
**Re: Prospective Study of
Colorectal Cancer Risk in Men
and Plasma Levels of
Insulin-Like Growth Factor
(IGF)-I and IGF-Binding
Protein-3**

We have followed with great interest the evolving evidence that circulating levels of insulin-like growth factor (IGF)-I and IGF-binding protein (IGFBP)-3 may be important predictors of risk for prostate, breast, and now colorectal cancers (1,2). Regarding colorectal cancer, most cancers are believed to develop from adenomatous polyps, known as the adenoma-carcinoma sequence (3). This sequence led us to investigate prospectively the relationship between serum IGF-I and IGFBP-3 and the presence of adenoma—as a surrogate marker of colorectal cancer risk—in an age-defined population (healthy 55- to 64-year-old males and females) undergoing flexible sigmoidoscopy screening. Three-hundred seventy-four

individuals were enrolled, among whom adenomas were found in 56 (15%). Blood was taken at the time of endoscopy. Serum IGF-I was measured, after acid-alcohol extraction, by radioimmunoassay with the use of a polyclonal rabbit antihuman serum (4), and serum IGFBP-3 was determined with the use of an immunoradiometric assay with reagents from Diagnostic Systems Laboratory (Houston, TX). The statistical analysis was performed in a similar manner to that used in the report by Ma et al. (1).

IGF-I correlated positively with IGFBP-3 (Pearson correlation coefficient = .59; $P < .001$). Serum levels (mean \pm standard deviation) for IGF-I were similar among case subjects (i.e., with adenomas) (193 ± 72 ng/mL) and control subjects (181 ± 59 ng/mL). Similarly, there were no differences in IGFBP-3 levels between case subjects (3246 ± 694 ng/mL) and control subjects (3105 ± 595 ng/mL). The lack of an association remained after adjustment (logistic regression) for sex, hormone replacement therapy status (current user or stopped use within the past month versus other) in women, and body mass index. We explored the joint effects of IGF-I and IGFBP-3 (categorized into tertiles based on the distribution among control subjects), but we found no excess of adenomas in any combination [Table 1, similar to Table 3 in (1)]. This lack of excess remained true when adenomas were categorized as either low or high risk (high risk was defined as >1 cm, severe dysplasia, tubulovillous or villous histology, or greater than two adenomas).

The lack of an association between IGF-I and IGFBP-3 and the presence of adenomas in our data does not, in itself, negate the findings of Ma et al. (1) but may provide an alternative hypothesis about the role of these circulating peptides in predicting tumor formation. One possible explanation for the apparent difference in results may be that IGF-I and IGFBP-3, while not predictive of neoplastic risk for all adenomas, may alternatively predict the transformation of late adenoma to adenocarcinoma. Our sample of individuals with high-risk adenomas ($n = 20$) may simply have been too small to detect such an effect.

If the findings of Ma et al. (1) are duplicated and evidence increases for an association between IGF-I and/or

Table 1. Odds ratio (OR)* of association between colorectal adenomas and tertiles of insulin-like growth factor (IGF)-I and insulin-like growth factor-binding protein (IGFBP)-3 in screened, healthy individuals aged 55–64 years

IGF-I	IGFBP-3		
	Tertile 1	Tertile 2	Tertile 3
Tertile 1			
OR	1.00	0.95	2.54
95% CI†	Referent	0.27–3.42	0.24–26.4
No. of adenoma subjects/No. of control subjects	8/65	4/36	1/4
Tertile 2			
OR	1.71	1.52	1.14
95% CI†	0.56–5.19	0.51–4.54	0.34–3.77
No. of adenoma subjects/No. of control subjects	7/33	7/38	5/39
Tertile 3			
OR	2.42	1.41	2.13
95% CI	0.41–14.4	0.45–4.47	0.84–5.35
No. of adenoma subjects/No. of control subjects	2/6	6/35	16/62

*Adjusted for sex and body mass index (weight in kg/[height in m]²).

†95% CI = 95% confidence interval.

IGFBP-3 and the presence of adenomas, colorectal cancer could join the ranks of breast and prostate cancers as an “endocrine-dependent” cancer. This finding would represent a major new perspective in our understanding of the biology of this disease. In contrast to breast and prostate cancers, however, the local expression of IGFs and their binding proteins may theoretically be influenced by the intraluminal environment (i.e., dietary) as well as systemic factors. To date, the regulation of the intestinal IGF system remains poorly understood and clearly warrants further research.

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RESPONSE

In a cross-sectional analysis, Renehan et al. found no statistically significant associations of plasma insulin-like growth factor (IGF)-I and IGF-binding protein (IGFBP)-3 with colorectal adenomas detected on flexible sigmoidoscopy screening. Their observation is somewhat consistent with our findings in a cohort of U.S. women among whom high plasma levels of IGF-I and low lev-

els of IGFBP-3 were statistically significantly associated with risk of colorectal cancer, nonsignificantly associated with “high-risk” (≥ 1 cm or tubulovillous/villous histology) adenomas and not associated with “low-risk” (< 1 cm and tubular histology) adenomas (1).

As Renehan et al. note, their overall study provides insufficient statistical power to yield precise estimates of risk. Further studies of this issue are necessary and are in progress.

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