Insulin-Like Growth Factor-Binding Protein-1 and Prostate Cancer

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There is growing and persuasive evidence, both experimental (1–4) and epidemiologic (5–7), that the peptide hormone insulin-like growth factor-I (IGF-I) is a critical factor in the development of prostate cancer. Because of their central role in the regulation of bioavailable IGF-I, the insulin-like growth factor-binding proteins (IGFBPs) have also come under scrutiny as potential mediators of prostate cancer risk (8–12). There is considerable disagreement concerning which, if any, of the IGFBPs are relevant to the development of prostate cancer. Epidemiologically, IGFBP-3 has been examined (5,7), primarily because more than 95% of circulating IGF-I is bound to this protein (13) together with an acid labile subunit (ALS, a protein synthesized in the liver). The IGF-I/IGFBP-3/ALS complex is too large (150 kD), however, to pass through blood vessel endothelial cells and affect target tissue (14). It is IGFBP-1 that effectively shuttles IGF-I across blood vessel membranes (15,16). Therefore, it would be expected that blood levels of IGFBP-1 be predictive of the amount of circulating IGF-I available to prostate tissue and thus of prostate cancer risk.

We measured IGFBP-1 levels in the serum of 208 patients with prostate cancer and in 70 healthy male control subjects. Informed written consent was obtained from all subjects, and the study was approved by the Research Ethics Committee at the Regional Hospital in Örebro, Sweden (Örebro Läns Landsting). Serum IGF-I and IGFBP-3 were previously measured in these control subjects, and the findings indicated that IGF-I increased the risk of prostate cancer, whereas no demonstrable effect of IGFBP-3 was noted (7). Details of this study have previously been published (7). Briefly, we identified all incident prostate cancer cases in Örebro County, Sweden, from January 1989 through September 1991 and frequency matched them (in 10-year age groups) to healthy control subjects selected from the county population register. Control subjects underwent a digital rectal examination and a serum prostate-specific antigen screening test to avoid inclusion of men with occult disease. Height and weight data were obtained during a physical examination of all participants. Blood samples were drawn from 240 case patients and 235 control subjects, all between 8:00 AM and 10:00 AM. The majority of the blood samples provided by case patients were collected within 4–6 weeks after the initial prostate cancer diagnosis. All samples were centrifuged at 1200 g for 10 minutes at room temperature and stored as serum at −70 °C. The imbalance of case patient and control subject serum specimens available for this analysis is a consequence of collecting more blood from the case patients than from the control subjects at the outset of the study.

Serum IGF-I and IGFBP-3 levels were determined as previously described (7), both with commercially available immunoradiometric kits (Diagnostic Systems Laboratories, Webster, TX). Serum levels of IGFBP-1 were measured by use of radioimmunoassay (17). The antibodies used were raised in rabbits against purified human amniotic protein, and the cross-reaction with IGFBP-2 and IGFBP-3 was less than 0.1%. The assay measures both nonphosphorylated and phosphorylated forms.

Case patients and control subjects were of similar age, height, and body mass index (weight in kilograms/height in meters squared), and case patients had higher levels of IGF-I and somewhat higher levels of IGFBP-3 (Table 1). Serum IGFBP-1 levels were markedly and statistically significantly higher among the case patients (mean, 23.7 ng/mL; standard deviation [SD], 18.3 ng/mL) than among the control subjects (mean, 14.4 ng/mL; SD, 11.6 ng/mL) (Student’s t test; two-tailed P < .0001).

We employed logistic regression to estimate the odds ratio (OR) associated with different circulating levels of IGFBP-1 (Table 2). We initially categorized IGFBP-1 according to approximate quartiles of the control distribution by using the lowest quartile (≤ 7.8 ng/mL) as the referent group. Prostate cancer risk for the second quartile (7.9–10 ng/mL) did not differ from that of the referent quartile; these two quartiles were, therefore, combined to achieve more stable effect estimates. Our results indicate that prostate cancer risk elevation is particularly striking for IGFBP-1 levels more than 17 ng/mL. After we controlled for age, body mass index, and height, circulating IGFBP-1 levels above 17 ng/mL corresponded to a more than fivefold increase in prostate cancer risk (OR = 5.1; 95% confidence interval = 2.4–10.7). After our results were further adjusted for IGF-1 and IGFBP-3, IGFBP-1 remained an equally strong and statistically significant risk factor for prostate cancer.

Serum IGFBP-1 levels vary substantially with metabolic state; they are highest in a fasting and lowest in a fed state (18,19). Although we could not account for variation in the time since last food consumption, all blood samples were taken during the same narrow time-of-day window. So far as time of day (in this case, between 8:00 AM and 10:00 AM) is associated with eating habits, we have controlled for this factor.

The size of our control group, al-

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though smaller than desired to afford maximum statistical power, is still much larger than most clinical studies of IGFBPs and was nevertheless sufficient to document the striking positive association between IGFBP-1 and prostate cancer risk. Prostate cancer is not known to affect circulating levels of IGFBP-1 or its binding proteins [epidemiologic findings from a cohort study by use of prediagnostic blood specimens (5) and those that indicate no association between serum IGFBP-1 levels and disease stage (7) provide some evidence that it does not, but the possibility that disease state altered the IGFBP profile of our cases should not be ruled out completely. It is, however, inconceivable that our results were an artifact of the imbalance between case patient and control subject sample sizes; serum IGFBP-1 levels could not reasonably be assumed to be related to the amount of blood originally obtained from the participants.

The IGFBPs are a family of proteins that, depending on a number of factors, are capable of exerting either an inhibitory or a stimulatory influence on IGF-1 action (13,14,20). The principal role of circulating IGFBP-3 is to prolong IGF-I half-life in the serum and limit the availability of free IGF-I. Accordingly, some (5,8,21) although not all (7) prior research has reported an inverse relationship between IGFBP-3 and prostate cancer risk. In contrast, IGFBP-1 appears to be involved in IGF-I transport across the capillary barrier (15,16). Direction of IGF-I out of the circulation and into extravascular space would be expected to increase prostate tissue availability of this potent mitogen. Thus, high levels of circulating IGFBP-1 could potentiate cancer risk by inciting cellular proliferation. Studies have also shown that IGFBP-1 is able to bind to membrane integrin receptors and have an independent and direct effect on cell growth (14,22,23). Although the precise mechanism requires some further elucidation, the results of this study offer compelling evidence in favor of the hypothesis that IGFBP-1 is a key factor in modulating IGF-associated prostate cancer risk.

**REFERENCES**


NOTES

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