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IGF-I and Prostate Cancer

June M. Chan *et al.* (1) report that plasma insulin-like growth factor-I (IGF-I) was associated with the risk of prostate cancer in a prospective study that paired 152 men with prostate cancer with age-matched healthy men (controls), aged 40 to 82 years at the start of the study. They found that prostate cancer risk increased with concentrations of IGF-I; men with IGF-I values in the highest quartile had 2.4 times [95% confidence intervals (CIs) 1.2 to 4.7] the risk of men in the lowest quartile.

We conducted a prospective study of IGF-I and several aging-related disorders including prostate cancer in a sample of 765 men, ages 60 to 91 years at the start of the study. The sample was randomly selected from 113,000 health plan members (all ages, both sexes) who had had a multiphasic health examination and gave blood samples in 1964 to 1970 (2). IGF-I (mean = 164.95 ng/ml; SD = 53.35) was measured by radioimmunoassay in the stored serum of all 765 men in 1994 (3). Record linkage to tumor registry data yielded 45 incident cases of prostate cancer in the sample of 765 men during the period 1971 to 1996. Mantel-Haenszel (4) age-adjusted estimates of relative risk (RR) and 95% CIs for the second through fourth quartiles of IGF-I as compared with the first (lowest) quartile were, respectively, 0.62 (0.25 to 1.55), 0.70 (0.31 to 1.58), and 0.81 (0.36 to 1.80) ($\chi^2_{\text{mh}} = 1.28$, $P = 0.74$). All of the CIs included 1.0, indicating that there was no association between rates of prostate cancer and serum concentrations of IGF-I. A second, separate analysis of the 45 cases and 179 age-matched controls selected from the sample of 765 men with the use of conditional logistic regression analysis confirmed the lack of association in our data. We recalculated RR in our study with the use of the same quartiles of IGF-I as were used by Chan *et al.*; the resulting RR values were slightly above 1.0, but all CIs included 1.0, and the lack of any association between IGF-I and prostate cancer remained.

The length of follow-up between blood collection and diagnosis with prostate cancer ranged from 1 to 21 years in our study; 10 cases occurred in the first 5 years after blood collection, and a total of 27 cases occurred in the first 10 years. However, RR of prostate cancer was not altered by the interval between serum collection and diagnosis in either study.

Median ages at the start of each study were different (60 in the report versus 71 years in our study). Chan *et al.* (1), how-

ever, found a stronger association in men above the median age than in the total sample. Although our study was smaller, statistical power was sufficient to detect RRs of the magnitude they reported, indicating that the lack of association in our study was not a result of small sample size. Unlike Chan *et al.* (1), we found no trend in the RR of prostate cancer with increasing IGF-I; rather, the highest incidence of prostate cancer was in the lowest quartile of IGF-I, and the incidence in the other quartiles of IGF-I was slightly lower but not statistically significantly different from incidence rates in the lowest quartile.

That endocrine growth factors affect tumor growth and development is plausible, but further studies are needed if we are to understand the relationship between plasma, autocrine or paracrine sources of growth factors, and cancer in humans.

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References and Notes

1. J. M. Chan *et al.*, *Science* **279**, 563 (1998).
2. M. F. Collen and L. F. Davis, *J. Occup. Med.* **11**, 355 (1969).
3. Radioimmunoassay for the quantitative determination of IGF-I levels in human plasma or serum was performed in the laboratory of the Orentreich Foundation for the Advancement of Science in Cold Spring-on-Hudson, NY, where the frozen serum samples had been stored since 1980. Information on the collection and storage of the serum samples is published in a study by G. D. Friedman *et al.* [*Am. J. Epidemiol.* **123**, 781 (1986)]. The assays utilized materials and a protocol supplied by Nichols Institute Diagnostics, San Juan Capistrano, CA.
4. N. E. Breslow and N. E. Day, *Statistical Methods in Cancer Research, vol. II, The Design and Analysis of Cohort Studies* (International Agency for Research on Cancer, Lyon, France, 1987), pp. 109–113.
5. Funding for the prospective study of 765 men was provided by Merck Research Laboratories and by the Orentreich Foundation for the Advancement of Science, Inc.

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Response: Schaefer *et al.* found no association between circulating IGF-I concentrations and prostate cancer risk. The discrepancy with our findings (1) could be the result of several differences in methods between the two studies.

In our prospective study, we observed

the strongest relative risks when adjusting for IGFBP-3, consistent with our hypothesis that IGFBP-3 determines, in part, the concentration of bio-available IGF-I in circulation. Schaefer *et al.* apparently did not measure IGFBP-3, and the confidence intervals for the relative risk for the fourth quartile of IGF-I in their study (0.36 to 1.80) do overlap with those in our analysis that is unadjusted for IGFBP-3 (1.23 to 4.74).

In our study, IGF-I concentrations were within the expected ranges for various age groups, and the intra-assay coefficients of variation from blinded repeated quality control samples imbedded within the case-control runs were low: 4.9% and 9.0% for IGF-I and IGFBP-3, respectively. Perhaps their samples (stored at -40° to -23°C) underwent more degradation than ours (stored at -82°C). Measurement misclassification resulting from variations in storage and measurement accuracy would tend to bias results toward a null association (2).

The length of follow-up was 1 to 21 years in the Schaefer *et al.* study, with 27 cases diagnosed within 10 years; average follow-up in our study was 7 years, with a maximum of 10 years. This difference in the length of time between serum collection and diagnosis between our two studies could contribute to the discrepancy in our results, though the induction period for IGF-I to influence prostate cancer risk remains unknown. The patient sample in study by Schaefer *et al.* was also smaller than ours ($n = 45$ cases versus $n = 152$), with less statistical power to detect associations.

An early small case-control study ($n = 52$ case-control pairs) in Greece (3), as well as a more recent larger case-control study in Sweden ($n = 210$ cases) (4), also found positive associations between IGF-I concentrations and the risk of prostate cancer. The findings by Schaefer *et al.* underscore the need for further prospective studies.

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