

## Null Results in Brief

# Null Association between Insulin-like Growth Factors, Insulin-like Growth Factor-binding Proteins, and Prostate Cancer in a Prospective Study

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### Introduction

IGF-1<sup>2</sup> regulates normal and neoplastic growth in the prostate (1), and higher serum IGF-1 levels (2) appear to increase prostate cancer risk in epidemiological studies. Other aspects of the IGF axis, such as IGFBP-3 (3), inconsistently affect risk. Retrospective studies dominate the literature on this topic, and we, therefore, investigated IGF-I and IGFBP-3 in a pilot study from the Clue I population, a prospective cohort study based on the Washington County Serum Bank in Maryland.

We hypothesized that higher serum IGF-1 and lower serum IGFBP-3 are associated with an increased risk of developing prostate cancer.

### Materials and Methods

The Washington County Serum Bank began in 1974, when 20,305 consenting adult residents donated blood samples from which serum has been stored at  $-70^{\circ}\text{C}$ . This study included 30 cases of histologically confirmed incident prostate cancer (International Classification of Diseases 185) diagnosed between 1976 and 1989 (mean age at diagnosis, 70.6 years; SD, 7.8 years; range, 58–86), selected from a group of 61 cancers from a previous analysis (4). We identified and matched 60 male controls (2:1) to cases on age (1 year), race (all were Caucasian), and date of blood draw (3 weeks) from the same study.

We shipped (on dry ice) 0.5 ml of serum for each study subject to Diagnostic Systems Laboratories (DSL; Webster, TX), who used ELISA to analyze samples in triplets (one case, two controls) that did not reveal case status. We included four randomly placed triplets of pooled serum for quality control. We measured IGF-1 and IGFBP-3 levels twice for each sample, re-assayed samples if duplicate measures differed by more than 10%, and used the mean value for statistical analysis. We used

SAS (SAS Institute Inc., Cary, NC) for logistic regression analysis and adjusted for age at blood draw ( $\leq 50$ ,  $51 < 60$ , and  $\geq 60$  years); no other potential confounders (e.g., education, marital status, tobacco use) mattered.

This study had 80% power to detect a relative risk of 3.1 or greater for the highest (*versus* the lowest) quartile, under the assumption that 25% of controls and 30% of cases would have IGF-1 levels in the highest quartile.

### Results

Cases (mean, 119.8 ng/ml; SD, 46.0) and controls (mean, 118.4 ng/ml; SD, 42.8) had nearly identical levels of IGF-1 (Table 1). IGFBP-3 levels were also similar in cases (mean, 1042.5 ng/ml) and controls (mean, 1022.6 ng/ml). *t* tests for case-control differences were nonsignificant. Regardless of variable format (e.g., continuous or categorical), neither IGF-1 nor IGFBP-3 was associated with prostate cancer. IGF-1 ORs changed only slightly after adjustment for IGFBP-3 (either continuous or categorical). We also assayed IGF-II and IGFBP-1; levels neither differed in cases *versus* controls nor were associated with prostate cancer.

### Discussion

Although this pilot study had statistical power to detect an association similar to that observed in another prospective study (3), we saw no association between IGFs or IGFbps and prostate cancer. Reproducible laboratory assays (interassay CVs for IGF-I and IGFBP-3 were 4.5 and 1.4%, respectively), histologically confirmed prostate cancer diagnoses (which occurred before widespread use of prostate-specific antigen screening), and complete case ascertainment in the Washington County Cancer Registry likely introduced minimal information bias. Although our sample size in this pilot was low by design, other similar pilot studies in the cohort have uncovered positive associations.

The strong association between prostate cancer and elevated IGF-1 levels in a larger study (3) stands out from other studies (2) because of its higher mean and range of IGF-1 levels. If the association is true, higher serum IGF-1 from samples taken years before diagnosis should, in theory, best predict risk (5) because IGF-1 levels fall with age and after prostate cancer diagnosis (1). Our data do not support that conclusion: we saw no increase in IGF-1 in the sera of men who received a diagnosis of prostate cancer between 6 and 18 years later. In conclusion, although IGFs appear to have a general role in carcinogenesis (1), the inconsistency of the reported association with prostate cancer warrants further investigation.

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<sup>2</sup> The abbreviations used are: IGF, insulin-like growth factor; IGFBP, IGF-binding protein; OR, odds ratio; CI, confidence interval.

Table 1 Levels of IGF-1 and IGFBP-3, with ORs and 95% CIs

Assay	Cases ( <i>n</i> = 30) mean (SD)	Controls ( <i>n</i> = 60) mean (SD)	<i>P</i> ( <i>t</i> test)	OR (95% CI) for Q4 <sup>a</sup> vs. Q1 (reference); <i>P</i> for trend
IGF-1	119.8 (46.0)	118.4 (42.8)	0.63	0.7 (0.2–2.3); 0.50 0.6 <sup>b</sup> (0.1–2.9); 0.54
IGFBP-3	1042.5 (285.3)	1022.6 (258.0)	0.51	1.1 (0.3–3.8); 1.00

<sup>a</sup> Q, quartile.

<sup>b</sup> Also adjusted for IGFBP-3, in fourths of the distribution among controls.

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