

IGF-I are based on 538 matched pairs. Intra-assay coefficients of variations were 9.5% for ALS and 5.8% for free IGF-I.

Statistical Analysis

All analyses were undertaken using the SAS statistical

we present data from the multivariable model additionally adjusted for BMI and height. Finally, in the multivariable model, we further controlled for total IGF-I and IGFBP3 levels. Adjusting for the prostate cancer risk factors, higher levels of ALS were associated with an increased risk of total prostate cancer. The elevation in risk was apparent beginning in the 2nd quartile, with a 50% higher risk compared with the lowest quartile. The data suggest a threshold effect, with no further increase in risk after the second quartile. Combining the 2nd through 4th quartiles, the RR was 1.6 (95% CI, 1.1-2.2). Controlling for total IGF-I and IGFBP3 did not appreciably change the RRs, suggesting that the association with the subunit was independent of the other IGF ternary components in circulation. To address concerns that the positive association with ALS could be due to the influence of subclinical disease on tumor production of the IGF-components, we excluded cases ($n = 49$) that were diagnosed during the first 3 years of follow-up. The results were the same (data available upon request), suggesting that the association with the subunit was not due to reverse causality. We observed no significant association between plasma levels of free IGF-I and total prostate cancer risk in any of the analyses (Table 3).

Because of prior observations that the associations for total IGF-I and IGFBP3 were stronger for advanced disease (2, 6), we examined the relation between ALS and free-IGF-I stratified by cancer stage and tumor grade (Table 4). In line with the previous study, we found a suggestion that the association of the subunit was stronger for advanced (stage T₃/T₄/N₁ or lethal prostate cancer) versus early-stage (stage T_{1/2}) cancers. Comparing the highest and lowest quartiles, the subunit was associated with a RR of 2.0 (95% CI, 0.8-4.6) for advanced prostate

IGF-I ($P_{\text{interaction}} = 0.10$) differed as a function of levels of ALS. The increase in risk of advanced prostate cancer associated with total IGF-I is confined to those in the lowest levels of ALS, with a RR of 9.3 (95% CI, 1.7-51.3) comparing the highest with lowest tertiles of total IGF-I, although the 95% CIs are wide. There is no evidence of a positive association between total IGF-I and advanced disease among those with higher levels of the subunit.

is intriguing in light of the observation that ALS circulates in excess compared with total IGF-I and its BP-3, shown in our own data as well as other studies (16, 27). Although based on a smaller number of advanced cancers, these data suggest a complex biological interplay of the IGF components on prostate cancer progression. For example, higher ALS may be more likely to restrict IGF-I to the circulation, and in this way, the local IGF effects on the prostate epithelium are mitigated. Such an effect has been observed in animal models in which overexpression of the ALS gene reduces the availability of IGF at the tissue level (20). Among individuals with low levels of ALS, in contrast, the bioavailability of IGF-I seems optimized. A larger, prospective study with sufficient numbers of advanced/lethal prostate cancer cases would help clarify the potential interaction of the IGF components.

We found no overall association between levels of free IGF-I and total prostate cancer risk, nor evidence of an association with advanced stage or lower grade tumors. The coefficients of variation for this assay were relatively good, suggesting that substantial measurement error in the assay is not likely. Although there is some debate that the free IGF-I assay is only measuring a subset of the more bioavailable IGF-I in the circulation, free IGF-I measured in this way does seem to have physiologic correlates (28), suggesting that the assay is capturing important information.

Bound in the ternary complex, the half-life of IGFBP3 is prolonged as well. IGFBP3 has been shown to have independent proapoptotic and cellular growth inhibition effects (14) over and beyond its influence on IGF-I bioavailability. We observed the strong protective effect of IGFBP3 among individuals with either high or low ALS, suggesting that ALS does not affect the independent effects of IGFBP3.

There are some strengths and limitations to consider in assessing the study findings. The IGF components were measured using prospectively collected samples, which reduce the potential for reverse causality. In a subgroup analysis, the exclusion of cases occurring during the first 3 years of follow-up did not influence

individual and joint effects of the ligands, their binding proteins, as well as additional IGF components.



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References

- 1. ... 1998;279:563-6.
- 2. ... 2002;94:1099-106.
- 3. ... 2000;85:4258-65.
- 4. ... 2007;16:1121-7.
- 5. ... 2000;92:1910-7.
- 6. ... 2004;22:3104-12.
- 7. ... 2000;92:1472-89.
- 8. ... 2002;3:298-302.
- 9. ... 2004;4:505-18.
- 10. ... 1999;33:90-4.
- 11. ... 2009;124:2416-29.
- 12. ... 2003;63:3991-4.
- 13. ... 38.50 (6/1) (11)