Cancer Causes and Control (2005) 16:255–262
DOI 10.1007/s10552-004-3484-8

Plasma insulin-like growth factor-1 and binding protein-3 and subsequent risk of prostate cancer in the PSA era☆

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Received 13 May 2004; accepted in revised form 20 September 2004

Key words: cohort study, insulin-like growth factor, prostate cancer, risk.

Abstract

Objective: The insulin-like growth factor (IGF) axis is thought to contribute to the growth and progression of prostate cancer. Some prospective studies support a direct association between IGF-1 and prostate cancer, in particular advanced disease, whereas both inverse and direct associations with prostate cancer have been reported for insulin-like growth factor binding protein-3 (IGFBP-3), the major IGF-1 binding protein in circulation. We prospectively investigated the associations of plasma IGF-1 and IGFBP-3 concentrations with prostate cancer detected in the PSA era.

Methods: We identified 462 prostate cancer cases diagnosed after providing a blood specimen in 1993, but before January 1998 among men in the Health Professionals Follow-up Study. Controls were 462 age-matched men without prostate cancer who had had a PSA test after providing a blood specimen. We measured plasma concentrations of IGF-1 and IGFBP-3 by ELISA. Conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) of prostate cancer.

Results: Men with higher concentrations of IGF-1 (comparing extreme quartiles OR = 1.37, 95% CI 0.92–2.03, *p*-trend = 0.05) and IGFBP-3 (OR = 1.62, 95% CI 1.07–2.46, *p*-trend = 0.08) had a higher risk of prostate cancer. After mutual statistical adjustment, these associations were attenuated for both IGF-1 (OR = 1.17, 95% CI 0.69–1.99, p-trend = 0.29) and IGFBP-3 (OR = 1.40, 95% CI 0.80–2.44, p-trend = 0.56). We found no significant association of IGF-1 with regionally invasive or metastatic (≥T3b, N1, or M1) prostate cancer, although the number of these cases was small (n = 42).

Conclusions: Our findings for IGF-1 and prostate cancer diagnosed in the PSA era are similar to most previous studies, albeit weaker in magnitude. Our suggestive positive findings for IGFBP-3 are similar to some studies, but in direct contrast to others.

☆Supported by Public Health Service grants CA55075 and CA72036 (National Cancer Institute) and HL35464 (National Heart, Lung, and Blood Institute) from the National Institutes of Health. Dr. Platz is supported by the Bernstein Young Investigator's Award.

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Introduction

Insulin-like growth factor-1 (IGF-1) may contribute to the growth and progression of prostate cancer *via* the promotion of proliferation and the inhibition of apoptosis, as demonstrated *in vitro* in normal and prostate cancer cells [1, 2]. IGF-1 is mainly produced in the

liver, but also in other tissues, including in the prostate. Most circulating IGF-1 is bound to IGF binding protein (IGFBP)-3. In the prostate, IGFBP-3 promotes apoptosis [3] by interactions with the retinoid X receptor [4].

Several previous epidemiologic studies reported that circulating concentration of IGF-1 measured in mid-life is associated with a higher risk of prostate cancer [5–12]. One prospective US study observed associations for advanced disease and cases diagnosed in the era prior to the routine screening for elevated PSA, but not for early stage cases or cases diagnosed in the PSA era [13], whereas a Swedish prospective study observed an association for IGF-1 and IGFBP-3 among men overall, with advanced disease, and with early stage disease, although more weakly so [12]. Although IGFBP-3 would be predicted to decrease the risk of prostate cancer by limiting the bioavailability of IGF-1 and independently of IGF-1 by promoting apoptosis, both inverse and direct associations with prostate cancer have been reported [14]. However, when IGFBP-3 concentration was statistically adjusted for IGF-1 concentration, in several studies an inverse association was suggested overall [6, 9, 11, 13] or at least in a subset of men [8].

With the widespread adoption of PSA testing in the US, the nature of diagnosed prostate cancer has shifted to largely small volume, organ-confined disease. Whether these early stage cases are susceptible to the growth and anti-apoptotic effects of IGF-1 and the apoptotic effects of IGFBP-3 is unknown. Thus, to address whether the IGF-axis is associated with risk of prostate cancer in the PSA era, we measured plasma concentrations of IGF-1 and IGFBP-3 in 462 prostate cancer cases diagnosed since 1993 and 462 matched controls nested in the prospective Health Professionals Follow-up Study.

Materials and methods

Study population

Incident prostate cancer cases and matched controls were selected from among participants in the prospective Health Professionals Follow-up Study. At enrollment in 1986, the 51,529 US men were aged 40–75 years. At baseline and then biennially the participants responded to a mailed questionnaire that included questions on demographics, lifestyle, and medical history. At baseline and then every four years they completed a semi-quantitative food frequency questionnaire. Deaths among cohort members were identified by reports from next-of-kin, the postal service, or searches of the National Death Index [15].

Between 1993 and 1995, 18,018 of the men provided a blood specimen, which was collected in tubes containing sodium EDTA and was shipped by overnight courier while chilled. After centrifuging and aliquotting into plasma, erythrocytes, and buffy coat, the samples were stored in liquid nitrogen freezers. Among the men who provided a blood specimen, 94.6% responded to the 1998 questionnaire and 3.5% died before the end of follow-up. We excluded from the analysis men with a cancer diagnosis (except non-melanoma skin cancer) that preceded the date that a blood sample was provided. This study was approved by the Human Subjects Committee at the Harvard School of Public Health.

Prostate cancer cases and controls

After receiving written permission from a participant who reported a prostate cancer diagnosis on a follow-up questionnaire, or from the next-of-kin of decedents, we sought medical and pathology records. Study investigators blinded to information from the questionnaire reviewed these records to confirm the diagnosis and to abstract stage at diagnosis and Gleason sum. Diagnosis records were not obtained for 7.1% of the men who provided a blood specimen and who reported prostate cancer, but we included these unconfirmed diagnoses as cases because we found that the reporting of a prostate cancer diagnosis by these health professionals was accurate. We excluded as cases men with T1a disease (*i.e.*, incidental microscopic focal tumors) to avoid detection bias due to differential rates of surgery for benign prostatic hyperplasia. Cases were classified as regionally invasive or metastatic (≥T3b, N1, or M1), organ/confined or minimal extraprostatic extension (T1b to T3a and N0M0), Gleason sum ≥ 7, and Gleason sum < 7. We confirmed 462 nonT1a prostate cancer cases between the date that a blood specimen was provided and January 31, 1998, the end of follow-up for this analysis.

Eligible controls were men still alive at the date of the case's diagnosis, who did not have a diagnosis of cancer, and who had had a PSA test after the date of blood draw (for opportunity for prostate cancer detection). From among these men, one randomly selected control was matched per case on year of birth (± 1 year), PSA test prior to blood draw (yes/no), and timing of blood draw – time of day (midnight to before 9 am, 9 am to before noon, noon to before 4 pm, 4 pm to before midnight), season (winter, spring, summer, fall), and year (exact).

Laboratory assays

Plasma IGF-1 and IGFBP-3 concentrations were measured by ELISA (Diagnostic Systems Laboratory, Webster, TX) in the laboratory of Dr. Michael Pollak as was done previously [6]. Case–control pairs were analyzed together, and laboratory personnel were blinded to case–control status. Cases diagnosed from the date of blood draw through January 1996 and their matched pairs and cases diagnosed from February 1996 through January 1998 and their matched pairs were assayed in separate batches. The mean intrapair coefficients of variation calculated from blinded quality control samples were 2.6% for IGF-1 and 3.5% for IGFBP-3. Intra-person consistency in IGF-1 and IGFBP-3 over time was determined by measuring for 144 men in this cohort free of cancer diagnosis plasma concentrations in blood specimens collected in 1993 and again in 1997 (mean of 3.03 ± 0.46 years apart). Spearman correlation coefficients between the two time points were 0.66 for IGF-1 and 0.67 for IGFBP-3 (both $p < 0.0001$) after adjusting for age and race.

Statistical analysis

To compare mean concentrations of IGF-1 and IGFBP-3 and their molar ratio between matched cases and controls, we used the paired *t*-test, and also linear regression using generalized estimating equations to mutually statistically adjust IGF-1 and IGFBP-3. Results from the paired *t*-test were similar to the results from the nonparametric Wilcoxon sign rank test. To estimate matched odds ratios (OR) of prostate cancer we entered into conditional logistic regression models indicator variables for quartiles of IGF-1, IGFBP-3, and the molar ratio of IGF-1 to IGFBP-3 with cutpoints based on the distributions among the controls. Separate quartile cutpoints for the plasma markers were defined for the two assay batches. To test for trend, we entered into the model a single ordinal variable with values of one to four corresponding to the quartile into which an individual's concentration fell. The results did not appreciably change after adjustment for the following risk factors for prostate cancer previously observed in this cohort: father or brother with prostate cancer, height, vigorous physical activity, diabetes mellitus, vasectomy, cigarette smoking in the past ten years, intake of energy, red meat, and fish, and intake of energy-adjusted lycopene, calcium, fructose, and α-linolenic acid, or after adjusting for use of vitamin E or selenium supplements. For this reason, fully adjusted results are not presented. In addition to evaluating the association of the molar ratio of IGF-1 to IGFBP-3, to take into account that the bioavailable proportion of IGF-1 in circulation is limited by the molar amount of IGFBP-3, in an alternate analysis we mutually statistically adjusted IGF-1 and IGFBP-3.

Because in the cohort we have previously observed that age, family history, and BMI have modified the associations of obesity [16] and energy intake [17] with prostate cancer, and energy intake with IGF-1 levels [18], we evaluated whether the associations for IGF-1 and IGFBP-3 and prostate cancer varied by age at diagnosis [< 64 (25^{th} percentile) and ≥ 64 years old], family history of prostate cancer (yes/no), or body mass index (< 25 versus ≥ 25 kg/m^2). To estimate the stratum-specific ORs, we ran the stratified conditional logistic regression models (age at diagnosis) or stratified logistic regression models adjusting for the matching factors. To test for statistical interaction between age, family history, and BMI and IGF-1 and IGFBP-3, we entered into the appropriate multivariate model the main effect terms and a term for the cross-product, the coefficient for which was evaluated by the Wald test. Analyses were conducted using SAS release 8.2 (SAS Institute, Cary, NC). Two-sided *p*-values are given for all hypothesis tests.

Results

The cases ranged in age from 47.7 to 84.3 years at the time of diagnosis (median = 68.6). Among the 85.3% of cases with known stage, 90.1% were organ confined at diagnosis (T1b – T2b) or had minimal extraprostatic extension (T3a). The most common Gleason sums were 5 (19.1%), 6 (33.0%), and 7 (29.2%) among the 85.9% of cases for whom grade was known. The median PSA concentration of diagnosis was 7.0 ng/mL among the 63.9% of cases for whom this information was available. 78.8% of cases and 79.7% of controls reported at least one PSA test prior to the time of blood draw. The mean time between blood draw and prostate cancer diagnosis was 2.2 ± 1.2 years.

Mean concentrations of both IGF-1 and IGFBP-3 were statistically significantly higher in cases than in controls, but after mutual adjustment there was no significant difference in the means for either analyte (Table 1). Mean molar ratio of IGF-1 to IGFBP-3 did not differ between cases and controls. Risk of total prostate cancer was higher in men with higher IGF-1 and in men with higher IGFBP-3 (Table 2). However, after mutual adjustment these associations were attenuated and were not statistically significant (Table 2). The molar ratio of IGF-1 to IGFBP-3 was not associated with total prostate cancer.

Table 1. Mean plasma IGF-1 and IGFBP-3 concentrations in prostate cancer cases and matched controls nested in the Health Professionals Follow-up Study, 1993–1998

	Prostate cancer cases	Controls	*p-value*[a]	*p*-value[b]
No.	462	462		
IGF-1 (ng/ml)	181 ± 56	173 ± 54	0.02	0.30
IGFBP-3 (ng/ml)	3003 ± 751	2905 ± 757	0.03	0.42
Molar ratio of IGF-1 to IGFBP-3	3.05 ± 0.63	3.03 ± 0.66	0.66	–

IGF-1 – insulin-like growth factor-1; IGFBP-3 – insulin-like growth factor binding protein-3.

[a] For the hypothesis test of no difference in means (paired *t*-test) between prostate cancer cases and controls. All tests are two-sided.

[b] For the hypothesis test of no difference in means between prostate cancer cases and controls after adjusting IGF-1 for IGFBP-3 by linear regression using generalized estimating equations. Mutual adjustment was done because IGF-1 and IGFBP-3 are moderately correlated (Pearson $r = 0.67$, $p < 0.0001$).

Excluding cases diagnosed within two years of blood draw, the ORs of total prostate cancer comparing the top to bottom quartiles were 1.88 (95% CI 1.09–3.23; *p*-trend = 0.02) for IGF-1 and 2.31 (95% CI 1.28–4.18; *p*-trend = 0.04) for IGFBP-3. After mutual statistical adjustment the ORs were 1.42 (95% CI 0.70–2.89; *p*-trend = 0.16) for IGF-1 and 1.76 (0.81–3.83; *p*-trend = 0.45) for IGFBP-3.

Compared to men who had low IGF-1 (bottom two quartiles) and high IGFBP-3 (top two quartiles), men who had high IGF-1 and low IGFBP-3 had an OR of prostate cancer of 1.51 (95% CI 0.87–2.62) and men who had high IGF-1 and high IGFBP-3 had an OR of prostate cancer of 1.53 (95% CI 0.95–2.47). When formally tested, no interaction between IGF-1 and IGFBP-3 was present (*p*-interaction = 0.58).

The associations of IGF-1 and IGFBP-3 with organ-confined disease or low Gleason sum (< 7) were similar to the overall findings (Table 3). High IGF-1 appeared to be inversely associated with regionally invasive/metastatic disease both before and after adjusting for IGFBP-3, whereas high IGFBP-3 appeared to be inversely associated before adjustment for IGF-1 and positively associated after adjustment for IGF-1 (Table 3). However, the analyses for regionally invasive/metastatic disease were based on only 42 cases and the confidence intervals were wide. For high Gleason sum (≥ 7) disease, IGF-1 was not associated with risk, but after adjusting for IGFBP-3, high IGF-1 appeared to be inversely associated, whereas high IGFBP-3 appeared to be positively associated before and after adjustment for IGF-1 (Table 3). None of the associations for IGF-1 or IGFBP-3 with regionally invasive/metastatic disease or high Gleason sum were statistically significant. When formally tested, there were no statistically significant differences in the associations between IGF-1 and IGFBP-3 by grade or stage, although suggestive differences between low *versus* high Gleason sum were present after mutual statistical adjustment of IGF-1 (across quartiles *p*-trend = 0.13) and IGFBP-3 (*p*-trend = 0.13). No statistically significant associations between the molar ratio of IGF-1 to IGFBP-3 were present by grade or stage (data not shown). However, when compared to high Gleason sum, the odds of low Gleason sum disease increased across quartiles of the ratio (ORs comparing to bottom quartile: 1.48, 1.60, 2.18, *p*-trend = 0.015).

No statistically significant interactions were observed between IGF-1 or IGFBP-3 and age at diagnosis, family history of prostate cancer, or BMI in relation to prostate cancer either before or after mutual statistical adjustment.

Discussion

In this prospective study conducted in the PSA era, we observed modest positive associations between both IGF-1 and IGFBP-3 and total prostate cancer, which were attenuated after mutual statistical adjustment. The associations for cases that were organ-confined or had minimal extraprostatic extension or that were of low Gleason sum were similar to the overall findings. Possible, but not statistically significant differences in the associations of IGF-1 or IGFBP-3 with stage at diagnosis or Gleason sum were observed.

In the present study, the OR of total prostate cancer was 1.37 in the top quartile of IGF-1 compared to the bottom quartile and was of borderline statistical significance when not adjusting for IGFBP-3. Because IGFBP-3 is the major carrier protein for IGF-1 in circulation, the bioavailable portion of IGF-1 in theory is better represented after taking into account level of IGFBP-3. However, after adjustment for IGFBP-3, risk of total prostate cancer was not elevated in men with higher plasma IGF-1. The finding of little to no independent association between IGF-1 and total prostate cancer in our study, in which early disease

Table 2. Association of plasma IGF-1 and IGFBP-3 concentrations with prostate cancer among 462 matched[a] pairs nested in the Health Professionals Follow-up Study, 1993–1998

	Quartile[b]				*p*-trend
	1	2	3	4	
IGF-1					
No. cases/controls	94/116	107/116	138/116	123/114	
OR	1.00	1.12	1.47	1.37	0.05
95% CI	Referent	0.77–1.64	1.02–2.12	0.92–2.03	
OR[c]	1.00	1.00	1.26	1.17	0.29
95% CI	Referent	0.66–1.52	0.80–1.99	0.69–1.99	
IGFBP-3					
No. cases/controls	86/116	135/116	113/115	128/115	
OR	1.00	1.64	1.36	1.62	0.08
95% CI	Referent	1.11–2.41	0.92–1.99	1.07–2.46	
OR[c]	1.00	1.50	1.19	1.40	0.56
95% CI	Referent	0.97–2.33	0.73–1.94	0.80–2.44	
Molar ratio of IGF-1/IGFBP-3					
No. cases/controls	105/113	114/116	138/118	105/115	
OR	1.00	1.08	1.30	1.02	0.80
95% CI	Referent	0.74–1.57	0.88–1.94	0.68–1.51	

[a]Matched on age, time of day, year, and season of blood draw, and PSA test prior to blood draw.

[b]The case–control pairs were assayed in two analytical batches, cases diagnosed after the date of blood draw through 1/1996 and their matched controls and cases diagnosed from 2/1996 through 1/1998 and their matched controls. Quartile cutpoints for batch 1 were: IGF-1 129.48, 168.93, 209.21 (ng/ml); IGFBP-3 2428.70, 2824.92, 3340.47 (ng/ml); and molar ratio of IGF-1 to IGFBP-3 ($x10^4$) 2.61, 2.89, 3.42. Quartile cutpoints for batch 2 were: IGF-1 138.02, 168.33, 204.78 (ng/ml); IGFBP-3 2348.80, 2943.44, 3401.17 (ng/ml); and molar ratio of IGF-1 to IGFBP-3 ($x10^4$) 2.58, 3.05, 3.51.

[c] IGF-1 and IGFBP-3 mutually adjusted using conditional logistic regression.

predominated, is not incompatible with the findings reported for early stage disease in a continuation of the Physicians' Health Study through 1995 [13]. In that study, IGF-1, adjusted for IGFBP-3, was not associated with prostate cancer stage A or B cases, but was only related to cases with an advanced stage at diagnosis (C or D), most of which had been diagnosed in the pre-PSA era [13]. Alternatively, when not adjusted for IGFBP-3, our results for total prostate cancer are consistent with the results of a meta-analysis that reported a summary OR of total prostate cancer of 1.47 (95% CI 1.23–1.77) comparing high to low IGF-1 when not adjusting for IGFBP-3 [14]. Our results also are consistent with the findings from the Northern Sweden Health and Disease Cohort, in which IGF-1 and IGFBP-3 were modestly and nonstatistically significantly associated with nonadvanced cases, associations that were attenuated after mutual adjustment [12].

The findings for low grade and early stage cases were similar to the overall findings. Explanations beyond chance for the possible lower risk of T3b or worse prostate cancer or high Gleason sum prostate cancer for higher IGF-1 and for the higher molar ratio of IGF-1 to IGFBP-3 and the possible higher risk for IGFBP-3 both after mutual statistical adjustment are not clear.

The prostate tumors included in this analysis were primarily detected by testing for elevated PSA. These preclinical cases may be of two varieties, those that would have progressed to clinical disease if their natural history had not been interrupted by screening and subsequent treatment, and those that never would have progressed to clinical disease during a man's lifetime. Whether IGF-1 influences both of these preclinical case types is unknown, although the modest association that we observed for IGF-1 could possibly be explained by the following: (1) IGF-1 level is more important later in the natural history of the former type of tumor (*e.g.*, those that would have progressed if their natural history had not been interrupted), and (2) the IGF-axis is not important in the etiology of the latter type of tumor.

It is interesting to note that some studies found that IGFBP-3 was associated with a reduced risk of prostate cancer, whereas in other studies it was associated with a higher risk of prostate cancer [14]; very few showed no association. This dichotomy suggests that the associations for IGFBP-3 in the literature are unlikely to be due

Table 3. Association of plasma IGF-1 and IGFBP-3 concentrations with prostate cancer by stage and grade among 462 matched[a] pairs nested in the Health Professionals Follow-up Study, 1993–1998

	Quartile				*p-trend*
	1	2	3	4	
Regionally invasive or metastatic					
IGF-1					
No. cases/controls	12/13	13/9	11/10	6/10	
OR	1.00	1.41	0.99	0.49	0.43
95% CI	Referent	0.42–4.71	0.24–4.06	0.09–2.67	
OR[b]	1.00	1.62	0.94	0.36	0.63
95% CI	Referent	0.44–6.03	0.17–5.18	0.04–3.29	
IGFBP-3					
No. cases/controls	11/9	15/13	6/10	10/10	
OR	1.00	0.77	0.46	0.77	0.49
95% CI	Referent	0.15–3.84	0.09–2.25	0.13–4.50	
OR[b]	1.00	0.75	0.41	1.37	0.75
95% CI	Referent	0.11–4.97	0.07–2.49	0.14–13.38	
Organ confined or minimal extraprostatic extension					
IGF-1					
No. cases/controls	72/88	75/90	106/85	98/88	
OR	1.00	0.99	1.53	1.41	0.04
95% CI	Referent	0.64–1.52	1.00–2.33	0.91–2.19	
OR[b]	1.00	0.85	1.23	1.13	0.34
95% CI	Referent	0.52–1.36	0.72–2.09	0.61–2.08	
IGFBP-3					
No. cases/controls	62/91	102/84	88/90	99/86	
OR	1.00	1.81	1.44	1.79	0.05
95% CI	Referent	1.16–2.81	0.92–2.24	1.12–2.86	
OR[b]	1.00	1.71	1.29	1.56	0.45
95% CI	Referent	1.03–2.83	0.73–2.28	0.83–2.95	
Gleason grade ≥ 7					
IGF-1					
No. cases/controls	38/37	32/39	43/37	38/38	
OR	1.00	0.80	1.13	0.98	0.78
95% CI	Referent	0.42–1.54	0.60–2.14	0.50–1.93	
OR[b]	1.00	0.72	0.90	0.63	0.38
95% CI	Referent	0.35–1.48	0.40–2.00	0.25–1.62	
IGFBP-3					
No. cases/controls	34/36	35/41	35/40	47/34	
OR	1.00	0.87	0.94	1.70	0.19
95% CI	Referent	0.43–1.74	0.48–1.83	0.81–3.56	
OR[b]	1.00	0.94	1.11	2.17	0.12
95% CI	Referent	0.44–2.00	0.48–2.60	0.80–5.90	
Gleason grade < 7					
IGF-1					
No. cases/controls	43/60	56/57	76/61	65/62	
OR	1.00	1.34	1.72	1.44	0.10
95% CI	Referent	0.78–2.35	1.03–2.90	0.84–2.48	
OR[b]	1.00	1.14	1.32	1.19	0.24
95% CI	Referent	0.63–2.06	0.69–2.54	0.56–2.51	
IGFBP-3					
No. cases/controls	40/64	77/56	60/57	63/63	
OR	1.00	2.21	1.64	1.66	0.25
95% CI	Referent	1.29–3.78	0.96–2.79	0.94–2.93	
OR[b]	1.00	1.95	1.41	1.43	0.94
95% CI	Referent	1.05–3.63	0.72–2.77	0.66–3.07	

[a] Matched on age, time of day, year, and season of blood draw, and PSA test prior to blood draw.
[b] IGF-1 and IGFBP-3 mutually adjusted using conditional logistic regression.

to chance alone, and that some other explanation(s), whether biological or methodological, should be explored. One possible explanation for the differences in the direction of association with prostate cancer may be related to the measurement of IGFBP-3. Recently, questions have been raised by one of our coauthors (MNP) and others about the influence on the OR of (1) the underestimation of IGFBP-3 at higher concentrations and (2) the array of IGFBP-3 forms (*e.g.*, intact, fragments, glycosylated, phosphorylated) detected by commercial ELISA kits. The extent of measurement error may have varied among studies and possibly within studies that have measured IGFBP-3 in batches across time. For example, if some kits detect fragmented plus intact IGFBP-3, but others detect only intact IGFBP-3, given that fragmented IGFBP-3 likely means more free IGF-1, then in studies using the former kit high IGFBP-3 might appear as a risk factor, whereas in studies use the latter kit high IGFBP-3 might appear as a protective factor. Studies are underway elsewhere to understand the characteristics of IGFBP-3 assays.

This study has several strengths, including its prospective design and large size. Because of widespread PSA screening advanced cases at diagnosis were few. We reduced the likelihood of observation bias by requiring controls to have had a PSA test after the date of blood draw. Although we did not independently confirm stage at diagnosis or Gleason sum, we do not believe that major error occurred when subclassifying cases into extremes of disease characteristics. To limit the likelihood that the modest associations present were due to growth factors produced by extant cancers, we excluded cases diagnosed within two years of blood draw. The ORs were not attenuated, but instead were enhanced. In addition to chance as an explanation for this finding, we cannot rule out the possibility that extant cancers influenced the associations of IGF-1 and IGFBP-3 with prostate cancer.

In conclusion, prostate cancer detected in the PSA era did not appear to be strongly linked with IGF-1 or IGFBP-3. Our findings do not preclude that the IGF-axis influences the transition from early to late stage; because cases that are regionally invasive or metastatic at diagnosis are uncommon in the PSA era we could not address this question.

Acknowledgements

We thank Jill Arnold, Stacey De Caro, Elizabeth Frost–Hawes, Mira Kaufman, Lydia Liu, Alan Paciorek, Olga Veysman, Alvin Wing, and Mildred Wolff for their continued efforts in conducting the Health Professionals Follow-up Study.

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