Serum Concentrations of Insulin-Like Growth Factor and Insulin-Like Growth Factor Binding Protein 3 and Recurrent Colorectal Adenomas

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Abstract

Insulin-like growth factor I (IGF-I) and its primary binding protein, IGFBP-3, have been associated with colorectal cancer incidence in prior epidemiologic studies. High concentrations of IGF-I generally result in increasing risk and high concentrations of IGFBP-3 in decreasing risk. Only one prior study of IGF-I and IGFBP-3 and adenoma recurrence has been reported. We assayed fasting serum from 375 subjects with and 375 subjects without a recurrent adenoma during the course of the Polyp Prevention Trial to determine baseline concentrations of IGF-I and IGFBP-3. To estimate relative risk of adenoma recurrence over the course of 4 years of follow-up for each of these serum measures, we calculated odds ratios (OR) and 95% confidence intervals (CI) using multivariable logistic regression models adjusting for age, gender, body mass index, intervention group, aspirin, smoking, ethnicity, and education. For both IGF-I and IGFBP-3, we found trends indicating decreased risk for subjects in the high compared with the low quartile (for IGF-I: OR, 0.65; 95% CI 0.41-1.01; for IGFBP-3: OR, 0.66; 95% CI, 0.42-1.05). The associations were even greater for advanced adenomas (for IGF-I: OR, 0.51; 95% CI, 0.21-1.29; for IGFBP-3: OR, 0.32; 95% CI, 0.13-0.82). These results showed an unexpected null association, or even the suggestion of a reduction in risk for recurrent adenoma, with not just high IGFBP-3 concentration but also with high levels of IGF-I. Why IGF-I would decrease risk of recurrent adenoma (as distinct from incident adenoma or colorectal cancer) is not clear. (Cancer Epidemiol Biomarkers Prev 2008;17(6):1493–8)

Introduction

Insulin-like growth factor I (IGF-I) has well-established and powerful, direct effects on somatic growth, cell proliferation, and apoptosis (1-3). These effects are mediated by the IGF receptor, a tyrosine kinase receptor expressed on a wide range of epithelial cells, including those of the colon and rectum. When activated, these receptors trigger a cascade of mitogenic signaling responses; thus, individuals with chronically elevated concentrations of IGF-I would be in a physiologic state that promoted increased cell turnover in epithelial tissues. Merely modest increases in rates of cell turnover would result in billions of additional mitoses (1), greatly increasing the probability that a single cell would accumulate somatic mutations in genes critical to the carcinogenic process.

The IGF family also includes at least six binding proteins (IGFBP-1 through IGFBP-6), and when bound to one of these, IGF-I is unable to interact with the IGF receptor. In fact, only a tiny fraction of all IGF-I in circulation is unbound, and roughly 90% of all circulating IGF-I is bound to just one of these binding proteins, IGFBP-3. As such, elevated IGFBP-3 concentrations will reduce the availability of IGF-I to bind to and activate the IGF receptor. Furthermore, IGFBP-3 seems to have direct effects on apoptosis that are independent of its ability to bind and sequester IGF-I (3-5). These features of IGFBP-3 suggest that elevated concentrations of this protein would reduce risk of colorectal cancer.

Almost all of the circulating IGF-I and IGFBP-3 is synthesized in the liver in response to the binding of growth hormone to its hepatic receptors (1). Insulin promotes increased hepatic growth hormone receptor activity and number, suggesting that elevated insulin concentration would result in an increased stimulatory pressure in the direction of IGF-I synthesis (3, 6), and this could help explain, in part, the observations supporting the hypothesis that hyperinsulinemia is a risk factor for colorectal cancer. But, as mentioned above, hepatic

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growth hormone receptor activation also stimulates production of IGFBP-3, which would decrease the mitogenic stimulus. Insulin also has a negative feedback effect on pituitary production of growth hormone itself (6), further highlighting the complexity of the relationships among these hormones. But despite this complexity, it remains reasonable to consider that elevated IGF-I or reduced IGFBP-3 concentrations, or perhaps more importantly, a comparatively high IGF-I to IGFBP-3 ratio would increase risk of colorectal cancer.

A small number of prospective epidemiologic studies have looked at IGF-I and IGFBP-3 as risk factors for of colorectal cancer (7-14). These studies have generally indicated an increased risk of disease with higher concentrations of IGF-I, although only two of these results (7, 9) were statistically significant. For IGFBP-3, the picture is considerably less clear with two studies showing strong inverse associations (7, 9), whereas most others produced results suggestive of positive associations between IGFBP-3 concentration and incident colorectal cancer (7-14). Only one study has looked prospectively at colorectal adenomas, and although Giovannucci and colleagues (7) found no evidence that elevated IGF-I or IGFBP-3 were associated with nonadvanced adenomas, they did observe strong associations between each of these serum measures and advanced adenoma. Until recently, no study had considered the effect of circulating concentrations of IGF-I or IGFBP-3 on risk of adenoma recurrence, although Jacobs and colleagues (15) have now reported an unexpected inverse association between IGF-I concentrations and recurrence.

We investigated whether elevated baseline concentrations of IGF-I or IGFBP-3 would modify risk of colorectal neoplasia in a sample of 750 subjects selected from a large randomized clinical trial designed initially to test the ability of a dietary intervention to prevent recurrence of adenomas.

Materials and Methods

Study Population. We selected the subjects for these analyses from participants in the Polyp Prevention Trial (PTT), a multicentered randomized trial of a dietary intervention designed to reduce the rate of recurrence for colorectal polyps. Details of the complete PTT protocol seem elsewhere (16). Briefly, subjects were men and women without a history of diabetes who were ages 35 y old or older and who had had at least one histologically confirmed colorectal adenoma removed during a qualifying colonoscopy within the 6 mo before randomization. A qualifying colonoscopy was one in which the cecum was visualized and all polyps were removed. The participating clinical centers identified potential subjects through referrals by endoscopists or reviews of records from the endoscopy service. These methods identified 38,277 potential subjects, and 2,079 of these enrolled in the study. Of those initially enrolled, 1,905 completed the protocol. The protocol included dietary assessment plus a fasting venous blood specimen at baseline, year 1, and year 4 follow-up clinic visits.

Colonoscopy. At 1 and 4 y after randomization, subjects returned for follow-up colonoscopies. The year 1 colonoscopy had to be at least 180 d but no >2 y after randomization and served to detect and remove any lesions missed at the baseline colonoscopy. In addition to the results from the year 1 and year 4 follow-up colonoscopies, we also obtained data from any unscheduled endoscopic procedures.

Two central pathologists assessed histologic features and degree of atypia for all lesions. We defined recurrent adenoma as an adenoma found during any endoscopic procedure after the 1-year colonoscopy or, for subjects who missed the 1-year exam, during any endoscopic procedure done at least 2 y after randomization. An endpoints committee composed of gastroenterologists evaluated complicated cases including those involving lost tissue specimens or failure to reach the cecum. The few colorectal cancers identified after the 1-year colonoscopy were also counted as recurrent lesions.

Of the 1,905 subjects who completed the protocol, 754 (39.6%) had recurrent lesions identified, and 125 of the 754 subjects with adenomas were identified to have advanced lesions (defined as having a maximal diameter of at least 1 cm or at least 25% villous elements or evidence of high-grade dysplasia including carcinoma).

To select a subset for this analysis from the 1,905 subjects who completed the protocol, we first excluded subjects with no available serum from the baseline visit (T0). For the case group, we selected all 114 individuals with recurrent adenomas who had advanced lesions and 261 subjects with nonadvanced recurrent adenomas. For the 261 subjects with nonadvanced recurrent adenomas, we sampled only from among subjects with at least 2 stored serum vials at T0. For each case, we then randomly selected controls matched on age (5-year age groups) and gender from among the subjects without recurrent adenomas and 2 or more vials of stored serum, a procedure that resulted in 375 pairs (or 750 subjects in total).

Blood Draw. As described above, all subjects provided fasting venous blood samples from which serum was separated at the baseline, year 1, and year 4 clinic visits. The serum was then aliquotted into 2-mL polypropylene cryovials (Nalgene 50000020) and stored at −70°C within 4 h from blood draw. From each of the 750 subjects included in these analyses, we selected one vial of frozen serum at each of three time points: baseline/randomization (T0), year 1 follow-up visit (T1), and year 4 follow-up visit (T4). We shipped these from the National Cancer Institute repository in Frederick, MD, to the Maine Center for Osteoporosis Research and Education in Bangor, ME, for IGF-I and IGFP-3 assays. We used a shipping protocol designed to insure none of the vials thawed in transit, and all vials arrived at the analytic laboratories frozen and in good condition.

Assays. Serum IGF-I concentration was measured using the IGF-I (IGFBP blocked) radioimmunoassay manufactured by American Laboratory Products Company. The calculated sensitivity of the assay is 0.02 ng/mL. The cross reactivity with IGF-I is small (<0.05%). Concentrations of IGFBP-3 in serum were measured using the ''Active'' IGFBP-3 IRMA kit manufactured by Diagnostic Systems Laboratories, Inc. The calculated sensitivity of the kit is 0.5 ng/mL. The kit uses a two-site immunoradiometric principle to measure nonglycosylated IGFBP-3 directly. All samples were

arranged in batches such that case and matching noncase samples were in the same batch, and each batch contained three identical control samples. The coefficient of variation for IGF-I was 6.4%, and for IGFBP-3, it was 8.0%.

Statistical Analyses. We calculated odds ratios (OR) and 95% confidence intervals (CI) in age and gender-adjusted and multivariable-adjusted conditional logistic regression models using SAS statistical software (version 8.2). Multivariate models included age, gender, body mass index (BMI = kg/m^2), intervention group (intervention versus control arm), aspirin use, smoking, ethnicity, and education. Age and BMI were both modeled as continuous variables. We tested baseline concentration of insulin as a potential confounder, but including it in the models made no material difference in the outcome (data not shown). When we considered change from baseline levels in one of the variables as the primary exposure, we also adjusted for the baseline value on that variable. We estimated separate ORs for biochemical baseline concentration of IGF-I and IGFBP-3 as well as the ratio of IGF-I to IGFBP-3, modeling the outcomes as any recurrent adenoma versus no recurrent adenoma during the follow-up period and then estimated an additional set of ORs for advanced recurrent adenoma versus no recurrent adenoma. Five cases of advanced recurrent adenoma were missing information on IGF-I or IGFBP-3, and these (along with their matched controls) were deleted from the analysis. We considered possible effect modification by gender, family history of colorectal cancer, type of adenoma (advanced versus nonadvanced) removed at qualifying colonoscopy, and presence of adenoma in the 5 years before qualifying colonoscopy but saw little evidence of interaction on any of these variables (data not shown).

Results

Baseline characteristics of the PTT subjects we included in this study, by quartile of IGF-I and IGFBP-3 concentrations at study entry, appear in Table 1. As it is well-established that concentrations of IGF-I and IGFBP-3 decline with age, it was not surprising that subjects in the highest quartile of each of these were significantly younger than those in the lowest ($P_{trend} < 0.0001$). Subjects in the highest quartile of IGF-I at baseline were also more likely to be in the control group for the PTT intervention study ($P = 0.01$), to be male, ($P < 0.01$), and to have more than a high-school education ($P = 0.01$). Although waist-to-hip ratio showed a statistically significant increase across quintiles of IGF-I ($P_{trend} < 0.0001$), the absolute magnitude of that increase (from 0.93 in Q1 to 0.96 in Q4) was nonetheless rather modest. Subjects in the highest quartile of IGFBP-3 at baseline were more likely to be women ($P_{trend} < 0.0001$) and to be of nonminority ethnicity ($P_{trend} = 0.02$). They also had significantly higher plasma total cholesterol (189 mg/dl in Q1 compared with 213 mg/dl in Q4; $P_{trend} < 0.0001$). All other characteristics were a little different between those with low and high concentrations of either IGF-I or IGFBP-3 at baseline.

Results from the logistic regression analyses of baseline values for IGF-I and IGFBP-3 as predictors of adenoma recurrence appear in Table 2. Contrary to our expectations, high quartile of baseline concentration of IGF-I showed a suggestive inverse association with recurrent adenoma in multivariate-adjusted models (OR, 0.65; 95% CI, 0.41-1.01). We observed a more pronounced inverse association for recurrence of advanced adenomas (OR, 0.51; 95% CI, 0.21-1.29), although in this instance, with fewer cases of advanced adenoma,

Table 1. Basic characteristics of study subjects by quartile of IGF-I and IGFBP-3 concentration at study entry

	IGF-I (ng/mL)				IGFBP-3 (ng/mL)			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
	<110	110-131	132-159	≥160	<3,377	3,377-3,936	3,937-4,421	≥4,422
	$n = 187$	$n = 186$	$n = 183$	$n = 184$	$n = 185$	$n = 185$	$n = 185$	$n = 185$
Age (y)*	63.7 ± 0.6	62.4 ± 0.7	60.3 ± 0.7	59.0 ± 0.7	64.5 ± 0.6	61.5 ± 0.7	59.0 ± 0.6	60.2 ± 0.7
Assigned to intervention group (%)	40.6	32.3	30.1	28.8	33.0	27.0	33.5	38.4
Male gender (%)	51.9	72.0	74.9	87.0	82.7	67.0	76.8	58.9
Minority ethnicity (%)	10.7	12.9	12.0	10.3	15.1	12.4	10.8	7.6
Above high school education (%)	61.5	71.0	73.8	73.4	64.9	69.2	77.8	67.6
Current smoker (%)	9.1	13.4	16.9	12.5	15.7	10.8	16.8	8.7
Alcohol (g/d)*	8.2 ± 1.1	8.3 ± 1.0	11.8 ± 1.4	6.0 ± 0.9	8.1 ± 1.0	7.4 ± 0.9	9.1 ± 1.3	9.6 ± 1.3
Current aspirin use (%)	23.0	25.8	21.9	20.7	24.3	23.8	21.1	22.2
Plasma total cholesterol (mg/dl)*	198 ± 4.2	201 ± 3.4	202 ± 3.5	199 ± 3.3	189 ± 3.7	199 ± 2.9	197 ± 3.5	213 ± 3.6
Serum total carotenoids (μg/dl)*	82 ± 4.2	102 ± 5.6	88 ± 3.7	95 ± 3.7	83 ± 3.9	96 ± 5.0	93 ± 4.7	95 ± 3.8
Family history of CRC (%)	26.7	26.3	25.1	27.7	26.0	24.9	29.7	25.4
Adenoma in prior 5 y (%)	17.7	26.3	17.5	16.3	22.7	16.8	19.5	18.9
Energy (kcals)*	1,876 ± 47	1,981 ± 44	2,016 ± 43	1,962 ± 41	1,976 ± 47	1,906 ± 41	2,045 ± 44	1,905 ± 42
Vig/moderate activity (h/wk)*	12.3 ± 0.93	13.1 ± 1.05	14.8 ± 1.10	13.8 ± 0.93	11.7 ± 1.00	14.1 ± 1.03	14.2 ± 1.00	13.9 ± 1.00
BMI (kg/m2)*	28.0 ± 0.29	27.3 ± 0.28	27.6 ± 0.29	27.5 ± 0.27	27.7 ± 0.28	27.4 ± 0.25	27.7 ± 0.30	27.6 ± 0.28
Waist-to-hip ratio*	0.93 ± 0.01	0.94 ± 0.01	0.95 ± 0.01	0.96 ± 0.01	0.95 ± 0.01	0.94 ± 0.01	0.95 ± 0.01	0.94 ± 0.01

Abbreviations: CRC, colorectal cancer; vig/moderate activity, vigorous/ moderate activity.
*Values are means ±SE.

Table 2. Age-adjusted and multivariate-adjusted ORs for recurrence of any colorectal adenoma or advanced colorectal adenoma by quartile of IGF-I and IGFBP-3 serum concentrations

	OR (95% CI)*				P_{trend}
	Q1	Q2	Q3	Q4	
IGF-I (ng/mL) at T0	<110	110-131	132-159	≥160	
Any adenoma (n = 370 cases)					
Age and gender adjusted	1.00 (reference)	0.91 (0.60-1.39)	0.65 (0.42-1.02)	0.67 (0.42-1.05)	0.03
Multivariate adjusted	1.00 (reference)	0.90 (0.59-1.39)	0.64 (0.41-1.01)	0.65 (0.41-1.01)	0.02
Advanced adenoma (n = 109 cases)					
Age and gender adjusted	1.00 (reference)	0.89 (0.41-1.91)	0.56 (0.25-1.26)	0.50 (0.21-1.15)	0.06
Multivariate adjusted	1.00 (reference)	0.98 (0.44-2.19)	0.60 (0.25-1.42)	0.51 (0.21-1.29)	0.09
IGFBP-3 (ng/mL) at T0	<3,377	3,377-3,936	3,937-4,421	≥4,422	
Any adenoma (n = 370 cases)					
Age and gender adjusted	1.00 (reference)	0.59 (0.38-0.91)	0.63 (0.39-1.01)	0.67 (0.43-1.06)	0.14
Multivariate adjusted	1.00 (reference)	0.58 (0.38-0.91)	0.62 (0.38-1.01)	0.66 (0.42-1.05)	0.14
Advanced adenoma (n = 109 cases)					
Age and gender adjusted	1.00 (reference)	0.40 (0.17-0.93)	0.36 (0.13-0.98)	0.36 (0.15-0.86)	0.04
Multivariate adjusted	1.00 (reference)	0.33 (0.13-0.83)	0.35 (0.12-1.01)	0.32 (0.13-0.82)	0.04

*All models adjust for age and gender, and multivariate models additionally adjust for BMI, control vs intervention randomization group, aspirin use, smoking, ethnicity, and education.

the CIs were wide and therefore still included 1.0. More consistent with our expectations, high concentration of IGFBP-3 at baseline showed a suggestive inverse association in multivariate-adjusted models with recurrence of any adenoma (OR, 0.66; 95% CI, 0.42-1.05) and a statistically significant inverse association with advanced adenoma (OR, 0.32; 95% CI, 0.13-0.82).

As described above, circulating levels of IGF-I and IGFBP-3 are both determined in large part by growth hormone–stimulated hepatic synthesis, and as a result, concentrations of each are highly correlated. This observation together with the fact that IGFBP-3 binding of IGF-I effectively sequesters it from interaction with the IGF-I receptor, suggest the need to consider not just the absolute amount of IGF-I in circulation but also the concentration of IGF-I relative to that of IGFBP-3. When in multivariate models, we further controlled for IGFBP-3; however, the association between IGF-I and recurrence of any (OR, 0.67; 95% CI, 0.39-1.14) or advanced (OR, 0.74; 95% CI, 0.26-2.08) adenoma was largely unchanged (Table 3). Likewise, IGFBP-3 associations with recurrent adenomas were very similar, if perhaps slightly attenuated, when we controlled for IGF-I concentration. If we considered the ratio of IGF-I to IGFBP-3, we saw a largely null association that, if anything, was suggestive of a small decreased risk with the high quartile of IGF-I/IGFBP-3 for any (OR, 0.70; 95% CI, 0.42-1.16) and for advanced recurrent adenoma (OR, 0.79; 95% CI, 0.30-2.07).

Because baseline concentrations of these biochemical markers may not be the most relevant indicators of risk, we also considered differences at the end of follow-up compared with baseline, controlling for baseline concentration, as predictors of adenoma recurrence (Table 4). In no case, however, did the change in concentration from baseline to year 1 or from baseline to year 4 show any association with adenoma recurrence.

Discussion

Although we did anticipate the observed inverse association between IGFBP-3 concentration and adenoma recurrence, we had expected a positive association between IGF-I and recurrence. Interestingly, a recent analysis of data from the Wheat Bran Fiber Trial found similarly unexpected inverse associations (15). In that study, subjects in the top tertile of serum IGF-I concentration at baseline had an adjusted OR for recurrent adenoma of 0.49 (95% CI, 0.26-0.91) compared

Table 3. Multivariate-adjusted ORs for recurrence of any colorectal adenoma or advanced colorectal adenoma for quartile of IGF-I and IGFBP-3 serum concentrations controlling for each other

	OR (95% CI)* for 1-Unit Change in Blood Variable				P trend
	Q1	Q2	Q3	Q4	
IGF-I (ng/mL) at T0 (controlling for IGFBP-3)	<110	110-131	132-159	≥160	
Any adenoma (N = 370 cases)	1.00 (reference)	0.91 (0.59-1.42)	0.66 (0.40-1.07)	0.67 (0.39-1.14)	0.07
Advanced adenoma (N = 109cases)	1.00 (reference)	1.06 (0.47-2.41)	0.71 (0.29-1.73)	0.74 (0.26-2.08)	0.40
IGFBP-3 (ng/mL) at T0 (controlling for IGF-I)	<3,377	3,377-3,936	3,937-4,421	≥4,422	
Any adenoma (N = 370 cases)	1.00 (reference)	0.62 (0.39-0.98)	0.68 (0.41-1.13)	0.77 (0.45-1.30)	0.49
Advanced adenoma (N = 109 cases)	1.00 (reference)	0.34 (0.13-0.86)	0.38 (0.12-1.16)	0.35 (0.13-0.93)	0.09
IGF-I/IGFBP-3 Ratio at T0	<0.029	0.029-0.034	0.035-0.040	≥0.041	
Any adenoma (N = 370 cases)	1.00 (reference)	0.78 (0.47-1.17)	1.03 (0.65-1.64)	0.70 (0.42-1.16)	0.44
Advanced adenoma (N = 109 cases)	1.00 (reference)	0.61 (0.25-1.50)	0.87 (0.36-2.08)	0.79 (0.30-2.07)	0.97

*All models adjust for age gender, BMI, control vs intervention randomization group, aspirin use, smoking, ethnicity, and education.

Table 4. Age-adjusted and multivariate-adjusted ORs for recurrence of any colorectal adenoma or advanced colorectal adenoma for changes in continuous measures of IGF-I and IGFBP-3

	OR (95% CI)* for indicated unit change in blood variable	
	Any adenoma	Advanced adenoma
10 ng/mL change in IGF-I (controlling for IGF-I at T0)		
Change from T0 to T1	*n* = 370 cases	*n* = 109 cases
Age and gender adjusted	0.99 (0.93-1.06)	0.92 (0.80-1.05)
Multivariable adjusted	1.00 (0.93-1.06)	0.93 (0.80-1.07)
Change from T0 to T4	*n* = 357 cases	*n* = 96 cases
Age and gender adjusted	0.97 (0.92-1.03)	0.91 (0.80-1.03)
Multivariable adjusted	0.98 (0.92-1.03)	0.91 (0.80-1.04)
100 ng/mL change in IGFBP-3 (controlling for IGFBP-3 at T0)		
Change from T0 to T1	*n* = 370 cases	*n* = 109 cases
Age and gender adjusted	1.01 (0.98-1.05)	0.99 (0.94-1.05)
Multivariable adjusted	1.02 (0.99-1.05)	1.01 (0.95-1.07)
Change from T0 to T4	*n* = 357 cases	*n* = 96 cases
Age and gender adjusted	0.98 (0.96-1.01)	0.96 (0.91-1.02)
Multivariable adjusted	0.99 (0.96-1.01)	0.98 (0.92-1.04)

*All models adjust for age and gender, and multivariate models additionally adjust for BMI, control vs intervention randomization group, aspirin use, smoking, ethnicity, and education.

with subjects in the lowest tertile. This was the first study to report on this association, and our results provide support for this surprising finding.

That we (as well as Jacobs and colleagues; ref. 15) saw a null or even an inverse association for IGF-I is contrary to much of the existing literature on IGF-I and colorectal cancer. Among the eight prospective studies that assessed IGF-I as a risk factor for colorectal cancer, all but one estimated ORs of >1.0. It should be noted, however, that of these, only two (7, 9) produced statistically significant associations.

The only previous prospective study of IGF-I as a risk factor for adenomas (7) found a nonsignificant OR of 2.78 for advanced adenoma, but no association for nonadvance adenoma. In a cross-sectional study, Schoen et al. (17) found a similar, much stronger association for advanced adenoma and IGF-I (OR, 3.44; 95% CI, 1.37-6.64) compared with nonadvanced adenoma, supporting the idea that IGF-I might be more important in the latter stages of adenoma development. But in our analysis, we found an even stronger inverse association for advanced adenom compared with all adenomas. Thus, our data do not support the hypothesis that elevated IGF-I concentrations increase risk of colorectal neoplasia and, by extension, cancer. It should be noted that we have emphasized the results from prospective studies rather than case control or cross-sectional studies due to inherent limitations of these other designs in the study of serum markers and prevalent adenomas.

That we observed this contrary result may not be entirely inexplicable, however. In advanced cancer, it is typical to observe cachexia and undernourishment, which, in a healthy population, would lead to lowered concentrations of IGF-I (1). In this way, it might be possible to observe an inverse association with colorectal cancer and IGF-I even if IGF-I acts as a promoter of disease at an earlier stage. Consistent with this hypothesis is the even stronger inverse association between IGF-I and advanced adenoma recurrence (OR, 0.51; 95% CI, 0.21-1.29) compared with all adenomas (OR, 0.65; 95% CI, 0.41-1.01). Furthermore, the PTT is a recurrence study, so prior neoplasia did exist that potentially could have affected IGF-I concentration at baseline, and subjects with advanced adenoma at the qualifying colonoscopy were also more likely to have recurrent adenoma. Thus, it is possible that advanced adenoma at the qualifying stage depressed IGF-I concentration and at the same time increased risk of recurrent adenoma producing the inverse association. Although this is a theoretical possibility, none of the current study subjects had advanced cancer, merely adenomas, and therefore, none were experiencing cachexia. It seems unlikely, therefore, that the acute effects of malnourishment would be a likely explanation for lowered IGF-I concentration in subjects who subsequently developed recurrent adenomas.

Even if we exclude the theoretical action of advanced adenomas to depress serum concentration of IGF-I as an explanation for our results, the apparent null association between IGF-I and recurrent adenoma does not rule out an important role for this growth factor in colorectal neoplasia. In a separate analysis of PTT data (18), we observed an ~50% increased risk of recurrent adenoma among subjects in the highest quartile of fasting insulin at baseline compared with those in the lowest quartile. Insulin acts to down-regulate IGFBP-1 and IGFBP-2, and although ~90% of circulating IGF-I is bound by IGFBP-3, variations in IGFBP-1 and 2 nonetheless still have potentially significant biological importance. Given the high correlation between IGF-I and IGFBP-3 concentrations (r = 0.52), it may be difficult to tease apart the independent effects of IGF-I on recurrent colorectal neoplasia. But with >99% of IGF-I in circulation bound to one of the six or more binding proteins, and with IGFBP-1 and IGFBP-2 varying in a manner that is largely independent of IGF-I, changes in the concentrations of these binding proteins could thus produce large changes in the relative amount of ''free'' IGF-I available to bind the IGF receptor. We did not have data on IGFBP-1 or IGFBP-2 in the PTT, but the previous association we observed for insulin would be consistent with this idea of

increased free IGF-I leading to higher risk of recurrent adenoma.

It is also possible that an inverse association between IGF-I and adenoma recurrence could be mediated through the inflammatory pathway. For example, both tumor necrosis factor α and interleukin-I have been shown to induce growth hormone resistance (19), meaning that a high concentration of IGF-I could merely be a marker for low levels of proinflammatory cytokines. In this way, if there was an underlying inflammatory process active in promoting tumor recurrence (a reasonable proposition given the above-mentioned increased risk of recurrence with impaired fasting glucose in this population), then it would make sense that low levels of IGF-I would also be associated with that recurrence.

Finally, the bioactivity of IGF-I is not determined solely (or perhaps even primarily) by circulating levels. Local expression of genes for IGF-I and IGFBP-3 with paracrine or autocrine effects may be the more important variables (1), and we could not capture that activity with our serum measures. It is also possible that serum concentrations of IGF-I are not critical in early stage events related to initial polyp formation but may be more relevant in later stages of progression from adenoma to invasive carcinoma. With our end point being recurrent adenoma, however, we cannot conclude that IGF-I would have had no effect on later-stage colorectal cancer development.

In summary, our results showed an unexpected null association, or even the suggestion of a reduction in risk, with not just high IGFBP-3 concentration but also with high levels of IGF-I. Adjusting the IGF-I and IGFBP-3 results to take into account relative concentrations of each with respect to the other did not change these findings. We cannot exclude, however, a role for IGF-I or IGFBP-3 in adenoma recurrence, and in fact, separate data on insulin and glucose in the PTT are consistent with an IGF-I effect mediated by the ability of insulin to lower IGFBP-1 and IGFBP-2 concentrations. Nonetheless, we found no evidence that elevated concentration of total circulating IGF-I or IGFBP-3 increases risk of adenoma recurrence.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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