

## Null Results in Brief

# No Association between Genetic Polymorphisms in IGF-I and IGFBP-3 and Prostate Cancer

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## Introduction

High levels of circulating insulin-like growth factor-I (IGF-I), or IGF-I in relation to IGF binding protein-3 (IGFBP-3), have been associated with an increased risk of prostate cancer (CaP) and other common epithelial cell malignancies (1). Twin studies estimate that 38% of the interindividual variability of IGF-I and up to 60% of that of IGFBP-3 are attributable to genetic factors (2). Recent work has identified a highly polymorphic cytosine-adenosine (CA)<sub>n</sub> dinucleotide repeat in the promoter region of the IGF-I gene and a single nucleotide polymorphism in the promoter region (−202) of the IGFBP-3 gene (3, 4). The IGF-I (CA)<sub>n</sub> repeat sequence is 1 kb upstream of the IGF-I transcription start site and contains specific regulatory elements (3, 4). Hence, we hypothesized that the length of (CA)<sub>n</sub> repeats might affect the transcription activity of the IGF-I gene, resulting in variable levels of IGF-I expression and affecting CaP risk or aggressiveness. Moreover, because previous studies have shown that the IGFBP-3 (−202) polymorphism is functional and is associated with circulating levels of IGFBP-3 (5), we anticipated that this variant might impact CaP risk as well.

## Materials and Methods

The design of our study has been described in detail elsewhere (6). Briefly, we recruited a study population of 920 brothers (440 cases and 480 controls) from 414 discordant families (*i.e.*, with at least one unaffected sibling) from the major medical institutions in the greater Cleveland, OH area and from the Henry Ford Health System in Detroit, MI. Institutional Review Board approval was obtained from the participating institutions and all study participants gave informed consent. Sibling sets consisted of probands with CaP diagnosed at age 73 or younger and at least one brother without CaP who was either older or no more than 8 years younger than the proband's age at diagnosis. This age restriction was

selected in an attempt to increase the potential for genetic factors affecting disease, and to help make certain that the controls were not unaffected due simply to being of a younger age. The study population comprised of 91% Caucasian 8% African-American, and 1% Hispanic and Asian-American.

Genotyping was undertaken according to assays recently described elsewhere (3–5).

**Statistical Analysis.** We first calculated allele and genotype frequencies by disease status, and then estimated age-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) by conditional logistic regression (matched on family) for the association between the polymorphisms and CaP. The IGF-I (CA)<sub>n</sub> repeat was modeled at the genotype- and allele-level. Because the most commonly reported CA repeat length is 19 (4, 5), we used the homozygous (CA<sub>19</sub>/CA<sub>19</sub>) as our referent for the genotype-level analysis, and created the following five genotype categories for comparison: (a) CA<sub>≤18</sub>/CA<sub>≤18</sub>; (b) CA<sub>≤18</sub>/CA<sub>19</sub>; (c) CA<sub>≤18</sub>/CA<sub>≥20</sub>; (d) CA<sub>19</sub>/CA<sub>≥20</sub>; and (e) CA<sub>≥20</sub>/CA<sub>≥20</sub>. We further collapsed these five comparison categories by combining those heterozygous for the 19 CA repeat (groups b and d above) and those without any 19 CA repeats (groups a, c, and e). At the allele level, we modeled chromosomes as a continuous variable, and with the following categorization: (a) CA<sub>19</sub> (referent); (b) CA<sub>≤18</sub>; and (c) CA<sub>≥20</sub>. IGFBP-3 was modeled with its three genotype categories, CC (referent), AC, and AA. To investigate the potential effect of these polymorphisms on CaP aggressiveness, we undertook analyses stratified by the cases tumor stage and grade at diagnosis; men with tumor stage of ≥T2c or Gleason score ≥7 (and their control brothers) were categorized as having high stage/grade; others were considered low stage/grade. In our regression models, we investigated the potential confounding by age, height, and BMI; the latter two did not materially alter our results, and all results reported here are adjusted for age only.

## Results and Discussion

One control's genotypes did not amplify, leaving 479 controls available for our analyses. No noteworthy differences were observed between the cases' and controls' frequency of IGF-I or IGFBP-3 polymorphisms, and neither of these was associated with CaP (Table 1).

Received 3/7/03; revised 6/5/03; accepted 10/24/03.

**Grant support:** NIH (CA88164, CA94211), Department of Defense (DAMD 17-98-1-8589), and Damon Runyon Cancer Research Foundation (CI-8 to L.L.).

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**Table 1. Frequency of IGF-I and IGFBP-3 variants, and ORs and 95% CIs for their association with CaP in sibling-based study**

Gene variant	Cases (%)	Controls (%)	OR (95% CI) <sup>a</sup>
IGF-I (CA) <sub>n</sub> repeats <sup>b</sup>			
≤17	30 (3.4)	38 (4.0)	
18 <sup>c</sup>	65 (7.4)	67 (7.0)	0.97 (0.67–1.41)
19	548 (62.3)	586 (61.2)	1.0 (referent)
20 <sup>d</sup>	170 (19.3)	180 (18.8)	0.99 (0.78–1.27)
≥21	67 (7.7)	87 (9.1)	
IGFBP-3 (–202)			
CC	126 (28.6)	115 (29.0)	1.0 (referent)
AC	217 (49.3)	225 (47.0)	0.81 (0.51–1.30)
AA	97 (22.1)	139 (24.0)	0.76 (0.40–1.44)

<sup>a</sup>Adjusted for age.<sup>b</sup>Allele counts from chromosomes (twice the total sample size).<sup>c</sup>OR and 95% CI for ≤18 repeats.<sup>d</sup>OR and 95% CI for ≥20 repeats.

Specifically, for IGF-I (CA)<sub>n</sub> we observed no association regardless of how this was modeled (for brevity's sake, we only report results from allele-level analysis). And we found no association for the IGFBP-3 polymorphism, whether using a two-category model, or one that assumed a particular mode of inheritance (*i.e.*, additive, dominant, or recessive). In particular, with an additive model, the trend-*p* from the logistic regression coefficient was >0.5 (others not shown). Stratifying these analyses by the cases' stage/grade of CaP, or age at diagnosis, did not materially alter our null results (not shown).

Furthermore, restricting the analyses to Caucasians only did not affect our findings.

By using a sibling-based design, our results are not susceptible to population stratification bias. But this design can be less efficient than a study of unrelated cases and controls. Nevertheless, our study had over 80% power to detect an OR ≥ 1.75 for the polymorphisms studied here. In conclusion, this moderately large case-control study did not detect an association between the IGF-I (CA)<sub>n</sub> repeats and IGFBP-3 (–202) polymorphisms and risk or aggressiveness of CaP. Because this is the first study to investigate this potential association, however, further research is warranted.

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*Cancer Epidemiol Biomarkers Prev* 2004;13:497-498.

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