0.39 (95% CI = 0.22–0.68; $P_{trend} < 0.001$) compared with men in the lowest tertile. In contrast, IGFBP-1 was not associated with risk of BPH after adjusting for both age and IGF-I.

ORs for BPH after further adjustment for 3α-diol G, believed to be a good indicator of intraprostatic androgenicity [19], as well as the steroid binding protein SHBG are also presented in Table III. Adjustment for these factors strengthened the risk associated with IGF-I; the OR comparing the highest with lowest tertiles was 4.00 (95% CI = 2.17–7.39), with a significant trend ($P_{trend} < 0.001$). The risk estimate for IGF-II was also increased after adjustment for 3α-diol G and SHBG, although the confidence interval for the highest vs. lowest tertile still included unity (OR = 1.72; 95% CI = 0.94–3.15). Adjustment for 3α-diol G and SHBG did not appreciably alter risk estimates for IGFBP-1 or IGFBP-3.

Logistic regression ORs and 95% CIs adjusted for age and either IGFBP-3 or IGF-I, after excluding possible BPH diagnoses from the control group, are shown in Table IV. After exclusion of controls with self-reported BPH, risk estimates for all four analytes were not different from those generated using all controls. Further exclusion of control subjects who had BPH detected during medical record review, physical exam, or both, did not materially alter the risk estimates, although a slight nonsignificant increased risk associated with IGF-II disappeared. Further exclusion of controls with possible BPH defined by PSA levels > 4 ng/ml also did not affect risk estimates for any of the four analytes.

DISCUSSION

In this population-based study conducted in China, we found that plasma levels of IGF-I were associated with a significantly increased risk of BPH, whereas levels of IGFBP-3 were significantly associated with a reduced BPH risk. IGF-II and IGFBP-1 levels were not associated with BPH risk in our study.

Involvement of the IGF axis in BPH etiology is biologically plausible. Prostate cells express IGFs, IGFBPs, and the type I IGF receptor [5], and prostate cell growth is stimulated by IGFs and inhibited by IGFBPs [6–9]. Furthermore, men with acromegaly-induced GH/IGF-I hypersecretion have enlarged prostates, and among acromegalic men with BPH, prostate size and IGF-I levels were shown to return to normal after treatment [12].

Our finding of a significantly elevated risk of BPH associated with increasing IGF-I levels supports the findings of one recent study [13], although another study found no such association [14]. Reasons for this discrepancy are unclear but may be attributable in part to the lack of measurement (and, therefore, adjustment) of IGFBP levels in the latter study [14]. Indeed, the IGF-I results observed in the previous study with positive findings were borderline significant only after adjustment for IGFBP-3 levels [13]. Our study, based on a much larger number of subjects than both earlier studies, revealed significant excess risks associated with IGF-I even without adjustment for IGFBP-3.

Our finding that IGFBP-3 was significantly associated with a decreased risk of BPH stands in contrast to the lack of association in the one previous study with this measurement [13]. However, the OR point estimates for quartiles 2, 3, and 4 in that study were all below unity, suggesting that a significant risk reduction might have been observed with a larger sample size [13]. Although IGFBP-1 was not associated with BPH in our study, it was nonsignificantly related to reduced risk in the previous study [13]. To our knowledge, our study is the first to evaluate plasma IGF-II levels in relation to BPH risk. The negative results are of interest because previous studies of prostate cancer, including our study in Shanghai, have revealed no association with IGF-II [20,21].

It is possible that circulating levels of androgens may influence IGF bioactivity levels, particularly because the androgen pathway influences IGF-mediated cellular regulation. Androgens promote expression of the type I IGF receptor [22], whereas anti-androgenic therapy increases IGFBP expression, thus increasing IGF bioavailability [23]. In our study, adjustment for 3α-diol G and SHBG yielded a much stronger association of IGF-I with BPH risk but did not affect the relationships observed for IGFBP-3, IGFBP-1, or IGF-II.

Recent studies have consistently shown that prostate cancer risk is associated with elements of the IGF axis, including a positive association with IGF-I, an inverse association with IGFBP-3, and no association with IGF-II [14,20,21,24,25]. This is of particular interest because BPH and prostate cancer share some risk factors, including advancing age and the requirement of functioning testes. The relation of the IGF axis to prostate cancer and to BPH suggest that both benign and malignant proliferations of the prostate may share pathogenic mechanisms, although there is no clear evidence that BPH predisposes to prostate cancer [26]. Indeed, the risk estimates reported previously for IGF-I and IGFBP-3 in a parallel study of prostate cancer in Shanghai [20] resemble those reported here for BPH. Prospective studies such as those that have been done for prostate cancer [21] are needed to confirm the findings for BPH.

TABLE IV. Odds Ratios and 95% Confidence Intervals for BPH in Relation to Plasma Levels of IGF-I, IGF-II, IGFBP-1, and IGFBP-3, Excluding Controls With Possible BPH by Self-report, Medical/Physical Diagnosis, or PSA Levels > 4 ng/ml*

		All controls		Excluding controls with self-reported BPH		Excluding controls with self-reported or physical exam-diagnosed BPH		Excluding controls with self-reported or physical exam-diagnosed BPH, or PSA > 4 ng/ml	
Analyte	Tertile	N_1/N_2[a,b]	OR (95% CI)[c]	N_1/N_2[a,d]	OR (95% CI)[c]	N_1/N_2[a,e]	OR (95% CI)[c]	N_1/N_2[a,f]	OR (95% CI)[c]
IGF-I	T1	43/100	1.00 (–)	43/92	1.00 (–)	43/72	1.00 (–)	43/63	1.00 (–)
	T2	52/101	1.43 (0.84–2.43)	52/94	1.42 (0.83–2.43)	54/74	1.40 (0.81–2.42)	57/65	1.51 (0.86–2.66)
	T3	105/101	2.85 (1.61–5.04)	105/93	2.91 (1.63–5.19)	103/73	2.89 (1.58–5.31)	100/64	2.86 (1.53–5.34)
		$P_{trend} < 0.001$		$P_{trend} < 0.001$		$P_{trend} < 0.001$		$P_{trend} < 0.001$	
IGF-II	T1	53/100	1.00 (–)	52/92	1.00 (–)	56/72	1.00 (–)	57/63	1.00 (–)
	T2	61/101	1.16 (0.70–1.91)	62/94	1.18 (0.71–1.96)	70/73	1.16 (0.69–1.95)	69/65	1.16 (0.68–1.99)
	T3	86/101	1.54 (0.86–2.77)	86/93	1.60 (0.88–2.89)	74/74	1.14 (0.61–2.14)	74/64	1.24 (0.65–2.37)
		$P_{trend} = 0.14$		$P_{trend} = 0.12$		$P_{trend} = 0.68$		$P_{trend} = 0.51$	
IGFBP-1	T1	81/98	1.00 (–)	84/91	1.00 (–)	81/71	1.00 (–)	78/62	1.00 (–)
	T2	70/99	1.04 (0.67–1.62)	67/91	0.97 (0.62–1.53)	70/72	0.99 (0.61–1.59)	61/63	0.88 (0.53–1.46)
	T3	47/99	0.90 (0.55–1.48)	47/92	0.86 (0.52–1.41)	47/72	0.83 (0.49–1.41)	59/63	1.04 (0.61–1.75)
		$P_{trend} = 0.72$		$P_{trend} = 0.56$		$P_{trend} = 0.51$		$P_{trend} = 0.92$	
IGFBP-3	T1	65/100	1.00 (–)	66/92	1.00 (–)	60/72	1.00 (–)	60/63	1.00 (–)
	T2	66/100	0.62 (0.38–1.01)	65/93	0.57 (0.35–0.95)	71/73	0.71 (0.42–1.20)	73/64	0.75 (0.44–1.29)
	T3	69/101	0.39 (0.22–0.68)	69/93	0.37 (0.21–0.66)	69/73	0.46 (0.25–0.83)	67/64	0.44 (0.24–0.84)
		$P_{trend} < 0.001$		$P_{trend} < 0.001$		$P_{trend} < 0.01$		$P_{trend} = 0.01$	

*BPH, benign prostatic hyperplasia; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; PSA, prostate-specific antigen; OR, odds ratio; CI, confidence interval; 3α-diol G, 5α-androstane-3α 17β-diol glucuronide; SHBG, sex hormone binding globulin.

[a]N_1 = number of cases; N_2 = number of controls.

[b]Tertile ranges: IGF-I (< 105.9, 105.9–< 139.7, ≥ 139.7 ng/ml); IGF-II (< 372.5, 372.5–< 486.5, ≥ 486.5 ng/ml); IGFBP-1 (< 71.07, 71.07–< 127.29, ≥ 127.9 ng/ml); IGFBP-3 (< 2,405.7, 2,405.77–< 3,052.2, ≥ 3,052.2 ng/ml).

[c]IGF-I and IGF-II adjusted for age (continuous) and IGFBP-3 (continuous); IGFBP-1 and IGFBP-3 adjusted for age (continuous) and IGF-I (continuous).

[d]Tertile ranges: IGF-I (< 105.8, 105.8–< 139.74, ≥ 139.74 ng/ml); IGF-II (< 371, 371–< 487, ≥ 487 ng/ml); IGFBP-1 (< 73.01, 73.01–< 127.29, ≥ 127.29 ng/ml); IGFBP-3 (< 2,416.2, 2,416.2–< 3,056.7, ≥ 3,056.7 ng/ml).

[e]Tertile ranges: IGF-I (< 104.82, 104.82–< 140.74, ≥ 140.74 ng/ml); IGF-II (< 377.5, 377.5–< 500, ≥ 500 ng/ml); IGFBP-1 (< 71.07, 71.07–< 127.62, ≥ 127.62 ng/ml); IGFBP-3 (< 2,389.8, 2,389.8–< 3,064.8, ≥ 3,064.8 ng/ml).

[f]Tertile ranges: IGF-I (< 106.16, 106.16–< 142.6, ≥ 142.6 ng/ml); IFG-II (< 378, 378–< 501, ≥ 501 ng/ml); IGFBP-1 (< 70.36, 70.36–< 118.6, ≥ 118.6 ng/ml); IGFBP-3 (< 2,391.6, 2,391.6–< 3,108.3, ≥ 3,108.3 ng/ml).

Due to the retrospective nature of this study, it is possible that the presence of BPH affected IGF and IGFBP levels among the cases. However, IGF and IGFBP levels did not differ significantly between BPH cases with PSA levels <4, 4–10, and >10 ng/ml, and levels of IGF-I, IGF-II, IGFBP-1, and IGFBP-3 did not differ significantly between controls with possible BPH (by self-report, medical/physical diagnosis, or PSA level >4 ng/ml) and controls without possible BPH by these three criteria. These observations suggest that BPH had little or no effect on IGF and IGFBP levels in this study. Selection bias should also be minimal, as the procedure used to select BPH cases for inclusion in the study minimized selection factors, whereas the controls in the study were a random sample of the population.

Because the IGF axis is associated with prostate cancer in this population [20], and because prostate cancer and BPH often co-exist, it is possible that, despite the exclusion of subjects with extremely elevated PSA levels (>50 ng/ml), undiagnosed prostate cancer among the BPH cases or population controls, or both, may have influenced the results. However, in analyses excluding all cases and controls with modestly elevated PSA levels (>10 ng/ml; $n=60$ and 20, respectively), the risk estimates for all four analytes were materially unchanged, thus reassuring that the observed risks are indeed due to BPH rather than undiagnosed prostate cancer.

Because the case group in this study was composed exclusively of men treated for BPH, all cases had clinically significant BPH. Given the high population prevalence of unrecognized or asymptomatic BPH among elderly men, it is possible that some control subjects may have had undiagnosed BPH; thus, their inclusion in the control group might bias the results toward the null. Because we collected data on possible BPH within the controls, we were able to assess the effect, if any, of disease misclassification among the control group. In analyses in which controls with self-reported BPH, a medical or physical diagnosis of BPH, or a PSA level greater than 4 ng/ml were excluded (a total of 36% of the controls), the risk estimates were not materially altered. These findings suggest that the observed associations, including the null results for IGF-II and IGFBP-1, were not due to misclassification of disease status.

CONCLUSIONS

The results of our study indicate that, similar to prostate cancer, BPH is positively associated with plasma IGF-I, inversely associated with plasma IGFBP-3, and unrelated to plasma IGF-II in China. We further observed that IGFBP-1, previously found to be inversely associated with prostate cancer risk in this study population, was unrelated to BPH. Although it appears that the IGF axis is etiologically relevant to both benign and malignant prostatic diseases, prospective studies are needed to confirm these findings and provide insights into pathogenic mechanisms.

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