

Letters to the Editor

Correspondence re: Giovannucci *et al.*, A Prospective Study of Plasma Insulin-like Growth Factor-1 and Binding Protein-3 and Risk of Colorectal Neoplasia in Women. *Cancer Epidemiol. Biomark. Prev.*, 9: 345–349, 2000

Letter

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Giovannucci *et al.* showed an increased risk of colorectal cancer in women with elevated prediagnostic blood levels of IGF-I,² but only when an adjustment was made for levels of IGFBP-3, IGF's principal plasmatic binding protein. In other studies, by the same Harvard group, adjustment for IGFBP-3 also strengthened the association of IGF-I risk of colorectum and prostate cancer in men (1, 2). In univariate analyses, cancer risk was either unassociated or mildly reduced at elevated levels of IGFBP-3, but multivariate models systematically showed a significant inverse association of risk with IGFBP-3 adjusted for IGF-I. By contrast, in a different series of prospective studies, we systematically observed increases in risk of cancers of the colorectum³ (3) and prostate (4) in subjects with elevated IGFBP-3, and adjustment for IGFBP-3 reduced or even abolished the associations of risk with IGF-I levels.

We speculated that these discrepancies might be related to differences in the specificity of IGFBP-3 assays. In the Harvard studies, IGFBP-3 was measured by an ELISA method from Diagnostic Systems Laboratories (Webster, TX). In our studies, an IRMA from Immunotech (Marseilles, France) was used² (3, 4). IGFBP-3 in blood and tissues undergoes proteolytic cleavage by specific enzymes. We hypothesized that subjects at increased cancer risk might have elevated levels of IGFBP-3, intact and proteolytically cleaved forms combined, and our

Immunotech assays would measure the sum of these. However, subjects at increased cancer risk might have reduced levels of intact (uncleaved) IGFBP-3, and the DSL-ELISA assay would be more specific for intact IGFBP-3.

To test this hypothesis, we remeasured IGFBP-3 by the DSL-ELISA method in our prospective study on colorectal cancer (3). IGF-I had been measured by an assay from Immunotech, which uses acid-ethanol to precipitate the IGFs. IGFBP-3 levels for cases and controls were 3019.8 ± 587.6 and 2921.7 ± 575.3 ng/ml (mean \pm SD), respectively, for IRMA-Immunotech and 4074.3 ± 938.6 and 3951.7 ± 778.8 ng/ml (mean \pm SD), respectively, for ELISA-DSL. Spearman's correlations between the two IGFBP-3 assays were 0.82. The odds ratio of colorectal cancer for the top quintile of IGFBP-3 was lower (1.24) for the DSL-ELISA measurement than for the measurements by Immunotech, somewhat in line with our speculation, but did not reflect a possible inverse association of risk with IGFBP-3 (Table 1). Furthermore, with neither of the IGFBP-3 assays used was there any clear increase in risk for elevated IGF-I levels adjusted for IGFBP-3, nor was there any inverse association of risk with IGFBP-3 adjusting for IGF-I (data not shown).

These data provide only weak support for the hypothesis that differences in assay specificity would explain the discrepant relationships between cancer and IGFBP-3 in different cohorts. However, the present evaluation is based on small numbers (102 cases, 200 matched controls), and should be repeated with larger studies.

References

1. Ma, J., Pollak, M. N., Giovannucci, E., Chan, J. M., Tao, Y., Hennekens, C. H., and Stampfer, M. J. Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-I and IGF-binding protein-3. *J. Natl. Cancer Inst.* (Bethesda), 91: 620–625, 1999.
2. Chan, J. M., Stampfer, M. J., Giovannucci, E., Gann, P. H., Ma, J., Wilkinson, P., Hennekens, C. H., and Pollak, M. Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. *Science* (Wash. DC), 279: 563–566, 1998.
3. Kaaks, R., Toniolo, P., Akhmedkhanov, A., Lukanova, A., Biessy, C., Dechaud, H., Rinaldi, S., Zeleniuch-Jacquotte, A., Shore, R. E., and Riboli, E. Serum C-peptide, insulin-like growth factor (IGF)-I, IGF-binding proteins, and colorectal cancer risk in women. *J. Natl. Cancer Inst.* (Bethesda), 92: 1592–1600, 2000.
4. Stattin, P., Bylund, A., Rinaldi, S., Biessy, C., Dechaud, H., Stenman, U. H., Egevad, L., Riboli, E., Hallmans, G., and Kaaks, R. Plasma insulin-like growth factor-I, insulin-like growth factor-binding proteins, and prostate cancer risk: a prospective study. *J. Natl. Cancer Inst.* (Bethesda), 92: 1910–1917, 2000.

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² The abbreviations used are: IGF, insulin-like growth factor; IGFBP, IGF-binding protein; IRMA, immunoradiometric assay; DSL, Diagnostic Systems Laboratories.

³ R. Palmqvist, G. Hallmans, S. Rinaldi, C. Biessy, R. Stenling, E. Riboli, and R. Kaaks. Plasma IGF-I, IGF-binding protein-3 and risk of colorectal cancer: a prospective study in Northern Sweden. *Gut*, in press, 2001.

Table 1 Odds ratios of colorectal cancer for quintiles of serum IGF-I, and of three different measures of IGFBP-3^a

	Quintiles					P for trend
	1	2	3	4	5	
IGF-I	1.00	1.49 (0.63–3.52)	1.30 (0.56–3.02)	1.52 (0.67–3.47)	1.88 (0.72–4.91)	0.25
IGFBP-3						
IRMA-Immunotech	1.00	1.70 (0.78–3.70)	1.15 (0.50–2.66)	0.92 (0.40–2.12)	2.46 (1.09–5.57)	0.19
ELISA-DSL	1.00	0.89 (0.41–1.94)	0.69 (0.30–1.57)	1.23 (0.55–2.76)	1.24 (0.54–2.86)	0.49
IGF-I adjusted for IGFBP-3; IGFBP-3 measured by						
IRMA-Immunotech	1.00	1.59 (0.73–3.47)	0.56 (0.23–1.39)	1.43 (0.61–3.36)	1.23 (0.47–3.22)	0.70
ELISA-DSL	1.00	1.48 (0.65–3.35)	1.07 (0.47–2.43)	1.23 (0.52–2.95)	1.03 (0.39–2.69)	0.93

^a Study based on 102 cases of colorectal cancer and 200 matched controls; see Kaaks *et al.*, (3) for details.

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