Serum Insulin-Like Growth Factor-I Levels and Prostatic Intraepithelial Neoplasia: A Clue to the Relationship Between IGF-I Physiology and Prostate Cancer Risk

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Abstract

Serum insulin-like growth factor-I (IGF-I) levels at the higher end of the reference range have been associated with increased risk for the future development of prostate cancer. We determined whether high serum IGF-I levels are associated with precancerous lesions of the prostate. We conducted a case-control study to determine whether high serum IGF-I levels were associated with the presence of high-grade prostatic intraepithelial neoplasia (HGPIN) among patients who presented for prostate biopsy because of an abnormal serum prostate-specific antigen level or digital rectal exam. We measured serum IGF-I and insulin-like growth factor binding protein-3 (IGFBP-3) prior to prostate biopsy and compared them between 103 men with HGPIN (cases) and 205 men with normal prostate histology (controls). The mean IGF-I level in patients with HGPIN (130.2 ng/mL) was significantly higher compared with controls (118.8 ng/mL, $P = 0.01$). The mean IGFBP-3 level in patients with HGPIN (2,393.9 ng/mL) was also higher compared with controls (2,276.0 ng/mL, $P = 0.06$). After adjusting for age, prostate-specific antigen, digital rectal examination, and ethnic background, the odds ratio for a HGPIN diagnosis among men in the highest relative to the lowest quartile of serum IGF-I level was 1.94 (95% confidence interval, 1.0-3.7; $P = 0.04$). The potential association between a high serum IGF-I level and the presence of HGPIN may represent an important clue to understanding the basis for the relationship between IGF-I physiology and prostate cancer risk. Larger studies will be required to confirm this relationship.

Introduction

There has been increasing interest in the relationship between insulin-like growth factor-I (IGF-I) and prostate cancer. High serum IGF-I levels seem to represent a risk factor, rather than a tumor marker for prostate cancer (1). It is therefore of interest to determine if there is an association between serum IGF-I levels and precancerous lesions of the prostate, namely high-grade prostatic intraepithelial neoplasia (HGPIN; ref. 2). To date, no studies have examined the relationship between serum IGF-I levels and HGPIN.

IGF-I is a growth factor with autocrine, paracrine, and endocrine activities [reviewed by Pollak (1)]. Male mice with deletion of the IGF-I gene are infertile and have a significant reduction in the mass of the prostate gland (1). IGF-I has mitogenic and antiapoptotic influences on human prostate epithelial cells (1).

Chan et al. (3) reported the first prospective study showing a positive association between serum IGF-I levels and the risk of developing prostate cancer. Men in the highest quartile of IGF-I levels had a relative risk of 4.3 for developing prostate cancer compared with men in the lowest quartile. Serum samples from these subjects were obtained, on average, 8 years prior to the diagnosis of clinically detected prostate cancer. Since this report, many other case-control and cohort studies have examined this relationship. The trend towards increased risk with increased serum IGF-I levels has been seen in all the prospective studies reported thus far (3-5), and in some (6-9), but not all (10-12) case-control studies.

HGPIN is a common histologic finding among patients who undergo a prostate biopsy for an abnormal prostate-specific antigen or digital rectal examination [reviewed by Epstein et al. (2)]. The prevalence of HGPIN among these patients ranges from 2% to 20% (2). Although HGPIN has a benign appearance, dysplastic cells are often seen along the prostatic acini and ducts (2). HGPIN is believed to be a precursor form of adenocarcinoma of the prostate and its presence is not correlated with prostate-specific antigen level (13, 14). It is estimated that patients with HGPIN detected at prostate biopsy have a risk of approximately 30% to 50% of subsequently developing prostate cancer (2).

Thus, if high serum IGF-I levels occur many years before the development of prostate cancer, it would be important to determine whether high serum IGF-I levels are associated with preneoplastic lesions of the prostate. To examine this relationship, we conducted a case-control study among men who were prescreened with serum prostate-specific antigen and measured serum IGF-I levels and insulin-like growth factor binding protein-3 (IGFBP-3) prior to prostate biopsy.

Materials and Methods

Study Subjects. Patients for this unmatched, case-control study were selected from a sample of 1,103 men who were consecutively referred to the University Health Network between June 1998 and June 2000, because of either a prostate-specific antigen value of ≥4.0 ng/mL or an abnormal digital rectal exam. Patients were excluded if there was a prior history

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of prostate cancer. Of the 1,103 patients, 1,031 (93.4%) consented to participate in the study. Blood samples were collected prior to clinical prostate examination. Plasma was separated from blood samples, and was stored at −70°C. The results of digital rectal examination, done by one evaluator (A. Toi) were recorded. All 1,031 patients underwent one or more systematic transrectal ultrasound-guided needle biopsies of the prostate (6 to 12 needle cores) and all histologic results were recorded. All research was conducted with informed consent and with the approval of the hospital research ethics board.

Selection of Cases and Controls. Cases were defined as patients found to have HGPIN from prostate biopsy. Patients were excluded if there was evidence of adenocarcinoma of the prostate on prostate biopsy in addition to HGPIN. All patients with HGPIN on prostate biopsy were required to undergo a repeat prostate biopsy to rule out the presence of concurrent prostate cancer within 1 year of the initial biopsy.

Controls were patients with no evidence of adenocarcinoma of the prostate or HGPIN from prostate biopsy. It is well established that 15% to 30% of patients who have an initial negative prostate biopsy could be found to have prostate cancer following repeat biopsy (15, 16). After having two negative prostate biopsies, the chances of having a malignancy is <5% (15, 16). Thus, to reduce the potential for misclassification of cases and controls, we restricted the selection of control patients to those who had at least two or more prostate biopsies that identified no evidence of cancer or HGPIN (i.e., negative biopsies).

Serologic Analysis. Three plasma proteins were examined including total prostate-specific antigen, IGF-I, and IGFBP-3. Total prostate-specific antigen levels were measured using commercially available kits, done on the Immulite System (Diagnostic Products Corporation, San Diego, CA). Plasma levels of IGF-I and IGFBP-3 were determined using assay kits based on ELISA with reagents from Diagnostic Systems Laboratory (Webster, TX; ref. 3).

Data Analysis. We compared the distribution of serum IGF-I and IGFBP-3 levels among patients with HGPIN (cases) and negative biopsy results (controls). The odds ratios for the presence of HGPIN by IGF-I and IGFBP-3 levels were calculated using univariate and multivariate unconditional logistic regression modeling. In the multivariate analysis, we adjusted for age, serum prostate-specific antigen level, digital rectal examination, and ethnic background. Because no risk factors have been established for predicting HGPIN, we used variables that have been strongly associated with increased prostate cancer risk. Also, because serum IGF-I and IGFBP-3 levels are well known to be highly positively correlated (17), in the multivariate regression model, we examined IGF-I and IGFBP-3 levels separately and together (18).

Serum IGF-I, IGFBP-3, and prostate-specific antigen levels were categorized into quartiles based on the distribution of the controls. Prostate-specific antigen was categorized into quartiles rather than known standard cutoffs because no cutoff has been established for HGPIN. Age was categorized into three groups: (*a*) <60 years, (*b*) 60 to 70 years, and (*c*) >70 years. Digital rectal examination was categorized into either normal or abnormal. Ethnicity was categorized into three groups: (*a*) Asian, (*b*) White, and (*c*) Black. All data analysis was done using the SAS System Version 8e (Carey, NC).

Secondary Analysis. We also measured serum IGF-I and IGFBP-3 levels for patients diagnosed with prostate cancer by biopsy. We conducted a separate, secondary analysis comparing IGF-I and IGFBP-3 levels between patients diagnosed with prostate cancer and those without cancer or HGPIN. We compared the distribution of serum IGF-I and IGFBP-3 levels among patients diagnosed with adenocarcinoma of the prostate from the original sample of 1,031 patients to our control patients.

Results

Of the 1,031 patients, 103 (10.0%) had HGPIN (cases), and 445 (43.2%) had no evidence of cancer from one or more prostate biopsies. The remaining 483 (46.8%) men were diagnosed with adenocarcinoma of the prostate. All 103 patients diagnosed with HGPIN had a subsequent repeat biopsy and no concurrent prostate cancer was identified. From the 445 patients with no prostate cancer or HGPIN from biopsy, 205 men underwent two or more prostate biopsies that identified no cancer or HGPIN (i.e., had negative biopsies). These 205 patients served as the control group.

The mean serum IGF-I level for patients with HGPIN (130.2 ng/mL) was significantly higher than for controls (118.8 ng/mL, $P = 0.01$; Table 1), and the mean IGFBP-3 level was slightly higher for patients with HGPIN (2,393.9 ng/mL) compared with controls (2,276.0, $P = 0.06$; Table 1). Also, prostate-specific antigen levels were significantly lower for patients with HGPIN than controls (Table 1).

Among the cases and controls, IGF-I and IGFBP-3 levels were strongly correlated ($r = 0.62$, $P < 0.0001$), and both IGF-I ($r = -0.29$, $P = <0.0001$) and IGFBP-3 ($r = -0.28$, $P < 0.0001$) negatively correlated with age at biopsy. Neither IGF-I ($r = -0.05$, $P = 0.37$) and IGFBP-3 ($r = -0.03$, $P = 0.56$) correlated with total prostate-specific antigen level.

The crude odds ratio for having HGPIN for patients with the highest quartile of serum IGF-I level compared with the lowest quartile group was 1.95 [95% confidence interval (CI), 1.0-3.7; $P = 0.04$; Table 2]. The crude odds ratio for having HGPIN for patients with the highest quartile of serum IGFBP-3 level compared with the lowest quartile group was 2.04 (95% CI, 1.1-3.9; $P = 0.03$; Table 2). Patients with prostate-specific antigen levels >9.0 ng/mL and older patients had the lowest risk for having HGPIN (Table 2). Digital rectal examination and ethnicity did not significantly affect the probability for HGPIN.

In multivariate analysis, the odds ratios for HGPIN remained similar for age, digital rectal examination, prostate-specific antigen, and ethnicity. However, for IGF-I levels, the odds ratios for HGPIN were not predictive. The adjusted odds ratios for patients in the fourth, third, and second quartile of IGF-I level was 1.28 (95% CI, 0.6-2.9; $P = 0.56$), 0.57 (95% CI, 0.2-1.4; $P = 0.21$), and 1.11 (95% CI, 0.5-2.4; $P = 0.79$), respectively. In contrast, the adjusted odds ratio for HGPIN for patients in the fourth, third, and second quartile of IGFBP-3 was 2.57

Table 1. Comparison of IGF-I and IGFBP-3 and other risk factors for prostate cancer between patients with HGPIN and the primary control group who had no evidence of cancer from two or more prostate biopsies

Factor	HGPIN ($n = 103$)	Control group ($n = 205$)	P
IGF-I (ng/mL)			
Mean ± SD	130.3 ± 43.3	118.8 ± 34.4	0.01
Median	121.1	115.9	0.03
IGFBP-3 (ng/mL)			
Mean ± SD	2,393.9 ± 508.8	2,276.0 ± 511.3	0.06
Median	2,337.0	2,297.6	0.08
Age at biopsy (years)			
Mean ± SD	64.4 ± 8.2	65.5 ± 6.3	0.22
Median	64.5	66.4	0.27
Mean total prostate-specific antigen (ng/mL)			
Mean ± SD	8.0 ± 5.5	11.0 ± 10.6	0.006
Median	7.0	9.0	0.003
Digital rectal examination			
Normal	63 (61.2%)	139 (67.8%)	0.25
Abnormal	40 (38.8%)	66 (32.2%)	
Ethnic background			
White	80 (77.7%)	170 (82.9%)	0.20
Black	14 (13.6%)	15 (7.3%)	
Asian	9 (8.7%)	20 (9.8%)	

Table 2. Univariate analysis for predicting the presence of HGPIN

Covariate	Crude odds ratio* (95% CI)	*P*
IGF-I (ng/mL)		
≤96.2	1.00	
96.2-115.9	1.11 (0.6-2.2)	0.76
115.9-138.5	0.70 (0.3-1.5)	0.35
>138.5	1.95 (1.0-3.7)	0.04
IGFBP-3 (ng/mL)		
≤1,983.7	1.00	
1,983.7-2,297.6	1.27 (0.6-2.6)	0.50
2,297.6-2,555.3	0.92 (0.4-1.9)	0.82
>2,555.3	2.04 (1.1-3.9)	0.03
Age (years)		
<60	1.00	
60-70	0.55 (0.3-0.9)	0.04
>70	0.82 (0.4-1.6)	0.55
Prostate-specific antigen level (ng/mL)		
<6.6	1.00	
6.6-9.0	0.59 (0.3-1.1)	0.09
9.0-12.8	0.33 (0.2-0.7)	0.002
>12.8	0.36 (0.2-0.7)	0.003
Digital rectal examination		
Normal	1.00	
Abnormal	1.33 (0.8-2.2)	0.25
Ethnic background		
Asian	1.00	
White	1.08 (0.5-2.4)	0.91
Black	2.07 (0.7-6.1)	0.18

*Test for linear trend calculated by assigning the median of the quartiles of the scores. IGF-I ($P = 0.07$) and IGFBP-3 ($P = 0.06$).

(95% CI, 1.1-6.1; $P = 0.03$), 1.14 (95% CI, 0.5-2.8; $P = 0.77$), and 1.44 (95% CI, 0.6-3.2; $P = 0.38$), respectively. However, because IGF-I and IGFBP-3 were highly correlated with each other ($r = 0.62$, $P < 0.0001$), we dropped IGFBP-3 levels from the regression model according to the method of Zhao et al. (18). When IGF-I alone was examined adjusting for age, digital rectal examination, prostate-specific antigen, and ethnicity, the odds ratio for HGPIN remained significant for patients with the highest quartile of IGF-I level (1.98, $P = 0.05$; Table 3). The odds ratios for age, prostate-specific antigen, digital rectal examination and ethnicity did not change. When we dropped IGF-I from the multivariate analysis and examined IGFBP-3 alone in the same manner, the adjusted odds ratios for HGPIN similarly remained significant (Table 3).

Secondary Analysis—Patients with Prostate Cancer. From the original sample of 1,031 patients, 483 patients were diagnosed with prostate cancer. The mean age was 66.6 years (range 42.7-90.8 years). The mean prostate-specific antigen was 15.9 ng/mL (median 8.8 ng/mL, range 0.6-498.8 ng/mL). Fifty-one percent of patients with prostate cancer had an abnormal digital rectal examination at presentation. The mean IGF-I level for patients with cancer was 119.4 ng/mL ($n = 483$) and was not significantly different from the 205 patients in the control group (118.8 ng/mL, $P = 0.85$). The mean IGFBP-3 level for patients with cancer (2,222.7 ng/mL) was also not significantly different to the control group (2,276.0 ng/mL, $P = 0.26$). As expected, patients with prostate cancer were significantly older (66.6 versus 65.5 years from 205 control patients, $P = 0.001$), had a higher prostate-specific antigen level (15.9 versus 11.0 ng/mL from 205 controls, $P = 0.005$) and a higher proportion (50.7% versus 32.2% from 205 controls, $P = 0.0001$) of an abnormal digital rectal examination.

Discussion

This is the first report of a possible association between serum IGF-I levels and the presence of HGPIN. These results are limited by our sample size which yielded borderline significant levels and lost sufficient power to handle the potential interactions between the IGF-I and IGFBP-3 variables. Even with the limited power, the test for a trend in the quartile levels of IGF-I and IGFBP-3 levels also had borderline significance, despite the differences of odds ratios for the detection of HGPIN between quartiles of IGF-I and IGFBP-3 levels. These findings are nonetheless novel to report as this is the first study to address a possible relationship between IGF-I and precursor forms of prostate cancer. There has been significant interest in the theory that high serum IGF-I levels are risk factors for the future development of prostate cancer, rather than a tumor marker (1). These findings may provide important clues to the relationship between IGF-I physiology and prostate cancer risk. It would be important to conduct larger studies to confirm these findings.

Our data and other reports (10-12) provide evidence against a positive association between the presence of prostate cancer and high circulating levels of IGF-I at diagnosis. This may be due to the presence of more advanced cancer associated with IGF-I suppressed by decreased caloric intake (19) or other mechanisms. Indeed, in our study, patients were drawn from an unselected population of men presenting for a biopsy. Thus, a significant proportion presented with a high prostate-specific antigen level or abnormal digital rectal examination (suggesting a higher proportion of more advanced cancer) which is reflected by the high cancer detection rate from our study. In contrast, several independent prospective studies (3-5) provide evidence for an association between IGF-I levels and the risk of a future development of prostate cancer.

In the Physicians' Health Study (3) and the Northern Sweden Health and Disease Cohort Study (5), serum samples for IGF-I analysis were collected 4 to 8 years prior to the diagnosis of prostate cancer. In this context, our findings that the presence of HGPIN may be associated with higher IGF-I levels is plausible, as HGPIN is argued to be a precursor lesion for prostate cancer (2). Recently, Woodson et al. (20), in a prospective study from the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, did not show a positive finding. However, these patients were all smokers and it remains unclear how IGF physiology are affected by smoking. Nonetheless, our results support the concept that IGF-I influences invasive prostate cancer risk at least in part by actions that occur early in carcinogenesis, prior to the development of HGPIN. Actions of IGF-I as a survival-promoting agent, decreasing the likelihood of apoptosis of partially transformed cells, may be important in this regard (1). Other case-control studies reporting a positive association (6-9) may have been due to the selection of patients with earlier stage and less advanced cancers.

Table 3. Multivariate analysis for predicting the presence of HGPIN for IGF-I and IGFBP-3

Covariate	Adjusted odds ratio* (95% CI)	*P*
IGF-I (ng/mL)		
≤96.2	1.00	
96.2-115.9	1.11 (0.6-2.2)	0.76
115.9-138.5	0.70 (0.3-1.5)	0.35
>138.5	1.95 (1.0-3.7)	0.04
IGFBP-3 (ng/mL)		
≤1,983.7	1.00	
1,983.7-2,297.6	1.27 (0.6-2.6)	0.50
2,297.6-2,555.3	0.92 (0.4-1.9)	0.82
>2,555.3	2.04 (1.1-3.9)	0.03

*Adjusted for age, prostate-specific antigen level, digital rectal exam and ethnicity. Test for linear trend calculated by assigning the medians of the quartiles of the scores. IGF-I ($P = 0.06$) and IGFBP-3 ($P = 0.01$).

We also found a positive association between serum IGFBP-3 levels and the presence of HGPIN. Past studies have shown both a negative and positive correlation with IGFBP-3 level and prostate cancer risk (3, 5, 8). The exact relationship between IGFBP-3 levels and prostate cancer remains unclear. There are technical considerations regarding IGFBP-3 measurements which may affect results, including the distinction between intact and fragmented IGFBP-3 (1). Past studies have used different antibodies for IGFBP-3, and their assays may vary in their ability to detect IGFBP-3 fragments (1). Newer tests have been developed such as by Koistinen et al. (21), to distinguish between these factors and should be used in future studies. IGFBP-3 levels can also be affected by prostate-specific antigen. Its protease activity could cleave IGFBP-3 (22). Further study will be required to determine the significance of IGFBP-3 with HGPIN and prostate cancer risk.

The observation that HGPIN is likely to occur in younger aged patients or patients with low prostate-specific antigen levels further support the idea that HGPIN is a precancerous lesion that occurs early. These findings are also consistent with the fact that prostate-specific antigen is a well-established tumor marker that increases with cancer and not HGPIN. That is, HGPIN cells do not seem to produce any detectable increases in prostate-specific antigen levels, whereas cancerous cells produce excess amounts. In the absence of cancer from biopsy, the negative correlation between HGPIN and prostate-specific antigen is likely attributed to the presence of benign prostatic hyperplasia in the controls, which has been well established to increase prostate-specific antigen levels (23). An interesting analysis would have been to examine the effect of prostate volume, which was beyond the scope of the current study. However, it would be premature to make decisions regarding biopsy strategies for patients with HGPIN on the basis of the current study given the small sample size, and further work is required in this regard. Nevertheless, this is also the first study that has examined whether risk factors for prostate cancer, including age, prostate-specific antigen, digital rectal examination, and ethnicity are important predictors for HGPIN.

A limitation of the study is that the prostate-specific antigen levels in the control group were high for a non-cancer population. This is because the study subjects were derived from a population of men already prescreened with prostate-specific antigen who required a prostate biopsy. Thus, prostate cancer could be missed on biopsy potentially misclassifying subjects. However, the control group underwent one or more repeat biopsies. Numerous studies have shown that the probability of having prostate cancer is <5% after repeat biopsies (15, 16). All patients with no cancer or HGPIN on initial biopsy were offered a repeat biopsy. Those who did not have a repeat biopsy either refused or were lost to follow-up. There were no significant differences in baseline factors between patients who did or did not undergo a repeat biopsy (data not shown). Another limitation is the cross-sectional nature of the analysis. In particular, because blood samples were obtained prior to biopsy, the elevated IGF-I and IGFBP-3 levels could be a result of HGPIN. Finally, our findings could be due to chance, given the observed level of statistical significance.

This study has shown a possible relationship between high serum IGF-I and IGFBP-3 levels and the presence of early prostate neoplasia. This is distinct from, but consistent with, earlier reports that IGF-I levels at the higher end of the reference range are associated with an increased risk of a future diagnosis of invasive prostate cancer. Larger cohorts of these patients will be required to confirm our observations.

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