Re: Insulin-Like Growth Factor-I (IGF-I) and IGF Binding Protein-3 as Predictors of Advanced-Stage Prostate Cancer

A recent study *(1)* suggested that elevated plasma levels of insulin-like growth factor-I (IGF-I) were a predictor of advanced-stage prostate cancer. We have studied IGF-I in prostate cancer and have found no relationship to disease stage.

We studied IGF-I in a group of 126 men with prostate cancer and benign prostatic hypertrophy (BPH). Participants in our study were found through urology and radiation oncology clinics, and all eligible patients were asked to take part. All cancer patients had initially been diagnosed on the basis of levels of prostate-specific antigen (PSA) or abnormal physical examination. All men with BPH had had negative prostate biopsy examinations. Histologic confirmation of cancer diagnosis was also obtained for all subjects. All participants gave written informed consent. All staging of cancer cases was clinical, because almost all of the patients were to receive ^{125}I seed implant therapy. Serum IGF-I was measured by use of the Nichols Advantage, an automated chemiluminescent immunoassay analyzer (Nichols Institute Diagnostics, San Juan Capistrano, CA).

There was no statistically significant difference in the IGF-I levels in men with BPH compared with those in men with prostate cancer, nor was there statistically significant variation of IGF-I level among men with stages T1, T2, or T3 prostate cancer ($P = .323$, one-way analysis of variance; Fig. 1). Multivariable linear regression revealed no statistically significant effect of PSA level, Gleason score, or T stage on IGF-I level ($P = .277$) in men with prostate cancer.

Shariat et al. *(2)* have shown that systemic levels of IGF-I are not associated with metastasis, established markers of biologically aggressive disease, or disease progression in patients with clinically localized prostate cancer. Our results agree with those of Shariat et al. and suggest that serum IGF-I levels are not related to advanced-stage prostate cancer.
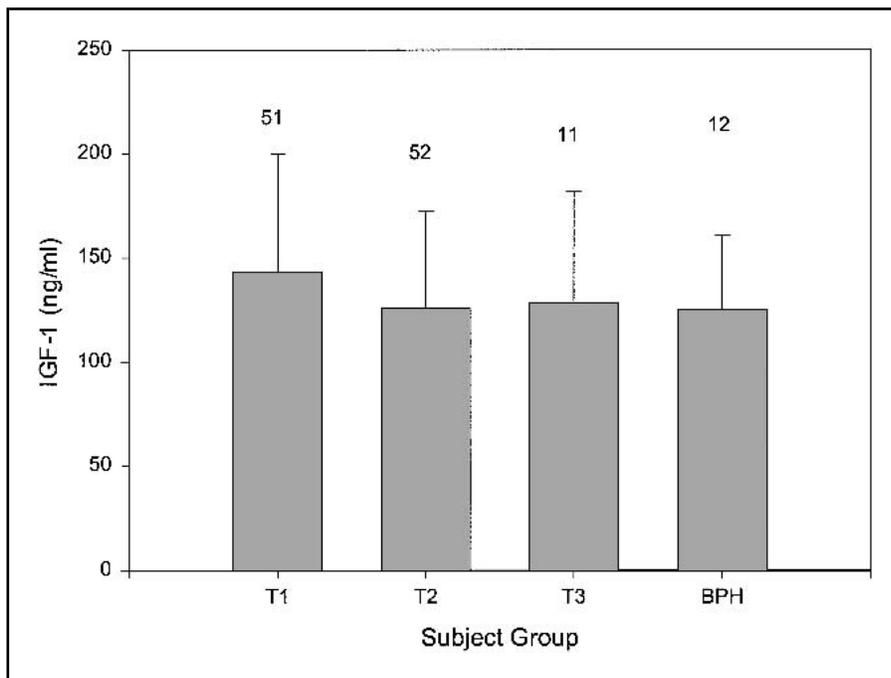
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Fig. 1. Serum insulin-like growth factor-I (IGF-I) levels in patients with stage T1, T2, and T3 prostate cancer and men with benign prostatic hypertrophy (BPH) without prostate cancer (bars represent mean + SD). The number of patients in each group is indicated above corresponding error bar. There is no statistically significant difference in IGF-I levels in the four groups ($P = .323$, one-way analysis of variance).

REFERENCES

(1) Chan JM, Stampfer MJ, Ma J, Gann P, Gaziano JM, Pollak M, et al. Insulin-like growth factor-I (IGF-I) and IGF binding protein-3 as predictors of advanced-stage prostate cancer. J Natl Cancer Inst 2002;94:1099–106.

(2) Shariat SF, Bergamaschi F, Adler HL, Nguyen C, Kattan MW, Wheeler TM, et al. Correlation of preoperative plasma IGF-I levels with pathologic parameters and progression in patients undergoing radical prostatectomy. Urology 2000;56:423–9.

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RESPONSE

We recently reported a strong, statistically significant association between serum insulin-like growth factor-I (IGF-I) and IGF binding protein-3 (IGFBP-3) and subsequent risk of advanced-stage prostate cancer in a nested case–control study in the Physicians' Health Study (relative risk [RR] = 5.1, 95% confidence interval [CI] 2.0 to 13.2 for IGF-I; RR = 0.2, 95% CI = 0.1 to 0.6 for IGFBP-3, comparing highest versus lowest quartiles) *(1)*. In contrast, Dr. Lehrer and colleagues observed no correlation between serum IGF-I levels and increasing tumor stage among 114 men with prostate cancer. Furthermore, they did not observe any difference in mean level of IGF-I between the 114 men with prostate cancer and 12 men with benign prostatic hypertrophy. They conclude that "serum IGF-I levels are not related to advanced-stage prostate cancer."

It is important to note several differences between these two reports that may explain any apparent discrepancies: 1) Our blood samples were collected long before diagnosis of prostate cancer (average time from blood collection to prostate cancer diagnosis among the case patients = 9 years). In contrast, Lehrer et al. assayed serum collected after diagnosis. The actions of IGF-I and IGFBP-3 may vary at different times in the course of tumor development. This difference is evident in Table 4 from our

paper, where the relative risks were stronger among men diagnosed later in the follow-up. 2) We compared levels of IGF-I and IGFBP-3 among 530 men who subsequently developed prostate cancer with that of 534 men who did not develop prostate cancer in the following 13 years. The results of Lehrer et al. are based on case–case comparisons and just 12 patients with benign prostatic hypertrophy, providing inadequate power to study this association. 3) Our assays were conducted in two waves, and the intra-assay coefficients of variation were very good for both waves (4.9% and 6.5% for IGF-I in waves 1 and 2, respectively). Lehrer et al. did not report any quality control data for their assays; nondifferential measurement error tends to bias associations to the null and could also partially explain any apparent lack of association.

Thus, these results suggest that IGF-I and IGFBP-3 play different roles in prostate cancer development at different times. Specifically, IGF may be related to an increased risk for the development of prostate cancer rather than act as a marker for the presence of tumor. The results of Lehrer et al. are not necessarily in conflict with ours. Our results indicate that serum IGF-I and IGFBP-3 may predict future risk of advanced stage prostate cancer several years before any clinical evidence of disease.

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(1) Chan JM, Stampfer MJ, Ma J, Gann P, Gaziano JM, Pollak M, et al. Insulin-like growth factor-I (IGF-I) and IGF binding protein-3 as predictors of advanced-stage prostate cancer. J Natl Cancer Inst 2002;94:1099–106.

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