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 colorectum[3] (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 used[2] (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 IGFBPs. IGFBP-3 levels for cases and controls were 3019.8 ± 587.6 and 2921.7 ± 575.3 ng/ml (mean ± SD), respectively, for IRMA-Immunotech and 4074.3 ± 938.6 and 3951.7 ± 778.8 ng/ml (mean ± 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.

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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.

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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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