Letters to the Editor


Letter

Rudolf Kaaks,1 Sabina Rinaldi, Annie Lukanova, Arslan Akhmedkhanov, Anne Zeleniuch-Jacquotte, and Paolo Toniolo


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 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.

References


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<td>1.49 (0.63–3.52)</td>
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<td>IGFBP-3 IRMA-Immunotech</td>
<td>1.00</td>
<td>1.70 (0.78–3.70)</td>
<td>1.15 (0.50–2.66)</td>
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<td>0.89 (0.41–1.94)</td>
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<td>IGF-I adjusted for IGFBP-3, IGFBP-3 measured by IRMA-Immunotech</td>
<td>1.00</td>
<td>1.59 (0.73–3.47)</td>
<td>0.56 (0.23–1.39)</td>
<td>1.43 (0.61–3.36)</td>
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<td>1.00</td>
<td>1.48 (0.65–3.35)</td>
<td>1.07 (0.47–2.43)</td>
<td>1.23 (0.52–2.95)</td>
<td>1.03 (0.39–2.69)</td>
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</table>

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

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