Plasma levels of acid-labile subunit, free insulin-like growth factor-1, and prostate cancer risk: a prospective study

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Plasma levels of acid-labile subunit, free insulin-like growth factor-1, and prostate cancer risk: a prospective study

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Abstract

Introduction—The acid-labile subunit (ALS) acts in the insulin-like growth (IGF) system by binding circulating IGF1 in a ternary complex with binding protein (IGFBP)-3 to prevent IGF1 from crossing the endothelial barrier. Given the role of the IGF system in prostate cancer, ALS may influence carcinogenesis by modulating IGF1 levels or bioavailability.

Materials and Methods—We undertook a prospective study nested in the Physicians' Health Study to examine ALS, free IGF1 and prostate cancer. We assayed circulating levels of ALS and IGF components among 545 incident cases and 545 matched controls. We calculated relative risks and 95% confidence intervals (RR, 95% CI) adjusted for lifestyle factors, total IGF1 and IGFBP3.

Results—ALS was positively correlated with total IGF1 (r=0.58), IGFBP3 (r=0.68), and free IGF1 (r=0.36). Comparing highest versus lowest quartiles, we found no association between free IGF1 and prostate cancer risk (0.9, 0.6–1.3). In contrast, ALS was positively associated with risk among men in the 2nd (1.5, 1.0–2.3), 3rd (1.6, 1.1–2.5) and 4th quartiles (1.4, 0.9–2.1) compared to lowest quartile. The association was stronger for advanced stage tumors (2.0, 0.8–4.6). Among men with low ALS, high total IGF1 was associated with a substantial increase in advanced prostate cancer (9.3, 1.7–51.3), while high IGF1 did not confer risk for those with higher ALS levels.

Discussion—Plasma ALS is positively associated with prostate cancer risk, and may interact biologically with IGF1 to affect carcinogenesis. These data provide further support for the role of the IGF axis in prostate cancer.

Keywords

IGF system; acid labile subunit; prostate cancer; epidemiology

INTRODUCTION

Growing epidemiological evidence implicates components of the insulin-like growth factor (IGF) axis in prostate carcinogenesis. In prospective studies, higher circulating levels of total

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IGF1 have been associated with an increased risk of prostate cancer (1–5), particularly for advanced stage disease (2,4). By binding with the IGF-receptor, IGF1 imparts mitogenic and anti-apoptotic effects on prostate epithelium (6). IGF is bound in circulation with a family of binding proteins, predominantly binding protein-3 (IGFBP3). Circulating levels of IGFBP3 may affect risk by modulating bioavailability of IGF1 (6–8), by competing for the IGF receptors (9), or by independently promoting apoptosis (7,8). Some studies have found that higher circulating IGFBP3 are linked with lower risk.(10) Still, the epidemiological data is not completely convergent, since some studies have found no association between total IGF1 (11,12) or IGFBP3 (4,11) and prostate cancer risk. A recent pooled analysis of individual level data found a relative risk of 1.4 (95% Confidence Interval 1.2–1.6) comparing extreme quintiles of IGF1, and no association for IGFBP3 after accounting for IGF1 levels.(13)

Approximately 80–85% of circulating IGF1 is bound in a ternary complex with its binding protein and the glycoprotein acid-labile subunit (ALS) (14,15). Synthesis of ALS occurs primarily in the liver, although local synthesis may occur in some tissues (16) under regulation by growth hormone (17), which also controls circulating IGF1 and IGFBP3 levels. Indeed, reductions in levels of the subunit are observed in conditions categorized as growth-hormone deficient.

ALS has no affinity for free IGF1, very low affinity for uncomplexed IGFBP3, but readily binds to binary complexes of IGF1 bound to IGFBP3. Given its high affinity, ALS in high concentrations leaves little free IGF1 in circulation. In the ternary complex, IGF1 cannot cross the endothelial cell barrier (16). However, its half-life in the circulation is prolonged, from 10 minutes in the free IGF1 form to 12 hours in the ternary complex(16). Levels of ALS appear to directly affect both IGF1 and IGFBP3 levels. In a mouse model with an inactivated *ALS* gene, circulating levels of IGF1 and IGFBP3 were substantially reduced compared to the wild-type genotype (18). This observation is striking given a lack of reduction in IGF1 or IGFBP3 synthesis, as evidenced by retained gene expression. Similarly, in a case report of a young patient with a genetic mutation which completely inactivated the *ALS* gene, there were marked decreases in serum levels of total IGF1 and IGFBP3 (19). Treatment of the patient with growth hormone stimulated levels of IGF1 and IGFBP3, albeit below normal levels, while levels of the subunit remained undetectable. Taken together, these data suggest that ALS is crucial in preventing degradation of IGF1 and IGFBP3 in circulation. On the other hand, there is evidence that overexpression of the *ALS* gene is associated with impaired postnatal growth in animal models, which is likely due to alterations in tissue availability of IGF rather than circulating levels (20).

ALS appears to have direct physiological effects on circulating and tissue concentrations of IGF. Given its importance in modulating availability IGF1 and IGFBP3, ALS may play a role in prostate carcinogenesis. Higher concentrations of ALS may be associated with a lower risk of prostate cancer risk by decreasing the bioavailability of IGF1 and prohibiting IGF1 access to tissue. Alternatively, the subunit may protect against degradation of IGF1 and IGFBP3 in circulation, and thus may prolong their respective biological effects.

Prior epidemiological studies of IGF1 have measured total levels in circulation, rather than the free form. Moreover, no published study has assessed the role of ALS within the normal physiologic range on prostate carcinogenesis and progression. To this end, we undertook a nested case-control study within the Physicians' Health Study to examine the relation between acid-labile subunit, free IGF1 and prostate cancer risk using prospectively collected plasma samples.

MATERIALS AND METHODS

Study population

Initiated in 1982, the Physicians' Health Study was a randomized controlled trial of aspirin and beta-carotene supplementation among 22,071 US male physicians ages 40–84. Participants were excluded from the study if they had 1-) Previous diagnoses of myocardial infarction, stroke, transient ischemic attack, or cancer (except non-melanoma skin cancer); 2-) Current renal or liver disease, peptic ulcer, or gout; and 3-) Current use of aspirin, vitamin A, or beta-carotene supplements. Participants are followed through annual questionnaires to collect data on diet, health and lifestyle behaviors, and medical history, and biannually through postcards to ascertain compliance and health endpoints, including prostate cancer. Follow-up of the participants for morbidity and mortality is 99% complete (21).

During 1982–84, physicians were sent blood collection kits to obtain baseline blood samples prior to randomization. Prospectively collected plasma samples are available from 14,916 (68%) of physicians who represent the study base for the nested case-control study. The Physicians' Health Study specimens were continuously frozen at −82°C, (and more recently at −142°C).

Case-control ascertainment

At each of the questionnaire and postcard mailings, physicians reported if they have been diagnosed with prostate cancer during the previous six months. The study investigators confirmed report of prostate cancer through review of medical records and pathology reports. This information was further used to describe the cancers pathologically. We defined advanced disease as those cases with advanced stage at diagnosis (T3/T4/M1/N1), or cases that died of prostate cancer. Localized cases were those with stage T1 or T2 cancer confined to the prostate and those who did not die of prostate cancer during the follow-up. Cancers were further classified on histological grade, and defined as high-grade (Gleason score ≥ 7 or poorly-differentiated tumors) or low-grade (Gleason score < 7 or well-differentiated) tumors. Through December 1995, 786 incident prostate cancer cases arose in the cohort of physicians who initially provided blood samples.

We sought to select controls randomly from participants who had not had a partial or total prostatectomy or prostate cancer by the date of the case's diagnosis, and whom had sufficient plasma for biochemical analyses. Controls were matched to cases on age (±1 year, ±5 years for elderly participants) and smoking status (current, former, never).

Measurement of the IGF axis

Plasma levels of free IGF1 and ALS were measured in the prospectively collected plasma in the laboratory of Dr. Michael Pollack. Data on IGF1 and IGFBP3 were previously measured in Dr. Pollack's laboratory and were included in the previous publication by Chan et al.(22) The mean time between collection of blood and case diagnosis was 8.5 years (range 0.2–13.2 years). All assays were conducted using enzyme-linked immunosorbent assays. Case-control pairs were assayed in adjoining wells, with blinding to case-control status. Assays for total IGF1 and IGFBP3 were conducted in three batches using reagents from Diagnostic Systems Laboratory, as previously described (2). Analyses of the subunit and free IGF1 were conducted in one batch. Included in the analyses were 545 cases and their matched controls that had sufficient plasma for biomarker assays; Of the cases, 161 were advanced stage at diagnosis or died of prostate cancer during follow-up, and 177 had high tumor grade. Free IGF1 data was not available for 6 controls and 1 case, and thus data on free IGF1 are based on 538 matched-pairs. Intra-assay coefficients of variations were 9.5% for acid-labile subunit and 5.8% for free IGF1.

Statistical analysis

All analyses were undertaken using the SAS statistical software (Version 9).

We calculated Pearson correlation coefficients to examine the correlation between the IGF-related components among the controls. Because IGF1 and IGFBP3 were measured in three different batches, we calculated partial coefficients adjusted for batch differences. We used the least square means procedure to estimate age-adjusted mean levels of ALS and free IGF1 in relation to baseline characteristics among the controls.

Conditional logistic regression models were employed to examine the relation between acid-labile subunit and free-IGF1 and prostate cancer risk, controlling for potential confounders. Conditional analyses also adjust for potential drift in the laboratory assays, since case-control pair samples are run in adjoining wells on the same plates. We categorized men into quartiles, based on the distribution of ALS and free IGF1 levels in the control group. Odds ratios, as an estimate of the relative risk, and 95 percent confidence intervals were calculated, with the lowest quartile as the reference category. To assess the linearity of acid-labile subunit and free-IGF1 and prostate cancer risk on the log scale, the median of quartiles were modeled and the results of trend tests are presented.

Conditional logistic regression models automatically adjusted for the matching factors age and smoking. We further considered as potential confounders the following variables measured at baseline: height (continuous), body mass index (categorical: <25.0, 25.0–29.9, 30.0+), vigorous physical activity (categorical- 5+ per week, less often/none), alcohol intake (categorical: 1+ drinks per day, <1 per day/none), tomato consumption (categorical: 1+ servings per day, less often/none), and multivitamin use (categorical: current, former, never). Covariates that changed the main effects for acid-labile subunit or free IGF1 by more than 10%, or were significant at alpha = 0.20 were retained in the models. Based on the biological interrelationships of the IGF-axis, we also adjusted for total IGF1 and IGFBP3 in subsequent analyses using batch-specific cutpoints.

As previously reported in the literature, total IGF1 and IGFBP3 appear to be more strongly linked to more advanced tumors (2,4). Thus, we examined the association between acid-labile subunit and free IGF1 levels stratified by prostate cancer tumor stage and grade. We also addressed whether these associations differed as a function of IGF1 and IGFBP3, by cross-classifying individuals on tertiles of these hormones.

This project was approved by the Institutional Review Board of Partners Healthcare.

RESULTS

Among controls, the mean (standard deviation) plasma level was 15.5 μg/ml (3.6) for acid-labile subunit and 0.48 ng/ml (0.24) for free-IGF1. The molar concentration of the subunit (177 nM) was 7.2-fold higher than total IGF1 (24.7 nM) and 1.7-fold higher than IGFBP3 (103 nM). Levels of the subunit were positively correlated with total IGF1 (r = 0.58), IGFBP3 (r = 0.68), and to a lesser extent, free IGF1 (r = 0.36) (Table 1). There was a significant but more moderate positive correlation between free and total IGF1 levels. Levels of each component of the IGF system decreased with increasing age at baseline.

In Table 2, we examine differences in mean plasma levels of acid-labile subunit and free IGF1by baseline covariates among the controls. Given the strong relation between age and IGF plasma levels, data in this Table are age-adjusted. Taller men tended to have lower levels of ALS. Greater physical activity and higher intake of tomatoes were modestly associated with

lower levels of the subunit, even after adjusting for age. Men who were current smokers had lower levels of free IGF1, whilst taller men had higher levels.

Table 3 shows the association of ALS and free IGF1 with prostate cancer from three modeling approaches. First, we adjust for the matching factors only. Second, we present data from the multivariable model additionally adjusted for body mass index and height. Finally, in the multivariable model we further controlled for total IGF1 and IGFBP3 levels. Adjusting for the prostate cancer risk factors, higher levels of ALS were associated with an increased risk of total prostate cancer. The elevation in risk was apparent beginning in the 2nd quartile, with a 50% higher risk compared to the lowest quartile. The data suggest a threshold effect, with no further increase in risk after the second quartile. Combining the 2nd through 4th quartiles, the relative risk was 1.6 (95% CI; 1.1–2.2). Controlling for total IGF1 and IGFBP3 did not appreciably change the relative risks, suggesting that the association with the subunit was independent of the other IGF ternary components in circulation. To address concerns that the positive association with ALS could be due to the influence of subclinical disease on tumor production of the IGF-components, we excluded cases (N=49) that were diagnosed during the first three years of follow-up. The results were the same (data available upon request), suggesting that the association with the subunit was not due to reverse causality. We observed no significant association between plasma levels of free IGF1 and total prostate cancer risk in any of the analyses (Table 3).

Because of prior observations that the associations for total IGF1 and IGFBP3 were stronger for advanced disease (2), we examined the relation between ALS and free-IGF1 stratified by cancer stage and tumor grade (Table 4). In line with the previous study, we found a suggestion that the association of the subunit was stronger for advanced (Stage T3/T4/N1 or lethal prostate cancer) versus early stage (Stage T1/2) cancers. Comparing the highest and lowest quartiles, the subunit was associated with a relative risk of 2.0 (95% CI; 0.8–4.6) for advanced prostate cancer and 1.5 (95% CI; 0.8–2.8) for early stage disease. Moreover, the increased risk associated with the subunit was restricted to the lower grade tumors, with no association between higher levels of the subunit and high-grade prostate cancer. The association between free IGF1 and prostate cancer risk was consistently null for advanced and early stage tumors, and for high versus low-grade cancers (Table 4).

The three components of the IGF system, IGF1, IGFBP3 and the subunit, interact biologically and this interplay influences the bioavailability and potential function of these components. Thus, we cross-classified individuals on tertiles of the subunit and total IGF1 (Table 5A), free IGF1 (Table 5B) or IGFBP3 (Table 5C). The effect of total IGF1 (p for interaction = 0.10) differed as a function of levels of ALS. The increase in risk of advanced prostate cancer associated with total IGF1 is confined to those in the lowest levels of ALS, with a relative risk of 9.3 (95% CI; 1.7–51.3) comparing the highest with lowest tertiles of total IGF1. There is no evidence of a positive association between total IGF1 and advanced disease among those with higher levels of the subunit. While we observed no effect of free IGF1 overall, men with low ALS had a 3.3 (95% CI; 0.7–15.4) fold increased risk of advanced disease associated with higher free IGF1. Among controls, 3% had both high total IGF1 and low ALS and 5% had both high free IGF1 and low ALS. The data suggest that the protective effect of IGFBP3 is consistent across ALS levels (p=0.84).

The data in Table 5 also indicate that the effect of ALS on risk differs as a function of the other IGF components. High levels of ALS were associated with a relative risk of 3.1 (95% CI; 0.9–10.8) among those with low total IGF1, 3.8 (95% CI; 1.1–13.3) for those with low free IGF1, and 6.1 (95% CI; 1.2–30.1) for those with low IGFBP3 levels. An increase in risk was apparent also for individuals with moderate levels of these IGF components, while in contrast, there was no association between ALS and advanced prostate cancer risk among those with high levels,

based on tertiles. The proportion of controls with high ALS levels and low/moderate levels of the IGF components was 11–16%.

DISCUSSION

In this large, prospective study nested within the Physicians' Health Study, we observed that circulating ALS was associated with a small increase in total prostate cancer risk, with an apparent threshold effect after the second quartile of the subunit. The association was consistent even after controlling for circulating levels of other IGF components. Our data further suggest that the association of ALS was stronger for advanced tumors, although the findings were not statistically significant. In an earlier analysis within this cohort, Chan *et al* noted that total IGF1 and IGFBP3 levels were more strongly associated with advanced rather than earlier stage disease (2). In light of these earlier findings, the data suggest that the ALS may influence the progression and aggressiveness of prostate cancer.

In our data, we also noted a stronger effect of the subunit on lower grade versus higher grade prostate cancer. Although high tumor grade is an important risk factor for prostate cancer death, (23,24) this finding could indicate that higher-grade cancer represents more autonomous tumors, whereas the more differentiated, lower grade cancer may be more susceptible to regulation and influence by levels of growth factors. A positive finding with low grade prostate cancer has been demonstrated previously for IGF1 (2).

We also saw suggestive evidence that the effect of ALS on advanced prostate cancer varied as a function of the other IGF components. High ALS was associated with a 3 to 6 fold increased risk among those with lower levels of total IGF1, free IGF1 or IGFBP3, while at the highest levels, there was no association with ALS. Although these interactions were evaluated based on biological plausibility, some strata are based on small sample sizes, and therefore these findings should be viewed cautiously.

It is unlikely that ALS itself has direct carcinogenic potential. Since expression of ALS is under growth hormone stimulation (17), the positive associations may reflect some other components regulated by growth hormone. For example, sex steroid hormones can influence secretion of growth hormone, and can impact production or clearance of IGF1 (25).

More likely, ALS affects prostate cancer risk and progression through its influence on IGF1 and IGFBP3 availability. Indeed, we noted that the associations between total and free IGF1 on advanced prostate cancer were influenced by levels of circulating acid-labile subunit. The substantial increase in risk associated with total IGF1 was limited to those with the lowest levels of the subunit. This finding is intriguing in light of the observation that ALS circulates in excess compared to total IGF1 and its BP-3, demonstrated in our own data as well as other studies (16,26). Although based on a smaller number of advanced cancers, these data illustrate the complex biological interplay of the IGF components on prostate cancer progression. For example, higher ALS may be more likely to restrict IGF1 to the circulation, and in this way the local IGF effects on the prostate endothelium are mitigated. Such an effect has been observed in animal models in which overexpression of the *ALS* gene reduces availability of IGF at the tissue level (20). Among individuals with low levels of ALS, in contrast, the bioavailability of IGF1 appears optimized. For this group, we observed 9.3-fold increased risk of advanced prostate cancer for those with the highest versus lowest total IGF1 levels.

We found no overall association between levels of free IGF1 and total prostate cancer risk, nor evidence of an association with advanced stage or lower grade tumors. The coefficients of variation for this assay were relatively good, suggesting that substantial measurement error in the assay is not likely. While there is some debate that the free IGF1 assay is only measuring a subset of the more bioavailable IGF1 in the circulation, free IGF1 measured is this way does

appear to have physiologic correlates (27), suggesting that the assay is capturing important information.

In our own data, we did observe an almost 4-fold excess risk of advanced disease among men with low ALS levels. While only a small proportion of men with high free IGF1 or total IGF also had low circulating ALS, these men carry a considerable increase risk of the most aggressive form of disease.

Bound in the ternary complex, the half-life of IGFBP3 is prolonged as well. IGFBP3 has been shown to have independent pro-apoptotic and cellular growth inhibition effects (14) over and beyond its influence on IGF1 bioavailability. We observed the strong protective effect of IGFBP3 among individuals with either high or low ALS, suggesting that ALS does not impact the independent effects of IGFBP3.

There are some strengths and limitations to consider in assessing the study findings. The IGF components were measured using prospectively collected samples, which reduce the potential for reverse causality. In a subgroup analysis, the exclusion of cases occurring during the first three years of follow-up did not influence the study outcome. The blood measurements were based on samples collected at only one point in time, and may not reflect long-term changes or variations in levels. In a pilot study in the Physicians' Health Study, we collected blood specimens twice during a 5-year interval among 79 men. We assayed for free and total IGF1 in the specimens, and found a high within person correlation (r=0.70 and 0.75, respectively) between the assays across time points. These findings agree with published data from the Health Professionals Follow-Up Study, which used similar blood collection and storage methods as in the Physicians' Health Study. Levels of IGF1 and IGFBP3 were assayed on blood specimens from 149 individuals collected twice at a three year interval. For IGF1 and IGFBP3, the correlation coefficients ranged between 0.6 and 0.7. These correlations, which incorporate both measurement error as well as biologic variation over time, indicate that a single measure provides a reasonable time-integrated level. We did not have pilot data for levels of ALS, however. Therefore, IGF measured at a single time point provides a reasonable estimate of exposure across time. The case-control study was nested within a well-defined cohort, and thus selection bias should not be a concern. In the analysis, we considered a number of potential confounders which should reduce the likelihood of residual confounding. It is, however, possible that the possible associations for the subunit may indicate higher levels of other components under growth hormone control. Information on family history of prostate cancer was not available from the baseline questionnaire.

In conclusion, higher levels of circulating acid-labile subunit are associated with an increased risk of prostate cancer, particularly for advanced disease. ALS appears to interact biologically with total and free IGF1 in directing their effects on the prostate epithelium, reflecting the complexity of the IGF axis in prostate carcinogenesis and progression.

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Table 1

Correlation coefficients* between IGF-related factors in plasma among controls (N=545†) at baseline, Physicians' Health Study, 1982–1984.

	Acid-labile subunit	Free IGF1	Total IGF1	IGFBP3	Age
Acid-labile subunit	1.0				
Free IGF1	0.36	1.0			
Total IGF1	0.58	0.39	1.0		
IGFBP3	0.68	0.23	0.67	1.0	
Age	−0.28	−0.09	−0.32	−0.22	1.0

*P-values for Pearson correlations between IGF components were <0.001, and for correlations between IGF components and age were <0.05.

†Data on free IGF1 was available for 538 controls

Table 2

Age-adjusted mean (standard error) levels of acid-labile subunit and free IGF1 according to baseline characteristics among controls, Physicians' Health Study, 1982–4.

	N*	Acid labile subunit, μg/ml (SE) N=545	Free IGF1, ng/ml (SE) N=538
Smoking status			
Current	47	15.4 (0.6)	0.40 (0.02)
Former	237	15.5 (0.2)	0.48 (0.01)
Never	261	15.4 (0.2)	0.49 (0.02)
Alcohol use			
Daily or more	167	15.6 (0.3)	0.47 (0.03)
Less often	372	15.2 (0.2)	0.47 (0.01)
Vigorous exercise			
5+ times/week	91	14.9 (0.4)	0.44 (0.02)
1–4 times/week	294	15.6 (0.2)	0.48 (0.01)
Less often	156	15.4 (0.3)	0.49 (0.03)
Tomato intake			
5 or more per week	167	15.2 (0.3)	0.45 (0.01)
Less/None	373	15.5 (0.2)	0.48 (0.01)
Body mass index, kg/m^2			
<23.0	138	15.0 (0.3)	0.46 (0.02)
23.0–24.9	184	15.4 (0.3)	0.50 (0.02)
25.0–29.9	209	15.6 (0.3)	0.46 (0.01)
30.0+	14	15.2 (1.0)	0.42 (0.06)
Height, inches			
<68	85	15.9 (0.4)	0.47 (0.02)
68–72	372	15.3 (0.2)	0.46 (0.01)
73+	88	15.2 (0.4)	0.52 (0.05)

* Sample size among N=545 controls with data on ALS; N's may not add up because of missing data on specific covariates

Table 3

Relative risk (RR) and 95% Confidence Interval (CI) of total prostate cancer associated with acid-labile subunit and free IGF1, Physicians Health Study, 1982–1995.

	Quartiles				P for trend
	Low (Q1)	**Q2**	**Q3**	**High (Q4)**	
Acid Labile Subunit, mean µg/ml (range) among controls	10.7 (2.9–12.9)	14.3 (12.9–15.5)	16.7 (15.5–18.1)	20.4 (18.1–29.0)	
RR (95% CI): adjusted for age/smoking	1.0 (REF)	1.5 (1.0–2.1)	1.4 (1.0–2.0)	1.2 (0.8–1.7)	0.56
RR (95% CI): multivariate adjusted *	1.0 (REF)	1.5 (1.0–2.1)	1.4 (1.0–2.0)	1.2 (0.8–1.7)	0.63
RR (95% CI): multivariate adjusted †	1.0 (REF)	1.5 (1.0–2.3)	1.6 (1.1–2.5)	1.4 (0.9–2.1)	0.28
	Low (Q1)	**Q2**	**Q3**	**High (Q4)**	**P for trend**
Free IGF1, mean ng/ml (range) among controls	0.27 (0.07–0.35)	0.40 (0.35–0.44)	0.50 (0.44–0.57)	0.74 (0.57–4.02)	
RR (95% CI): adjusted for age/smoking	1.0 (REF)	0.8 (0.6–1.1)	1.1 (0.8–1.5)	1.0 (0.7–1.4)	0.73
RR (95% CI): multivariate adjusted *	1.0 (REF)	0.7 (0.5–1.0)	1.0 (0.7–1.5)	0.9 (0.7–1.3)	0.90
RR (95% CI): multivariate adjusted †	1.0 (REF)	0.7 (0.5–1.0)	1.0 (0.7–1.4)	0.9 (0.6–1.3)	0.78

*Adjusted for age, smoking status, height, and body mass index in conditional logistic regression model

†Also adjusted for total IGF1 and IGFBP3

Table 4

Relative risk (RR)* and 95% Confidence Interval (CI) of prostate cancer associated with quartiles of acid-labile subunit and free IGF1, by cancer stage and grade, Physicians' Health Study, 1982–1995.

	N Case-Control pairs	Quartiles				
Acid-Labile Subunit		**Low (Q1)**	**Q2**	**Q3**	**High (Q4)**	**P for trend**
Tumor Stage						
Advanced disease†	161	1.0 (REF)	1.7 (0.8–3.4)	2.2 (1.0–4.7)	2.0 (0.8–4.6)	0.11
Localized disease‡	304	1.0 (REF)	1.5 (0.9–2.7)	1.4 (0.8–2.5)	1.5 (0.8–2.8)	0.32
Tumor Grade						
High tumor grade§	177	1.0 (REF)	1.0 (0.5–2.0)	1.7 (0.8–3.6)	1.0 (0.4–2.5)	0.62
Low tumor grade5	317	1.0 (REF)	1.9 (1.1–3.3)	1.7 (1.0–3.0)	1.4 (0.8–2.6)	0.55
Free IGF1		**Low (Q1)**	**Q2**	**Q3**	**High (Q4)**	**P for trend**
Tumor Stage						
Advanced disease†	158	1.0 (REF)	1.2 (0.6–2.5)	1.2 (0.6–2.6)	0.9 (0.4–2.0)	0.83
Localized disease‡	302	1.0 (REF)	0.5 (0.3–0.8)	0.9 (0.6–1.4)	0.7 (0.4–1.1)	0.43
Tumor Grade						
High tumor grade§	176	1.0 (REF)	1.3 (0.7–2.4)	0.9 (0.5–1.8)	1.2 (0.6–2.4)	0.79
Low tumor grade//	313	1.0 (REF)	0.5 (0.3–0.8)	1.1 (0.7–1.7)	0.7 (0.4–1.2)	0.64

*Data adjusted for age, smoking status, height, BMI, total IGF1, and IGFBP3 using conditional logistic regression

†Advanced disease = Stage T3/T4/N1/M1 at cancer diagnosis, or death from prostate cancer

‡Localized disease = Stage T1 or T2 at cancer diagnosis and did not die from prostate cancer

§High grade = Tumor graded as Gleason score of 7 or higher or poorly-differentiated

//Low grade = Tumor graded as Gleason score of 6 or lower or well-differentiated

Table 5

Relative risk (95% CI) of advanced prostate cancer associated with tertiles of acid-labile subunit and total IGF1 (A), free IGF1 (B) or IGFBP3 (C), cross-classified, Physicians' Health Study, 1982–1995.

Table 5A. P for interaction = 0.10

		Total IGF1 (tertiles) N Exposed Cases/RR (95% CI)		
Acid labile subunit (tertiles)		**Low**	**Medium**	**High**
	Low	26	11	8
		REF	1.5 (0.5–4.7)	9.3 (1.7–51.3)
	Medium	15	17	23
		4.0 (1.1–14.0)	2.6 (0.9–7.5)	6.0 (1.9–18.9)
	High	10	28	22
		3.1 (0.9–10.8)	6.6 (2.1–20.4)	5.0 (1.5–16.1)

Data are adjusted for age, smoking, height, body mass index, and IGFBP3 using conditional logistic regression

Table 5B. P for interaction = 0.29

		Free IGF1 (tertiles) Exposed Cases/RR (95% CI)		
Acid labile subunit (tertiles)		**Low**	**Medium**	**High**
	Low	21	14	8
		REF	1.4 (0.5–3.9)	3.3 (0.7–15.4)
	Medium	17	18	19
		4.1 (1.3–13.5)	2.7 (0.9–8.5)	3.3 (1.0–10.5)
	High	11	20	29
		3.8 (1.1–13.3)	7.1 (2.1–24.2)	3.2 (1.1–9.2)

Data are adjusted for age, smoking, height, body mass index, and IGFBP3 using conditional logistic regression

Table 5C. P for interaction = 0.84

		IGFBP3 (tertiles) N Exposed Cases/RR (95% CI)		
Acid labile subunit (tertiles)		**Low**	**Medium**	**High**
	Low	32	10	3
		REF	0.8 (0.2–2.6)	0.4 (0.1–2.9)
	Medium	14	30	11
		1.8 (0.6–5.3)	1.6 (0.6–4.1)	0.5 (0.1–1.5)
	High	8	22	30
		6.1 (1.2–30.1)	2.0 (0.7–5.7)	0.7 (0.3–1.6)

Table 5C. P for interaction = 0.84

	IGFBP3 (tertiles) N Exposed Cases/RR (95% CI)

Data are adjusted for age, smoking, height, body mass index, and total IGF1 using conditional logistic regression