Insulin-Like Growth Factor 1 and Prostate Cancer Risk: a Population-Based, Case–Control Study

Alicja Wolk, Christos S. Mantzoros, Swen-Olof Andersson, Reinhold Bergström, Lisa B. Signorello, Pagona Lagiou, Hans-Olov Adami, Dimitrios Trichopoulos*

Background: Recent epidemiologic investigations have suggested an association between increased blood levels of insulin-like growth factor 1 (IGF-1) and increased risk of prostate cancer. Our goal was to determine whether an association exists between serum levels of IGF-1 and one of its binding proteins, insulin-like growth factor-binding protein 3 (IGFBP-3), and prostate cancer risk. Methods: An immunoradiometric assay was used to quantify IGF-1 levels and IGFBP-3 levels in serum samples as part of a population-based, case–control study in Sweden. The study population comprised 210 patients with newly diagnosed, untreated prostate cancer and 224 frequency-matched control subjects. Data were analyzed by use of unconditional logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Reported P values are two-sided. Results: The mean serum IGF-1 level for case patients (158.4 ng/mL) was significantly higher than that for control subjects (147.4 ng/mL) (P = .02); corresponding mean serum IGFBP-3 levels were not significantly different between case patients (2668 ng/mL) and control subjects (2518 ng/mL) (P = .09). We found a moderately strong and statistically significant (P = .04) positive association between serum levels of IGF-1 levels and risk of prostate cancer (OR = 1.51; 95% CI = 1.0–2.26 per 100 ng/mL increment); the association was particularly strong for men younger than 70 years of age (OR = 2.93; 95% CI = 1.43–5.97). No association was found between serum IGF-1 levels and disease stage. Serum IGFBP-3 levels were not significantly associated with increased risk of disease, and adjustment for IGFBP-3 had little effect on the association between IGF-1 levels and risk of prostate cancer. Conclusion: Elevated serum IGF-1 levels may be an important predictor of risk for prostate cancer. However, our results do not support an important role for serum IGFBP-3 as a predictor of risk for this disease. [J Natl Cancer Inst 1998;90:911–5]

Until recently, the search for endocrine factors that may be involved in prostate carcinogenesis has focused on sex steroid hormones and on sex hormone-binding globulin. Although supported by animal studies (1), epidemiologic investigations have not unequivocally supported the hypothesis that sex hormones and their associated receptors and/or binding proteins are the most important endocrine factors involved in prostate cancer (2–4). Therefore, it is likely that other factors are involved in development of the disease.

Insulin-like growth factor 1 (IGF-1) has mitogenic and antiapoptotic effects on prostate epithelial cells in vitro (5,6). These results prompted epidemiologic studies to determine the role of IGF-1 in human prostate carcinogenesis. In a study of 52 prostate cancer patients and an equal number of control subjects in Greece, Mantzoros et al. (7) reported that increased serum IGF-1 level (by an increment of about one standard deviation; 60 ng/mL in their study) was associated with a doubling of the disease risk. Chan et al. (8) also determined that an increased risk of prostate cancer was associated with increased blood levels of IGF-1 in a nested case–control study within the Physicians’ Health Study, using prospectively collected blood samples from 152 case subjects and 152 control subjects. Chan et al. also found that one major circulating IGF-1-binding protein, insulin-like growth factor-binding protein 3 (IGFBP-3), after adjustment for IGF-1, was inversely related to the risk of prostate cancer. They attributed this effect to the reduction of bioavailable IGF-1 with increasing levels of IGFBP-3. If the association between increased serum levels of IGF-1 and increased prostate cancer risk were confirmed by independent investigations, this relationship could represent an important finding with considerable diagnostic and therapeutic value.

To study the association of IGF-1 and IGFBP-3 serum levels with prostate cancer risk, we made use of data from a large, population-based, case–control study in Sweden consisting of newly diagnosed prostate cancer cases that were cytologically and histologically confirmed.

Subjects and Methods

Subjects

All men under the age of 80 years, born in Sweden and living in Örebro County, Sweden, at any time from January 1989 through September 1991, formed the study base. Patients in this population with newly diagnosed prostate cancers, cytologically and histologically confirmed, were eligible to participate in the study. Clinical records from the three participating hospitals (Örebro Medical Center and hospitals in Karlskoga and Lindsberg) and the Department of Pathology at Örebro Medical Center allowed complete case ascertainment, confirmed through cross-checking the clinical records of case subjects with the regional cancer registry (9,10). All tumors were staged clinically in accordance with the tumor-node–metastasis classification system (11); among them, 26.6% were surgically staged. Control subjects were identified contemporaneously with case subjects. Selected every 3rd month from the county population register, control subjects were frequency-matched to case subjects in 10-year age groups. All potential control subjects underwent a digital rectal examination by one of us (S.-O. Andersson). Men with a palpable nodule and/or serum levels of prostate-specific antigen higher than 10 ng/mL underwent further diagnostic testing.

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through ultrasound-guided biopsy (four to six random samples). If interpretation of the initial biopsy specimens failed to confirm a diagnosis of cancer, the procedure was repeated 6 months later. Only those individuals whose biopsy specimens showed no evidence of cancer were deemed eligible as control subjects (10). Less than 3% of potential control subjects who were diagnosed with cancer by analysis of tissue obtained through biopsy were included in the current study as case subjects. Subjects eligible for the study were mailed a food-frequency questionnaire for self-administration at home. A majority of prostate cancer patients received the questionnaire without knowledge about the cancer diagnosis. Height, weight, and body mass index data for multivariate analysis were obtained during the physical examination.

**Collection of Serum Specimens**

Blood samples were drawn on any given day between 8:00 AM and 10:00 AM from 240 case subjects (86% of those eligible to participate in the study) and 235 control subjects (82% of those eligible to participate), before digital rectal examination was performed or any treatment to the case subjects was given. Most of the blood samples from case subjects were collected within 4–6 weeks after diagnosis (none collected later than 3 months). Potential control subjects who did not provide blood were generally similar (age and body mass index) to those control subjects who did. Blood samples were centrifuged at 1200g for 10 minutes at room temperature and stored as serum at ~70°C.

Serum samples, packed in dry ice, were shipped in the winter of 1997 from Örebro Medical Center (Örebro, Sweden) to Beth Israel Deaconess Hospital (Boston, MA). The coded samples arrived frozen and in good condition. They were analyzed by experienced laboratory personnel (who had no knowledge of case-control status) under the supervision of one of us (C. S. Mantzoros).

**Laboratory Assays**

Serum IGF-1 levels were determined by a commercially available immunoradiometric kit (Diagnostic Systems Laboratories, Webster, TX). The sensitivity of the assay was 2 ng/mL with a 3.9% intra-assay coefficient of variation. Cross-reactivity between IGF-1, IGF-2, or other peptide hormones with the IGF-1 antiseraum supplied in this assay was virtually nondetectable. No significant interference of IGF-1-binding proteins was detected (12). Serum IGFBP-3 levels were determined by use of an active IGFBP-3 DSL immunoradiometric assay kit (Diagnostic System Laboratories). The sensitivity of the assay was 0.5 ng/mL, with an intra-assay coefficient of variation of 1.8%–3.9%. No significant cross-reactivity with IGF-1, IGF-2, or other IGFBP-binding protein was detected.

**Statistical Analysis**

Pairwise comparison of data groups was performed by t tests (standard t tests and the Welch approach, which allows unequal variances) and by nonparametric Mann–Whitney tests. Each of the methods yielded similar results. The unconditional logistic regression model was used in both the univariate and multivariate modeling (13). Estimates obtained by the maximum likelihood method were converted to odds ratios (ORs) with 95% confidence intervals (CIs). Models were obtained both with continuous variables in their original untransformed form (denoted “trend tests”) and in categorized form with categories based on quartiles. In some cases, the assumption of a linear relationship between an explanatory variable and the log (odds) is not obvious, and the results of the “continuous form” modeling should be interpreted cautiously in such cases.

Data were collected by frequency matching, which means that the number of control subjects in various age groups was chosen to be one subset of the age estimates of the age distribution taken from recent official incidence figures in the Swedish Cancer Registry for prostate cancer. Because the age distributions among case and control subjects were not equal, we adjusted for age in the analyses. However, the adjustment for age had little effect on the estimates of prostate cancer risk. Further adjustments for height, body mass index, and total energy intake also had little effect on the risk estimates. Therefore, we sometimes just reported one set of results. Finally, for statistical analyses, we used 210 prostate cancer case subjects and 224 control subjects with IGF-1 and IGFBP-3 serum levels that had been determined. The covariate information available was nearly complete. (The age of one control subject was missing, and the disease stage of three case subjects was uncertain; therefore, in some analyses, we treated these data as missing.)

**Results**

The mean level of serum IGF-1 (standard error [SE]) was 158.4 ng/mL (3.7 ng/mL) among the prostate cancer case subjects and 147.4 ng/mL (3.2 ng/mL) among the control subjects. The difference between the two determinations was statistically significant (P = .02). Case subjects had slightly higher levels of IGFBP-3 than control subjects (mean values [SEs] = 2668 ng/mL [72 ng/mL] and 2518 ng/mL [52 ng/mL], respectively) (P = .09). Table 1 presents the means and standard deviations of IGF-1 and IGFBP-3 serum levels by disease stage at the time of diagnosis.

The data in Table 2 show ORs for prostate cancer by control-defined quartiles of IGF-1 serum levels and IGFBP-3 serum levels. In analyses with all four quartiles, the OR for both IGF-1 and IGFBP-3 did not differ for the two lowest quartiles (1.0 and 0.69 [95% CI = 0.39–1.23] and 1.0 and 1.06 [95% CI = 0.62–1.82], respectively). Therefore, these two quartiles were combined to form the reference group in subsequent analyses. Combining the data in this way increased the precision of the OR estimates in the two higher quartiles. In addition, ORs for increments of IGF-1 levels and IGFBP-3 levels (equal to about two standard deviations for these variables) among control samples, i.e., 100 ng/mL and 1500 ng/mL, respectively, were calculated to assess trends based on models with the variables in continuous form. The OR for prostate cancer was significantly increased with increasing levels of IGF-1, although the pattern was irregular and there was an indication of a threshold near the median value (144.7 ng/mL). No statistically significant trend was evident with respect to IGFBP-3 levels, although there appeared to be a positive association between the serum level of this binding protein and prostate cancer risk.

IGF-1 levels and IGFBP-3 levels were positively correlated, and the Pearson correlation coefficient among control samples was .53. Because IGFBP-3 binds more than 95% of the IGF in serum (14), IGFBP-3 can be thought of as an essential modifier of the IGF-1 effect. Comparison of the association of increased IGF-1 levels with prostate cancer risk among men

<p>| Table 1. Mean value and SD of IGF-1 levels and IGFBP-3 levels among control subjects and prostate cancer case subjects, by stage of disease at time of diagnosis* |
|-----------------------------------|------------------|------------------|</p>
<table>
<thead>
<tr>
<th>Group</th>
<th>Mean, ng/mL</th>
<th>SD</th>
<th>Mean, ng/mL</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control subjects</td>
<td>224</td>
<td>147.4†</td>
<td>47.6</td>
<td>2518†</td>
</tr>
<tr>
<td>Case subjects, all†</td>
<td>210</td>
<td>158.4†</td>
<td>53.8</td>
<td>2668†</td>
</tr>
<tr>
<td>Localized tumor</td>
<td>99</td>
<td>160.6</td>
<td>57.2</td>
<td>2639</td>
</tr>
<tr>
<td>Locally advanced tumor</td>
<td>71</td>
<td>158.4</td>
<td>51.6</td>
<td>2616</td>
</tr>
<tr>
<td>Metastatic tumor</td>
<td>37</td>
<td>152.0</td>
<td>51.4</td>
<td>2754</td>
</tr>
</tbody>
</table>

*SD = standard deviation; IGF-1 = insulin-like growth factor 1; IGFBP-3 = insulin-like growth factor-binding protein 3.

†P values based on t tests that allow for unequal variances for comparison of all case subjects with control subjects: for IGF-1, P = .02; for IGFBP-3, P = .09.

‡All tumors were staged clinically in accordance with the tumor–node–metastasis classification system (11) into one of three mutually exclusive groups: localized (T<sub>1</sub>, M<sub>0</sub>), locally advanced (T<sub>2</sub>–T<sub>3</sub>, M<sub>3</sub>), or metastatic (T<sub>4</sub>, M<sub>3</sub>) disease. For three patients, the disease stage was uncertain.
with lower serum levels of IGFBP-3 (below median, i.e., <2465 ng/mL) and among men with higher levels at or above the median revealed no significant difference between the two groups. Case subjects in the third IGF-1 quartile with IGFBP-3 levels below the median were more likely to have higher IGF-1 levels than control subjects. The two cut points between the three categories correspond to the 50th percentile (Q1 + Q2 = reference group) and 75th percentile in the distributions. Case subjects in the third and fourth IGF-1 quartiles were more likely to have higher IGF-1 levels than control subjects. Using this approach, we determined that the positive association of increased IGFBP-3 levels with increased prostate cancer risk was slightly weakened (from OR = 1.51 to OR = 1.39 per 100 ng/mL). In addition, the weak but non-significant positive association of increased IGFBP-3 levels with increased risk of the disease actually became weaker (from OR = 1.31 to OR = 1.16). Finally, an interaction term between IGF-1 and IGFBP-3 in this logistic model was insignificant (P = .44).

The association between IGF-1 levels and IGFBP-3 levels and prostate cancer risk did not differ among men with localized and locally advanced disease (Table 3). To take into account potential changes in total energy intake due to the development of prostate cancer, we adjusted these models for caloric intake. Risk estimates for metastatic disease were unstable because of the small number of case subjects.

We examined the association of IGF-1 levels and IGFBP-3 levels with prostate cancer risk among men younger than 70 years (mean age of case subjects in our study) and men who were older (Table 4). The risk of prostate cancer among persons younger than 70 years who were in the third and fourth IGF-1 quartiles was greater than for individuals in the reference group (OR = 2.52; 95% CI = 1.16–5.46 and OR = 2.94; 95% CI = 1.28–6.73, respectively). However, among persons 70 years of age or older, there was essentially no association of IGF-1 levels and IGFBP-3 levels with prostate cancer. Introducing IGFBP-3 as a continuous variable into the multiple logistic regression model that evaluates IGF-1 did not change the results. Among case subjects less than 70 years of age, the OR per unit increment was reduced from 2.93 to 2.59, whereas the corresponding OR was reduced from 1.05 to 1.01 among those 70 years of age or older. A similar, but considerably weaker, pattern of association was noted with respect to IGFBP-3 levels. Moreover, the moderately strong association of increased IGFBP-3 levels with risk for prostate cancer in the group less than

Table 2. OR for prostate cancer with 95% CIs in the two highest IGF-1 and IGFBP-3 quartiles and by specified increments of IGF-1 and IGFBP-3 concentration

<table>
<thead>
<tr>
<th>Quartile†</th>
<th>Q1 + Q2 (ref.)</th>
<th>Q3c OR (95% CI)</th>
<th>Q4c OR (95% CI)</th>
<th>Continuous variable‡</th>
<th>P for trend§</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-1, ng/mL</td>
<td>144.7 &lt; 147.7</td>
<td>177.7 &gt; 100 ng/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>1.0 1.0</td>
<td>1.46 (0.92–2.32) 1.56 (1.05–2.31)</td>
<td>.03 .03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1.0 1.0</td>
<td>1.47 (0.91–2.36) 1.56 (1.05–2.31)</td>
<td>.03 .03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariate</td>
<td>1.0 1.0</td>
<td>1.43 (0.88–2.33) 1.51 (1.01–2.26)</td>
<td>.04 .04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGFBP-3, ng/mL</td>
<td>2465 &lt; 2955</td>
<td>2955 &gt; 2465 ng/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>1.0 1.0</td>
<td>1.21 (0.77–1.90) 1.32 (0.96–1.81)</td>
<td>.09 .09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1.0 1.0</td>
<td>1.20 (0.76–1.90) 1.31 (0.95–1.81)</td>
<td>.10 .10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariate</td>
<td>1.0 1.0</td>
<td>1.21 (0.75–1.93) 1.31 (0.95–1.82)</td>
<td>.10 .10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*OR = odds ratio; CI = confidence interval; IGF-1 = insulin-like growth factor 1; IGFBP-3 = insulin-like growth factor-binding protein 3.
†Quartiles (Q1–Q4) are based on distributions of IGF-1 and IGFBP-3 serum levels among control subjects.
‡Adjusted for age, height, body mass index, energy intake, and, simultaneously, for serum IGF-1 level and IGFBP-3 concentration.
§Trend analysis based on continuous variables.

Table 3. OR for prostate cancer with 95% CI grouped according to quartiles of serum IGF-1 and IGFBP-3 levels and by stage of disease

<table>
<thead>
<tr>
<th>Cancer stage and quartile†</th>
<th>No. of case subjects/ control subjects</th>
<th>IGF-1, OR‡ (95% CI)</th>
<th>IGFBP-3, OR‡ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized disease Q1 + Q2</td>
<td>38/112 1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>30/56 1.58 (0.89–2.81)</td>
<td>0.67 (0.36–1.24)</td>
<td></td>
</tr>
<tr>
<td>Q2</td>
<td>31/56 1.63 (0.92–2.89)</td>
<td>1.00 (0.57–1.76)</td>
<td></td>
</tr>
<tr>
<td>P for trend§</td>
<td>.032 .025</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Locally advanced disease Q1 + Q2</td>
<td>27/112 1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>22/56 1.63 (0.85–3.12)</td>
<td>1.19 (0.62–2.28)</td>
<td></td>
</tr>
<tr>
<td>Q2</td>
<td>22/56 1.63 (0.85–3.12)</td>
<td>1.25 (0.66–2.38)</td>
<td></td>
</tr>
<tr>
<td>P for trend§</td>
<td>.097 .036</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic disease Q1 + Q2</td>
<td>15/112 1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>16/56 2.13 (0.98–4.63)</td>
<td>1.33 (0.56–3.16)</td>
<td></td>
</tr>
<tr>
<td>Q2</td>
<td>6/56 0.80 (0.29–2.17)</td>
<td>1.60 (0.70–3.65)</td>
<td></td>
</tr>
<tr>
<td>P for trend§</td>
<td>.58 .14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*OR = odds ratio; CI = confidence interval; IGF-1 = insulin-like growth factor 1; IGFBP-3 = insulin-like growth factor-binding protein 3.
†Quartiles (Q1–Q4) are based on distributions of IGF-1 and IGFBP-3 serum levels among control subjects.
‡Adjusted for age, height, body mass index, energy intake, and, simultaneously, for serum IGF-1 level and IGFBP-3 level.
§Trend analysis based on continuous variables.
70 years of age was largely explained by the positive association of increased IGF-1 levels with increased IGFBP-3 levels. Thus, introduction of IGF-1 as a continuous variable into the multiple logistic regression model evaluating IGFBP-3 reduced the OR per unit increment from 1.70 to a nonsignificant 1.21 (*). The regression model evaluating IGFBP-3 as a continuous variable into the multiple logistic regression model evaluating IGF-1 reduced the OR per unit increment from 1.37 to a nonsignificant 1.08 (*). P for trend

**Discussion**

The goal of the current study was to determine if increased serum levels of IGF-1 and IGFBP-3 were associated with an increased risk of prostate cancer. The structure of our study has several strengths. The case subjects were generated from a well-defined study base, and control subjects were representative of the study base. The lack of screening practices for prostate cancer in the study area at the time of data collection minimizes selective overrepresentation of health-conscious men. In addition, potential control subjects with clinically significant prostate cancer were identified and excluded from the control group. Response rates were high, and they were similar between the case subject and control subject groups, thus minimizing selection bias. Finally, levels of IGF-1 and IGFBP-3 were determined by personnel who had substantial expertise and who were blinded to clinical outcome.

Case–control studies are generally criticized for selection bias, information bias, and inability to directly address the time sequence of exposure and outcome. In our population-based study, however, selection bias is unlikely because the laboratory assays that were used had high sensitivity. Moreover, all case subjects were newly diagnosed before any treatment was administered, and it is not clear how disease progression might affect levels of either IGF-1 or IGFBP-3, since the serum levels for each of the two proteins were similar in various disease stages (Table 3).

Two analytical epidemiologic studies (7,8) have previously examined the relationship of IGF-1 levels to prostate cancer risk; both reported statistically significant positive associations. In addition, both studies reported that an increase of 60–100 ng/mL in blood IGF-1 level corresponded to an approximate twofold increase in prostate cancer risk. The results of our study are in agreement with those studies. For IGFBP-3, the OR per unit increment was 1.05 (0.63–1.75) for 100 ng/mL and 1.08 (0.70–1.65) for 1500 ng/mL.

The lack of association between IGF-1 and IGFBP-3 levels and disease stage in our data is in agreement with the results of Chan et al. (8) and based on prospectively collected blood samples, suggesting that IGF-1, although important for the occurrence of clinical prostate cancer, does not appear to differentially affect progression to more advanced stages of the disease. However, we cannot exclude the possibility that prostate cancer could itself influence serum levels of IGF-1.

In contrast, the results of our study did not support an important role for IGFBP-3 as a risk factor for prostate cancer; in this respect, our data are in conflict with the findings of Chan et al. (8). The biologic role of IGF-1 is complex, because normal and malignant prostate cells produce not only IGF-1, but also several of its binding proteins (17,18). Moreover, it has recently been reported that IGFBP-3 may signal apoptosis independently of sequestering free IGF-1 (15). Thus, it is not immediately obvious how these factors should be modeled in relation to prostate cancer risk. Nevertheless, in every model we used, we did not find that IGFBP-3 levels were inversely related to prostate cancer risk. However, we cannot exclude the possibility that, for our case–control study, prostate cancer progression influenced serum levels of IGFBP-3.

Our limited understanding of the risk profile of prostate cancer and of IGF-1 epidemiology hinders integration of the newly established association of en-
hanced IGF-1 levels with increased risk of prostate cancer with the descriptive epidemiology of the disease. It may be relevant, however, that other factors may also be important predictors of the disease. For example, physical stature has been shown to be a risk factor for prostate cancer (19,20). In addition, increased IGF-1 levels have been reported to be positively associated with height (21). Energy intake has also been reported to be associated with increased risk of prostate cancer development (22). By lowering energy intake, IGF-1 levels may be reduced; favoring cell apoptosis over cell proliferation and, thus, slowing tumor progression (23).

In conclusion, all three epidemiologic studies that examined an association between blood IGF-1 levels and prostate cancer risk found positive, statistically significant associations. The consistency of the epidemiologic evidence is strengthened by the biologic credibility of the hypothesis linking IGF-1 to prostate cancer, since IGF-1 has been shown to have mitogenic and antiapoptotic influences on prostate epithelial cells (5,6). On the basis of the evidence from our study, increased serum IGF-1 levels appear to be a strong risk factor for prostate cancer in men under the age of 70 years, and IGF-1 likely plays an important role in the etiology of the disease. In the search for causes of prostate cancer, high priority should be given to further studies of IGF-1 and external factors that may influence serum levels of this growth factor.

References


Notes

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