Prediagnostic plasma IGFBP-1, IGF-1 and risk of prostate cancer

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Insulin-like growth factor (IGF)−1 is associated with a higher risk of prostate cancer. IGF-binding protein (IGFBP)−1, a marker for insulin activity, also binds IGF-1 and inhibits its action. Data on IGFBP-1 and prostate cancer risk are sparse and whether the IGF and insulin axes interact to affect prostate cancer carcinogenesis is unknown. We evaluated the independent and joint influence of prediagnostic plasma levels of IGFBP-1 (fasting) and IGF-1 on risk of prostate cancer among 957 cases and 1,021 controls with fasting levels of IGFBP-1 and 1,709 cases and 1,778 controls with IGF-1 nested within the Health Professionals Follow-up Study. Unconditional logistic regression adjusting for matching factors was used to estimate the odds ratio (OR) and 95% confidence interval (CI). Higher prediagnostic fasting IGFBP-1 levels were associated with lower risk of prostate cancer (highest *vs.* lowest quartile OR = 0.67, 95% CI 0.52–0.86, $p_{trend} = 0.003$), which remained similar after adjusting for IGF-1. Prediagnostic IGF-1 was associated with increased risk of prostate cancer (highest *vs.* lowest quartile OR = 1.28, 95% CI = 1.05–1.56, $p_{trend} = 0.01$). The associations with each marker were primarily driven by lower-grade and non-advanced prostate cancer. Being low in IGFBP-1 and high in IGF-1 did not confer appreciable additional risk ($p_{interaction} = 0.42$). In summary, prediagnostic fasting IGFBP-1 may influence prostate cancer carcinogenesis. Being low in IGFBP-1 or high in IGF-1 is sufficient to elevate the risk of prostate cancer.

Prostate cancer is the most commonly diagnosed cancer in the western world. Insulin is involved in homeostatic regulation of glucose and energy metabolism, but also has potent mitogenic and growth-stimulatory effects on the prostate that may contribute to the development of malignancy.[1] Because hepatic expression of the insulin-like growth factor-binding protein (IGFBP)−1 is down-regulated by insulin,[2] plasma levels of IGFBP-1 are thought to robustly reflect end organ stimulation by insulin.[3]

In addition to reflecting target tissue insulin exposure, IGFBP-1 binds IGF-1 with high affinity and inhibits IGF-1 action, and thereby decreases free or bioactive IGF-1 levels.[4] Although higher circulating IGF-1 levels are consistently associated with increased risk of prostate cancer in epidemiologic studies,[5] especially low-grade disease,[6] whether the insulin and IGF axes interact to affect prostate cancer carcinogenesis is unknown. Despite the potential importance of IGFBP-1, few studies have examined the association between circulating IGFBP-1 and risk of prostate cancer, with limited sample sizes.[7–10]

To address these, we examined the association between prediagnostic fasting plasma levels of IGFBP-1 and risk of prostate cancer among men in the Health Professionals Follow-up Study (HPFS) and the joint influence of IGFBP-1 and IGF-1. With 4 more years of follow-up and an additional 445 cases than our prior publication on IGF-1,[6] we were also

Key words: IGFBP-1, IGF-1, insulin, prostate cancer, risk

Additional Supporting Information may be found in the online version of this article.

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What's new?

Increased levels of insulin-like growth factor 1 (IGF-1) in the circulation are linked to an elevated risk of prostate cancer. The bioavailability of IGF-1 is limited, however, by IGF binding protein-1 (IGFBP-1), though little is known about the relationship between IGFBP-1 and prostate cancer. In this prospective case-control study, increased prediagnostic fasting plasma IGFBP-1 levels were found to be associated with a reduced risk of prostate cancer, and the positive association between circulating IGF-1 levels and prostate cancer risk was confirmed. The associations were most significant for low-grade and non-advanced disease.

able to investigate the grade- (Gleason score 7 separately from 8–10) and stage-specific associations with more power.

Material and Methods

Study population

The HPFS is a cohort study of 51,529 US male health professionals aged 40–75 years at enrollment in 1986. Participants have been mailed questionnaires every 2 years since baseline to collect data on demographics, lifestyle factors, medical history and disease outcomes, and every 4 years to report update in dietary intake. The overall follow-up rate was greater than 94%, and ascertainment of deaths was more than 98% complete.[11] This case–control study is nested in the HPFS blood cohort, which includes 18,018 (35%) participants who provided blood specimen between 1993 and 1995.

Prostate cancers were identified from self-reports on questionnaires or from death certificates and then confirmed by medical record review through 2008. Staging was classified using the tumor–node–metastasis staging system. Histological grade was assessed using Gleason scores and summed. We used pathological stage and grade when available and clinical measures if pathological information was not available. Prostate cancer cases with T1a disease were excluded because small volume tumors incidentally detected during benign prostatic hyperplasia surgery are susceptible to detection bias. Biennial follow-up questionnaires were mailed to prostate cancer survivors to collect information on treatment and disease progression (*e.g.*, metastases). Vitality status was assessed *via* repeated mailings, telephone calls and searches of the National Death Index. Causes of deaths were confirmed through review of medical records and death certificates. Follow-up for prostate cancer-specific death was complete through March 31, 2012. All reviews were conducted blinded to exposure information.

Eligible controls were participants with an available blood sample, who were alive and free of prostate cancer at the time when the case participant was diagnosed. One randomly selected control was matched to each case on age (year of birth $\pm$ 1 year), prostate-specific antigen (PSA) test before blood draw (yes *vs.* no), timing of blood collection (midnight to before 9 AM, 9 AM to before noon, noon to before 4 PM and 4 PM to before midnight), season (winter, spring, summer and fall) and year. We also required controls to have a PSA test within 2.5 years before the date of diagnosis of their matched case to allow occult prostate cancers to be diagnosed.

For both cases and controls, we excluded anyone who had cancer (except nonmelanoma skin cancer) before blood draw. For IGFBP-1 analysis, we excluded cases ($n = 39$) and controls ($n = 51$) with diabetes before blood draw because IGFBP-1 levels among diabetic patients may not reflect their long-term insulin exposure.[12] We also limited the analysis to fasting samples ($\geq$8 hrs since last meal) because fasting IGFBP-1 levels are a good indicator of long-term insulin levels.[13] This study was approved by the Human Subjects Committee at the Harvard School of Public Health.

Laboratory assays

The cases and matched controls were identified in five waves of follow-up resulting in five assay batches: blood-draw to 1996, 1996–1998, 1998–2000, 2000–2004 and 2004–2008. Plasma concentrations of IGF-1 and IGFBP-1 were measured in duplicate by enzyme-linked immunosorbent assay (Diagnostic Systems Laboratory, Webster, TX) in the laboratory of Dr. Pollak, and the mean of the replicates was used in the analysis. Cases and their matched controls were analyzed together but in random within-pair order, and laboratory personnel were blinded to case–control status. For IGFBP-1, the mean intrapair coefficients of variation (CV) calculated from blinded quality control samples were 13.2, 17.2, 13.1, 2.2 and 14%, respectively. For IGF-1, the CVs were below 10% for all batches, except for the 1998–2000 batch (CV = 13.1%). Measurement of other biomarkers included in this analysis (C-peptide and IGFBP-3) was described in detail elsewhere.[6,14]

Statistical analysis

We used t and χ^2 tests to compare continuous and categorical characteristics of cases and controls, respectively. Partial Spearman's correlation coefficients adjusted for age at blood draw and batch were used to examine the relationships among the various biomarkers, height, body mass index (BMI) and vigorous physical activity among the controls. We used unconditional logistic regressions to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of prostate cancer by batch-specific quartiles of fasting IGFBP-1 and IGF-1 defined among the controls, adjusting for matching factors, including age at blood draw, PSA test before blood draw, batch and season of blood draw, year and follow-up time. We also ran the corresponding conditional logistic

regressions using the matched case and control pairs (707 pairs for IGFBP-1 and 1,708 pairs for IGF-1); however, the results were similar, and the estimates from the unconditional models were more stable because of the inclusion of all controls. We therefore present the results for the unconditional models only. Tests for trend were done by treating the median concentration for each quartile as a continuous variable. We also estimated the OR per standard deviation using continuous IGFBP-1/IGF-1 standardized for batch.[15] We considered the following potential confounders assessed before blood draw: BMI, family history of prostate cancer, height, history of vasectomy, vigorous physical activity, smoking status, coffee intake and history of diabetes (only in the IGF-1 analysis). We also ran separate models adjusting for IGF-1 and C-peptide (another marker of insulin[14]) for the IGFBP-1 analysis and IGFBP-3 for the analysis of IGF-1.

We assessed the associations between the two markers and prostate cancer by grade and stage. Cases were defined as low (Gleason score 2–6), intermediate (Gleason score 7) or high-grade (Gleason score 8–10) and non-advanced (T1b to T3a and N0M0) or advanced/lethal if participant had regionally invasive or metastatic disease ($\geq$T3b, N1 or M1) at diagnosis or developed metastases or died from prostate cancer during follow-up. We also evaluated whether the associations were different by age at diagnosis ($<$65 and $\geq$65 years). We tested for heterogeneity using a χ^2 statistic.

We investigated whether any association varied by BMI ($<$25 and $\geq$25 kg/m^2)[16,17] and height ($<$70 and $\geq$70 inches),[17,18] as well as family history of prostate cancer (yes/no) to explore if association differed by genetic predisposition. Cross-product term of the above factors and continuous IGFBP-1 or IGF-1 were entered into the corresponding model along with the main effect terms, and Wald test was used to evaluate interaction.

In the subset of cases and controls with fasting IGFBP-1, we cross-classified IGFBP-1 and IGF-1 to assess their joint association with prostate cancer risk, using the top tertile of IGFBP-1 and the bottom tertile of IGF-1 as the referent group. We assessed interaction by entering a product term of continuous IGFBP-1 and IGF-1, and the p-value for interaction was determined by a Wald test.

To consider the possibility of reverse causation that undiagnosed tumor could potentially change IGFBP-1/IGF-1 levels, as sensitivity analysis, we excluded cases diagnosed within the first 2 years after blood draw. For IGFBP-1, we also conducted sensitivity analysis including cases and controls with diabetes before blood draw. All the analyses were performed using SAS v 9.3 (SAS Institute, Cary, NC), and the statistical tests were two-sided.

Results

We included a total of 1,709 men with incident prostate cancer diagnosed between 1993 and 2008 and 1,778 controls in the IGF-1 analysis, and 957 cases and 1,021 controls with fasting levels of IGFBP-1 in the IGFBP-1 analysis (Table 1). Few statistically significant differences of potential confounders were observed between cases and controls. IGFBP-1 was inversely associated with IGF-1 in fasting controls (Table 2). BMI and vigorous physical activity were associated with IGFBP-1 but not IGF-1.

Fasting IGFBP-1 was associated with lower risk of total prostate cancer (highest *vs.* lowest quartile OR = 0.67, 95% CI = 0.52–0.86, $p_{trend} = 0.003$) among non-diabetic men (Table 3). The association remained similar after additionally adjusting for confounders, IGF-1, or C-peptide, indicating the robustness of the inverse association and its independence of circulating IGF-1 and C-peptide levels. The associations were similar when we included cases and controls with history of diabetes (996 cases, 1,072 controls; highest *vs.* lowest quartile OR = 0.71, 95% CI = 0.55–0.91, $p_{trend} = 0.009$) or excluded cases diagnosed 2 years within blood draw (830 cases and 1,021 controls; highest *vs.* lowest quartile OR = 0.66, 95% CI = 0.51–0.87, $p_{trend} = 0.004$).

Plasma IGF-1 levels were positively associated with risk of total prostate cancer (Table 3). ORs of total prostate cancer comparing highest with lowest quartile of IGF-1 were 1.28 (95% CI = 1.05–1.56, $p_{trend} = 0.01$). When potential confounders were adjusted in addition to the matching factors, the association remained similar. When we additionally adjusted for IGFBP-3, the association for IGF-1 was attenuated (highest *vs.* lowest quartile OR = 1.10, 95% CI = 0.86–1.40, $p_{trend} = 0.30$). After exclusion of the cases in the first 2 years of follow-up, the results were not remarkably different (1,493 cases and 1,788 controls; highest *vs.* lowest quartile OR = 1.32, 95% CI = 1.07–1.62, $p_{trend} = 0.009$), suggesting that preclinical disease did not influence our results.

Fasting IGFBP-1 was strongly inversely associated with low- and intermediate-grade but not high-grade prostate cancer (Table 4). A statistically significant inverse association was also observed between fasting IGFBP-1 and non-advanced disease but not with advanced/lethal prostate cancer. Higher IGF-1 was significantly associated with increased risk of low-grade prostate cancer, but not with intermediate- or high-grade prostate cancer. We also observed significant positive association between IGF-1 and non-advanced prostate cancer, but not with advanced/lethal prostate cancer. Tests of heterogeneity were not significant for the above comparisons (Table 4), and findings should be interpreted with caution because of small sample sizes in high-grade and non-advanced disease.

Both the inverse and positive associations between fasting IGFBP-1, IGF-1 and total prostate cancer were slightly stronger for cases diagnosed at or above the age of 65 (Table 4). For both markers, we found no interactions with either BMI or height (Table 5 and Supporting Information Table 1). For IGF-1, the association with prostate cancer was stronger among men with family history than among those without family history ($p_{interaction} = 0.045$).

In fasting samples, IGF-1 was similarly associated with prostate cancer as in the total samples after adjusting for

Table 1. Characteristics of prostate cancer cases and controls in the Health Professionals Follow-up Study, 1993–2008

	IGFBP-1 (fasting)[1]			IGF-1[2]		
	Cases ($n = 957$)	Controls ($n = 1,021$)	p^3	Cases ($n = 1,709$)	Controls ($n = 1,778$)	p^3
Sampling period, *n* (%)						
Blood draw (1993–1995) to 1996	118 (12.3)	123 (12.1)		207 (12.1)	208 (11.7)	
1996–1998	151 (15.8)	158 (15.5)		257 (15.0)	257 (14.5)	
1998–2000	123 (12.9)	125 (12.2)		229 (13.4)	235 (13.2)	
2000–2004	310 (32.4)	361 (35.4)		571 (33.4)	630 (35.4)	
2004–2008	255 (26.7)	254 (24.9)		445 (26.0)	448 (25.2)	
Age at blood collection (yr), mean (SD)	63.2 (8.1)	63.2 (8.0)	0.92	63.2 (8.0)	63.1 (8.0)	0.64
Age at diagnosis (yr), mean (SD)	70.0 (7.6)	–		70.0 (7.4)	–	
Time to diagnosis from blood draw (yr), median (IQR)	6.5 (3.5–9.9)	–		6.5 (3.5–9.8)	–	
Family history of prostate cancer, %	14.3	11.5	0.06	14.0	11.3	0.02
Personal history of diabetes, %	0	0		5.2	5.3	0.86
History of vasectomy, %	29.7	29.1	0.77	28.2	29.5	0.39
Current smoker, %	3.8	3.2	0.52	3.6	3.4	0.68
Height (inch), mean (SD)	70.2 (2.7)	70.2 (2.6)	0.98	70.2 (2.7)	70.2(2.6)	0.97
BMI (kg/m^2), mean (SD)	25.8 (3.3)	25.8 (3.5)	0.84	25.8 (3.3)	25.8(3.4)	0.63
Vigorous physical activity (MET-hrs/wk), mean (SD)	12.0 (21.2)	14.2 (24.2)	0.03	12.8 (22.8)	13.3(22.4)	0.52
Coffee intake (servings/d), mean (SD)	1.9 (1.6)	1.9 (1.6)	0.63	1.9 (1.6)	2.0(1.6)	0.36
Fasting at blood draw, %	100	100		59.6	61.0	0.40
Plasma IGFBP-1, median (IQR)[4]	18.5 (10.5–25.7)	19.5 (11.0–28.4)	0.01	15.6 (6.70–25.1)	15.9 (7.43–25.3)	0.07
Plasma IGF-1, median (IQR)[4]	177 (147–211)	172 (142–208)	0.009	178 (147–212)	173 (142–208)	0.003
Plasma IGFBP-3, median (IQR)[4]	3,546 (3,065–4,061)	3,445 (2,932–3,956)	0.001	3,513 (3,078–4,032)	3,469 (2,925–3,972)	0.002
Plasma C-peptide, median (IQR)[4]	1.61 (1.20–2.22)	1.59 (1.14–2.24)	0.61	1.85 (1.27–2.91)	1.87 (1.24–2.96)	0.20

[1]Excluded participants with diabetes before blood draw.
[2]About 189 cases and 195 controls did not have IGFBP-1 measurement, and 12 cases and 13 controls did not have C-peptide measurement.
[3]*t*-test for continuous variables and χ^2 test for categorical variables.
[4]Standardized for batch.

matching factors and potential confounders (highest *vs.* lowest quartile OR = 1.28, $p_{trend} = 0.04$). We did not observe significant multiplicative interaction between fasting IGFBP-1 and IGF-1 levels for their associations with total prostate cancer. Men in the bottom IGFBP-1 and top IGF-1 tertiles had 78% increased risk of prostate cancer compared with men in the top IGFBP-1 and bottom IGF-1 tertiles (OR = 1.78, 95% CI = 1.26–2.51; $p_{interaction} = 0.42$) (Fig. 1). Being low in IGFBP-1 or high in IGF-1 was sufficient to elevate the risk of prostate cancer.

Discussion

In this large prospective nested case–control study, we found evidence for an inverse association between fasting plasma IGFBP-1 and risk of prostate cancer. The association was independent of circulating IGF-1 and C-peptide, not confounded by known risk factors of prostate cancer, and primarily driven by low- and intermediate-grade and non-advanced prostate cancer than by high-grade and advanced/lethal prostate cancer. With extended follow-up, we also confirmed the positive association between

Table 2. Partial Spearman's correlation coefficients between IGFBP-1 (fasting), IGF-1 and other variables among controls

	IGFBP-1	IGF-1	IGFBP-3	C-peptide	Height	BMI	Vigorous physical activity
Controls in the IGFBP-1 analysis (fasting, $n = 1{,}021$)							
IGFBP-1	1.00						
IGF-1	−0.18[1]	1.00					
IGFBP-3	−0.14[1]	0.61[1]	1.00				
C-peptide	−0.56[1]	0.10[1]	0.11[1]	1.00			
Height	−0.08[1]	0.07[1]	0.04	0.07[1]	1.00		
BMI	−0.47[1]	0.01	0.02	0.47[1]	−0.01	1.00	
Vigorous physical activity	0.19[1]	0.05	0.03	−0.16[1]	0.03	−0.19[1]	1.00
Controls in the IGF-1 analysis[2] ($n = 1{,}778$)							
IGFBP-1	1.00						
IGF-1	−0.15[1]	1.00					
IGFBP-3	−0.14[1]	0.62[1]	1.00				
C-peptide	−0.56[1]	0.10[1]	0.08[1]	1.00			
Height	−0.06[1]	0.05[1]	0.003	0.07	1.00		
BMI	−0.42[1]	−0.01	0.04	0.36	−0.01	1.00	
Vigorous physical activity	0.14[1]	0.03	0.02	−0.14	0.03	−0.19[1]	1.00

[1]$p < 0.05$.
[2]About 195 controls did not have IGFBP-1 measurement, and 13 controls did not have C-peptide measurement.

Table 3. Plasma IGFBP-1 (fasting), IGF-1 and risk of prostate cancer

	Quartiles					
	Q1	Q2	Q3	Q4	p_{trend}	OR (95% CI) per SD
Fasting IGFBP-1						
Ca/Co (957/1,021)	287/253	235/256	237/258	198/254		
OR (95% CI)[1]	1.00 (ref)	0.81 (0.63–1.04)	0.79 (0.62–1.01)	0.67 (0.52–0.86)	0.003	0.88 (0.80–0.97)
OR (95% CI)[2]	1.00 (ref)	0.79 (0.62–1.02)	0.79 (0.61–1.03)	0.67 (0.51–0.89)	0.01	0.89 (0.81–0.98)
OR (95% CI)[3]	1.00 (ref)	0.81 (0.64–1.04)	0.81 (0.63–1.04)	0.69 (0.53–0.90)	0.01	0.89 (0.81–0.98)
OR (95% CI)[4]	1.00 (ref)	0.77 (0.60–1.00)	0.74 (0.57–0.97)	0.63 (0.47–0.85)	0.004	0.87 (0.79–0.96)
IGF-1						
Ca/Co (1,709/1,778)	377/443	395/445	469/446	468/444		
OR (95% CI)[1]	1.00 (ref)	1.06 (0.87–1.28)	1.27 (1.04–1.54)	1.28 (1.05–1.56)	0.01	1.12 (1.05–1.21)
OR (95% CI)[2]	1.00 (ref)	1.05 (0.87–1.28)	1.26 (1.04–1.53)	1.29 (1.06–1.57)	0.005	1.12 (1.05–1.21)

[1]Unconditional logistic regression adjusted for matching factors: age at blood collection (year), prostate-specific antigen test before blood collection (yes/no), year of blood collection, timing of blood collection (midnight to 9 AM, 9 AM to before noon, noon to before 4 PM and 4 PM to before midnight), batch (blood collection [1993–1995]–1996, 1996–1998, 1998–2000, 2000–2004 and 2004–2008), season (winter, spring, summer and fall) and follow-up time; Quartile cut points for IGFBP-1 (ng/mL) were 14.2, 21.9 and 35.0 for Batch 1; 15.8, 26.3 and 40.3 for Batch 2; 10.6, 19.2 and 30.9 for Batch 3; 12.5, 22.6 and 39.1 for Batch 4 and 2.1, 3.8 and 6.7 for Batch 5; Quartile cut points for IGF-1 (ng/mL) were 129.5, 168.9 and 209.2 for Batch 1; 138.0, 168.3 and 204.8 for Batch 2; 153.8, 181.9 and 224.4 for Batch 3; 176.3, 210.2 and 256.1 for Batch 4 and 106.0, 127.5 and 150.4 for Batch 5.
[2]In addition to matching factors, adjusted for potential confounders, including BMI (<25, 25–30 and ≥ 30 kg/m^2), history of diabetes (for IGF-1 analysis only), family history of prostate cancer, height, history of vasectomy, vigorous physical activity (quintiles), smoking status (never, past, current and unknown) and coffee intake (quartiles).
[3]Adjusted for IGF-1 in addition to matching factors.
[4]Adjusted for C-peptide in addition to matching factors.

circulating IGF-1 and prostate cancer risk, primarily driven by low-grade and non-advanced prostate cancer. Being low in IGFBP-1 or high in IGF-1 was sufficient to elevate the risk of prostate cancer, and being low in IGFBP-1 and high in IGF-1 did not confer appreciable additional risk.

Previous studies on circulating IGFBP-1 and risk of prostate cancer were conducted in European[9,10] or non-white

Table 4. Plasma IGF-1 (fasting), IGFBP-1 and risk of prostate cancer by tumor characteristics

	Quartile										
	Q1		Q2		Q3		Q4				
	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)	p_{trend}	OR (95% CI) per SD	$p_{heterogeneity}$
Fasting IGFBP-1											
Gleason score											
Low (2–6; 453 cases)	137/253	1.00 (ref)	106/256	0.77 (0.56–1.05)	122/258	0.86 (0.64–1.17)	88/254	0.63 (0.45–0.87)	0.01	0.87 (0.77–0.98)	0.81
Intermediate (7; 339 cases)	108/253	1.00 (ref)	87/256	0.82 (0.58–1.14)	81/258	0.75 (0.53–1.05)	63/254	0.61 (0.42–0.88)	0.01	0.85 (0.74–0.97)	
High (8–10; 100 cases)	29/253	1.00 (ref)	25/256	0.86 (0.49–1.52)	19/258	0.58 (0.31–1.08)	27/254	0.80 (0.45–1.42)	0.41	0.90 (0.72–1.13)	
Stage											
Non-advanced (799 cases)	247/253	1.00 (ref)	195/256	0.80 (0.62–1.03)	205/258	0.81 (0.63–1.05)	152/254	0.61 (0.47–0.81)	0.001	0.85 (0.76–0.94)	0.41
Advanced/lethal (119 cases)	34/253	1.00 (ref)	31/256	0.87 (0.51–1.48)	24/258	0.63 (0.36–1.13)	30/254	0.74 (0.43–1.29)	0.26	0.92 (0.76–1.11)	
Age at diagnosis (yr)											
<65 (249 cases)	91/253	1.00 (ref)	58/256	0.76 (0.49–1.18)	63/258	1.00 (0.64–1.57)	37/254	0.70 (0.42–1.16)	0.30	0.88 (0.73–1.07)	0.91
≥65 (708 cases)	196/253	1.00 (ref)	177/256	0.80 (0.61–1.06)	174/258	0.69 (0.52–0.92)	161/254	0.61 (0.46–0.82)	0.001	0.85 (0.77–0.94)	
IGF-1											
Gleason score											
Low (2–6; 816 cases)	164/443	1.00 (ref)	180/445	1.10 (0.85–1.41)	239/446	1.44 (1.13–1.84)	233/444	1.41 (1.10–1.81)	0.002	1.17 (1.08–1.28)	0.19
Intermediate (7; 576 cases)	128/443	1.00 (ref)	136/445	1.01 (0.77–1.34)	151/446	1.10 (0.83–1.44)	161/444	1.15 (0.87–1.52)	0.26	1.07 (0.97–1.18)	
High (8–10; 188 cases)	51/443	1.00 (ref)	43/445	0.92 (0.60–1.42)	44/446	1.01 (0.65–1.56)	50/444	1.19 (0.78–1.83)	0.36	1.06 (0.90–1.24)	
Stage											
Non-advanced (1,417 cases)	297/443	1.00 (ref)	323/445	1.07 (0.87–1.32)	387/446	1.27 (1.04–1.56)	412/444	1.35 (1.09–1.66)	0.002	1.14 (1.06–1.23)	0.07
Advanced/lethal (207 cases)	61/443	1.00 (ref)	46/445	0.83 (0.55–1.25)	57/446	1.09 (0.73–1.62)	41/444	0.88 (0.57–1.37)	0.83	1.01 (0.87–1.18)	
Age at diagnosis											
<65 (434 cases)	52/443	1.00 (ref)	71/445	0.81 (0.52–1.27)	131/446	1.17 (0.78–1.76)	180/444	1.25 (0.84–1.86)	0.06	1.12 (0.98–1.27)	0.59
≥65 (1,275 cases)	325/443	1.00 (ref)	324/445	1.14 (0.92–1.41)	338/446	1.36 (1.10–1.68)	288/444	1.24 (1.00–1.55)	0.03	1.10 (1.02–1.19)	

Note: The models were adjusted for matching factors: age at blood collection, prostate-specific antigen test before blood collection, year of blood collection, timing of blood collection, batch, season and follow-up time.

Table 5. Plasma IGFBP-1 (fasting) and risk of prostate cancer by BMI, height and family history of prostate cancer (joint analysis)

	Quartile of fasting IGFBP-1								
	Q1		Q2		Q3		Q4		
	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)	$p_{interaction}$
BMI (kg/m^2)									
<25	70/57	1.00 (ref)	91/91	0.81 (0.51–1.28)	119/134	0.70 (0.46–1.08)	135/181	0.59 (0.39–0.90)	0.13
≥25	217/196	0.91 (0.61–1.35)	144/165	0.72 (0.47–1.09)	118/124	0.76 (0.49–1.18)	63/73	0.69 (0.42–1.12)	
Height (inches)									
<70	97/78	1.00 (ref)	78/82	0.77 (0.50–1.19)	83/103	0.64 (0.42–0.97)	88/100	0.70 (0.46–1.06)	0.80
≥70	190/175	0.87 (0.61–1.26)	157/174	0.72 (0.50–1.05)	154/155	0.78 (0.53–1.13)	110/154	0.55 (0.37–0.82)	
Family history									
No	253/221	1.00 (ref)	197/229	0.75 (0.58–0.98)	200/228	0.75 (0.57–0.97)	170/226	0.64 (0.48–0.84)	0.75
Yes	34/32	0.95 (0.56–1.59)	38/27	1.24 (0.73–2.11)	37/30	1.08 (0.64–1.81)	28/28	0.85 (0.49–1.49)	

Note: The models were adjusted for matching factors: age at blood collection, prostate-specific antigen test before blood collection, year of blood collection, timing of blood collection, batch, season and follow-up time.

Figure 1. Joint association of plasma fasting IGFBP-1 and IGF-1 and risk of prostate cancer. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

populations (African, Japanese-American and Latino[8] or Chinese[7]) with mixed findings (two nonsignificant but inverse associations,[7,10] one null[8] and one positive association[9]). Limitations of these studies included small number of cases and controls[7,9,10] and using blood samples collected 4–6 weeks after case diagnosis[9] or right before treatment.[7]

It is unclear whether fasting IGFBP-1 influences prostate cancer development through reflecting insulin levels, modulating IGF-1 activity and/or exerting independent effects. However, direct epidemiologic evidence linking circulating insulin and prostate cancer risk is limited and mixed: a case–control[19] and a recent case–cohort study[20] observed positive associations, whereas three other prospective studies observed no association.[10,21,22] In addition, findings are inconclusive between C-peptide, a marker for insulin secretion, and risk of prostate cancer,[14,23–25] including a recent analysis in HPFS (highest *vs.* lowest quartile OR = 1.05, 95% CI = 0.82–1.34, $p_{trend} = 0.95$).[14]

The modulation of IGF-1 activity by IGFBP-1 is complex. In fasting state, IGFBP-1 levels are high due to the low inhibitory effect of insulin and the stimulatory effect of cortisol and glucagon on hepatic IGFBP-1 transcription. Because the affinity of IGFBP-1 for IGF-1 exceeds that of IGF-1 for the type-1 IGF-receptor, high IGFBP-1 levels may reduce IGF-1 available to bind to IGF-1 receptors and thus reduce the insulin-like activity of IGF-1 on peripheral metabolism.[12] Preclinical studies also suggest that IGFBP-1 may exert inhibitory effects on cancer cell growth and migration in an IGF-1-dependent manner.[4,26,27] Among a cohort of men participating in a low-fat diet and exercise program, the addition of IGFBP-1 to their baseline serum induced a significant reduction in cell growth and increased apoptosis of LNCaP cell cultures, and IGFBP-1 antagonized the IGF-I growth stimulatory effects on LNCaP cell growth and induced apoptosis.[27] Although we observed minimal multiplicative interaction between fasting IGFBP-1 and IGF-1 levels on risk of total prostate cancer, more research of the joint influence of IGFBP-1 and IGF-1, particularly by subtypes of prostate cancer, is needed.

In addition, evidence has emerged showing that IGFBP-1 could activate cell-surface receptors directly, and IGF-1

independent stimulation of integrin-FAK (focal adhesion kinase)-ILK (integrin-linked kinase)-PI3k-Akt constitutes a putative mechanism by which IGFBP-1 modulates insulin sensitivity[28,29] and influences cancer development.[30]

Our findings on IGF-1 and overall risk of prostate cancer are consistent with a previous meta-analysis.[5] A stronger association with low-grade prostate cancer was observed in a pooled analysis of 12 prospective studies[31] and in a recently updated report from EPIC (European Prospective Investigation into Cancer and Nutrition).[32] The additional 445 cases than our prior publication[6] allowed us to evaluate Gleason score 7 (intermediate-grade) separately from Gleason score 8–10 (high-grade) and found that the association between IGF-1 and prostate cancer was primarily driven by low-grade disease compared with intermediate and to high-grade prostate cancer although *p*-value for heterogeneity was not significant and power was limited. This finding further supports our previous hypothesis that growth of poorly differentiated cancers may be more autonomous because the PI3k-Akt pathway is constitutively active due to molecular defects (*e.g.*, loss of PTEN, which is associated with higher-grade tumors). Thus, high-grade prostate cancers may be less sensitive to the action of IGF-1 than low-grade cancers.[6] In fact, a recent pooling analysis among 2,424 prostate cancer patients also supported that IGF-1 was minimally involved in prostate cancer progression,[33] although results from other studies had mixed findings.[34,35] A recent report from a large case–control study from the United Kingdom and a meta-analysis also suggested that IGF-1 was associated with routinely but not PSA-detected disease[36]; therefore, the role of IGF-1 in prostate cancer progression could not be completely ruled out and requires further research.

The strengths of this study include its prospective nature and large sample size, strict quality control for measurements of biomarkers, the use of methods to handle absolute differences in the biomarkers among the analytical batches (batch-specific quartiles and continuous measures adjusting for batch), the adjustment for a number of potential confounders and the ability to investigate associations by Gleason score and tumor stage, as well as the joint association of IGFBP-1 and IGF-1. The study also has some limitations, including a single measurement of the biomarkers, which may not reflect long-term circulating levels, potential measurement errors and Gleason grading errors and limited power to assess heterogeneity by stage and grade and to evaluate the joint influence of both biomarkers by subtypes of prostate cancer. In addition, lower IGFBP-1 and/or higher IGF-1 may be associated with increased risk of enlarged prostate, which may lead to elevated PSA levels and detection of prostate cancer. However, enlarged prostate, in general, would make cancer detection harder.

In summary, higher prediagnostic fasting IGFBP-1 levels were associated with lower risk of prostate cancer, whereas higher IGF-1 levels were associated with increased prostate cancer risk. The associations were primarily driven by lower-grade and non-advanced prostate cancer. Because high BMI, sedentary life style and consumption of Western diet lead to low levels of IGFBP-1,[37] our findings imply that dietary and lifestyle modifications may play an important role for prostate cancer prevention. Research to better understand the role of IGFBP-1 as well as interaction of the insulin and IGF axes in prostate cancer development, in particular, by subtypes of prostate cancer, is warranted.

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