Plasma Insulin-Like Growth Factor I Is Inversely Associated with Colorectal Adenoma Recurrence: A Novel Hypothesis

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Abstract

The insulin-like growth factor I (IGF-I) axis has been proposed to be a significant factor in the development of certain cancers, including colorectal. However, results from epidemiologic studies suggest modest effects on colorectal cancer risk. Using cross-sectional and prospective study designs within the same cohort of men who had at least one adenoma at baseline, we investigated whether plasma IGF-I, IGF-I binding protein 1, and IGF-I binding protein 3 were associated with colorectal adenoma characteristics at baseline and whether their levels were related to odds for adenoma recurrence. Plasma levels of each marker were measured at baseline in 299 male participants in the Wheat Bran Fiber Trial, who were followed prospectively for recurrence of their adenomatous lesions. In cross-sectional analyses, plasma IGF-I was significantly positively associated with the presence of adenomas with any villous features (P = 0.04). In contrast, IGF-I levels were inversely associated with odds of colorectal adenoma recurrence, with adjusted odds ratios (95% confidence interval) of 0.55 (0.29-1.01) and 0.49 (0.26-0.91) for the second and third tertiles of IGF-I, respectively, compared with the first tertile (P_{trend} = 0.02). The inverse association was stronger for advanced adenoma recurrence (P_{trend} = 0.02) than for non-advanced recurrence (P_{trend} = 0.10). These results suggest that, once an adenoma is removed, higher IGF-I levels reduce the odds of the formation of new lesions in the colorectum. (Cancer Epidemiol Biomarkers Prev 2008;17(2):300–5)

Introduction

It has been proposed that the insulin-like growth factor (IGF) system (1), including IGF-I, multiple IGF-I binding proteins (IGFBP), and IGF receptors (2), is associated with the development of colorectal neoplasia (3). For example, IGF-I has mitogenic and antiapoptotic properties, plays a role in angiogenesis, and, as such, has been hypothesized to increase the risk of colorectal neoplasia (1). IGFBP-3 is the primary carrier of IGF-I, with ~90% of circulating IGF-I bound to this protein (3). Higher levels of IGFBP-3 are associated with reductions in both free and total circulating levels of IGF-I and, thus, by reducing the availability of IGF-I at the tissue level, are thought to be protective for colorectal neoplasia (1, 3). Additionally, IGFBP-3 has growth inhibitory effects on cancer cells *in vitro* independent of IGF-I binding (1-3). Another IGFBP, IGFBP-1, might also have protective effects on colorectal neoplasia (4). Higher insulin levels, in part related to greater body size, reduce the synthesis of IGFBP-1 (4), which in turn increases circulating free IGF-I levels and potentially leads to elevated risk for precancerous or cancerous lesions (3).

Results from several epidemiologic studies that have explored the link between the IGF system and risk for colorectal cancer have, in general, shown modest, non-statistically significant positive associations for IGF-I (5-14), possibly related to limited statistical power. In a meta-analysis of five cohort studies, Renehan et al. (15) showed an odds ratio [OR; 95% confidence interval (95% CI)] of 1.58 (1.11-2.27) for colorectal cancer when comparing the highest and lowest IGF-I levels. No significant association was reported for IGFBP-3 (15). A more recent meta-analysis by Morris et al. (7) showed similar results among seven prospective studies of IGF-I and colon cancer, with an OR (95% CI) of 1.37 (1.05-1.78) for individuals in the highest versus lowest quartile of IGF-I, whereas consistent with other studies, there was no association between colon cancer risk and IGFBP-3.

Results of investigations of colorectal adenoma tend to mirror those for cancer, demonstrating modest positive associations with IGF-I levels and modest inverse relationships with IGFBP-3 (16-22). The majority of the adenoma studies have used cross-sectional designs (17-21), with a few exceptions (16, 22); hence, it is difficult to address temporal relationships between circulating levels of members of the IGF family and the

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development of colorectal adenoma. To our knowledge, only a single study of the IGF axis and colorectal adenoma recurrence has been reported in the literature, which was a small study in acromegalics (23), who are known to have extremely high IGF-I levels. In the current work, we first investigated the association between plasma levels of IGF-I, IGFBP-1, and IGFBP-3 and characteristics of baseline adenomas. We then prospectively assessed the relation between these biomarkers and recurrence of adenomatous lesions. The latter approach allows assessment of the role of the IGF system in the formation of new lesions.

Materials and Methods

Study Population. A total of 299 nonsmoking men with no personal history of prostate cancer were randomly selected for the analyses of plasma IGF-I, IGFBP-1, and IGFBP-3 from participants who were enrolled in the Wheat Bran Fiber Trial, a randomized, double-blind, controlled intervention trial described in detail elsewhere (24). The original trial was designed to assess whether a cereal supplement of 13.5 g/day of wheat bran fiber reduced the risk of colorectal adenoma recurrence compared with a supplement of 2.0 g/day (24). A total of 1,429 participants were randomized to the trial, and 1,304 completed it by having had one or more colonoscopies after randomization (24). No significant effect of the high-dose fiber supplement was observed (24). The subpopulation of men in the current study was originally randomly selected among nonsmoking male participants of the Wheat Bran Fiber Trial for an analysis of the fiber intervention effects on circulating IGF-I and IGFBPs; no significant differences were detected by treatment arm in this relatively homogeneous population. Currently, this subsample of the Wheat Bran Fiber Trial comprises the only participants for whom we have conducted measurements for IGF-I and its binding proteins. The study was approved by the University of Arizona Human Subjects Committee and local hospital committees and is in accordance with an assurance filed with and approved by the Department of Health and Human Services. Informed consent was obtained from each participant before commencement of the study.

Clinical Chemistry. As part of the Wheat Bran Fiber clinical trial protocol, baseline fasting blood samples were collected for all study participants for use in standard clinical analyses of blood chemistry. These samples were processed to serum and plasma in the recruitment clinics and sent on the day of collection for standardized diagnostic measures of fasting plasma glucose and serum lipid levels, including triglycerides, total cholesterol, low-density lipoprotein, and high-density lipoprotein (HDL). All blood biochemical markers were done in CLIA-certified diagnostic laboratories, ensuring high quality measurements. Additional plasma samples were stored at −80°C and were not previously thawed before use in this study.

Determination of Plasma Levels of IGF-I, IGFBP-1, and IGFBP-3. Baseline plasma IGF-I, IGFBP-1, and IGFBP-3 concentrations were measured using ELISA kits purchased from Diagnostic Systems Laboratory, Inc. All assays were done in a blinded fashion. Assay variability was monitored by including ~10% of blinded quality control samples in each batch of samples analyzed. The intraassay and interassay technical errors were 8.7% and 15.2%, respectively, for IGF-I; 13.0% and 15.3%, respectively, for IGFBP-1; and 8.8% and 26%, respectively, for IGFBP-3.

Exposure Variables. Baseline dietary data for participants were extracted from the Arizona Food Frequency Questionnaire, a self-administered, semiquantitative, scannable instrument with 113 items, which was previously evaluated for reliability and validity (25). Participants were asked to report their usual intake of food for the prior 12-month period (26). Additionally, self-administered questionnaires provided information regarding health and medication history, demographic data, and life-style characteristics, such as smoking and aspirin use.

Outcome Variables. Adenoma characteristics (i.e., number, size, location, and histology) were obtained from the medical record and the pathology report for each subject (27). A recurrent adenoma was defined as any colorectal adenoma detected at colonoscopy at least 5 months after randomization. Adenomas were classified as advanced if they had a diameter of 1 cm or more and/or tubulovillous or villous histology. Colorectal adenocarcinomas were included in the advanced recurrence group. All other adenomas were considered nonadvanced. In subjects with more than one adenoma, size and characterization of the histologic type were based on the largest and/or most advanced adenoma.

Statistical Analysis. All analyses were conducted using the STATA statistical software package (version 9.0, Stata Corporation). For comparisons of baseline characteristics by baseline tertile of IGF-I, *P* values were calculated with χ^2 analyses for categorical variables and regression analyses for continuous variables. For determination of the association between IGF-I pathway biomarkers and odds of adenoma recurrence, unconditional logistic regression modeling was used. Multinomial logistic regression analysis was used for calculation of ORs for nonadvanced and advanced recurrence.

Potential confounding variables were assessed using logistic regression modeling and included age; race; family history of colorectal cancer; presence of previous polyps; use of aspirin; self-report of diabetes; physical activity; dietary intake of protein, energy, fat, saturated fat, alcohol, fiber, calcium, and milk; and baseline adenoma characteristics, including size, histology, number, and location. Confounders were defined as variables that changed the point estimate by 10% or greater (28) and were included in the final adjusted model. Additionally, calcium was added to the adjusted model due to its significant association with both IGF-I and colorectal adenoma recurrence. The final model thus included age, calcium intake, number of adenomas at baseline, and number of colonoscopies as continuous variables, as well as a categorical variable for previous polyp (yes or no). A categorical variable for tertile of baseline IGF-I levels was included in models for IGFBP-1 and IGFBP-3.

We specifically assessed whether IGFBP-3 was a confounder in the models for IGF-I and colorectal adenoma recurrence and found that inclusion of IGFBP-3 did not materially change the point estimates

for recurrence. Therefore, to achieve the most parsimonious model, we elected not to include IGFBP-3 in the final models for IGF-I. We did, however, construct a variable for IGF-I/IGFBP-3 molar ratio, as suggested by previous work (12, 21). The conversion factor for IGF-I is 1 μg/mL = 0.130 nmol/L, whereas for IGFBP-3, it is 1 μg/mL = 0.036 nmol/L (21). In addition, we created a variable for the triglyceride/HDL ratio, as this variable has recently been proposed to be a reliable indicator of insulin resistance (29, 30).

Results

Table 1 presents the baseline characteristics of the study population by tertile of baseline IGF level. For the dietary variables, only intake of protein and calcium showed positive associations with IGF-I (P = 0.05). Plasma triglyceride levels and the triglyceride/HDL ratio were significantly inversely related to IGF-I (P = 0.02), whereas low-density lipoprotein (P = 0.03) and IGFBP-3 (P = 0.01) were positively associated.

We assessed the characteristics of baseline adenomas by tertile of IGF-I (Table 2). Villous histology in baseline colorectal adenomas was significantly more common in those in the highest tertile of IGF-I (30.3%) compared with the lower tertiles (16.2%). Large adenoma size (>10 mm) and the presence of advanced lesions (size, >10 mm and/or presence of any villous features) were also more common in those with higher IGF-I levels; however, these results were not statistically significant. Subjects with higher IGF-I levels were less likely to have proximal lesions, although these results were not significant.

The relation between several IGF-related biomarkers and risk for colorectal adenoma recurrence is presented in Table 3. A higher IGF-I concentration was associated with a significantly lower odds of adenoma recurrence in both the unadjusted (P_{trend} = 0.02) and adjusted (P_{trend} = 0.02) models. No significant associations were observed for IGFBP-1, IGFBP-3, or IGF-I/IGFBP-3. When recurrences were separated into nonadvanced and advanced (Table 4), we observed an inverse association between IGF-I and both endpoints; however, the association for advanced recurrence was stronger and statistically significant (P = 0.02). None of the other plasma biomarkers showed significant associations with colorectal adenoma recurrence.

Discussion

In the current work, we showed a statistically significant positive association for serum IGF-I levels and colorectal adenomas with villous histology at baseline in cross-sectional analyses. Conversely, we observed an inverse association between baseline IGF-I levels and colorectal adenoma recurrence, whereas no statistically significant

Table 1. Baseline characteristics of participants by tertile of baseline IGF-I levels

	Tertile of baseline IGF-I (mean, ng/mL)			
	1 (68.0 ± 22.8)	2 (116.4 ± 12.2)	3 (176.3 ± 35.5)	P* analyses for categorical variables
n	100	99	99	
Age	65.6 ± 7.8	65.5 ± 9.0	63.9 ± 8.9	0.17
BMI (kg/m^2)	28.8 ± 4.6	28.4 ± 4.1	27.9 ± 4.0	0.15
White (yes, %)	94 (94.0)	94 (94.9)	95 (96.0)	0.82
Family history (yes, %)†	17 (17.0)	17 (17.2)	16 (16.2)	0.98
Previous polyp (yes, %)‡	34 (38.2)	34 (41.5)	25 (29.4)	0.24
Aspirin use (yes, %)§	32 (32.0)	29 (29.3)	27 (27.3)	0.76
Diabetes (yes, %)‖	15 (15.5)	9 (9.6)	6 (6.3)	0.11
Physical activity (kcal/d)	2498.7 ± 673.1	2582.6 ± 702.7	2544.8 ± 677.7	0.63
Dietary variables				
Protein (g/d)	75.8 ± 26.5	80.4 ± 26.5	83.4 ± 28.2	0.05
Energy (kcal/d)	1998.7 ± 699.4	2072.3 ± 629.6	2144.6 ± 678.5	0.13
Total fat (g/d)	72.4 ± 30.1	76.1 ± 27.9	77.3 ± 30.8	0.24
Saturated fat (g/d)	23.8 ± 11.0	25.2 ± 10.3	25.4 ± 11.1	0.29
Alcohol (g/d)	7.4 ± 12.4	7.6 ± 10.4	6.1 ± 9.0	0.42
Total fiber (g/d)	22.8 ± 9.1	23.1 ± 9.7	24.8 ± 11.0	0.14
Calcium (mg/d)	892.9 ± 395.8	913.2 ± 386.7	999.8 ± 387.2	0.05
Milk (servings/d)	1.16 ± 1.2	1.13 ± 1.1	1.47 ± 1.3	0.07
Blood biomarkers				
Glucose (mg/dL)	112.1 ± 27.1	107.6 ± 25.5	107.6 ± 26.7	0.23
Cholesterol (mg/dL)	210.1 ± 40.5	211.4 ± 38.7	213.4 ± 39.0	0.56
Triglycerides (mg/dL)	186.8 ± 137.7	166.6 ± 85.9	155.4 ± 72.6	0.03
HDL (mg/dL)	46.1 ± 12.8	46.1 ± 12.2	46.5 ± 10.7	0.81
LDL (mg/dL)	123.9 ± 44.2	133.2 ± 39.3	136.7 ± 36.6	0.03
TG/HDL ratio	4.7 ± 5.0	4.1 ± 2.6	3.6 ± 2.0	0.02
IGFBP-1 (ng/mL)	32.2 ± 24.4	33.0 ± 25.6	34.8 ± 27.9	0.47
IGFBP-3 (ng/mL)	3156.6 ± 1097.1	3512.0 ± 1207.1	4526.6 ± 1349.8	0.01

Abbreviations: LDL, low-density lipoprotein; TG/HDL, triglyceride/HDL; BMI, body mass index.
*P values were calculated with regression models for continuous variables and χ.
†History of colorectal cancer in one or more first-degree relatives.
‡History of polyps before baseline.
§Aspirin use in the last month at baseline.
‖Self-reported diagnosis of diabetes; data missing for 12 subjects.

Table 2. Baseline adenoma characteristics by tertile of baseline IGF-I levels

Adenoma characteristics	Tertile of baseline IGF-I (mean, ng/mL)			
	1 (68.0 ± 22.8)	2 (116.4 ± 12.2)	3 (176.3 ± 35.5)	*P* value
Large adenoma*	36 (36.4)	40 (40.8)	45 (45.5)	0.43
Villous histology†	16 (16.2)	19 (19.4)	30 (30.3)	0.04
Number of adenomas	1.8 ± 1.1	2.0 ± 2.3	2.0 ± 1.4	0.27
Proximal location only	32 (32.3)	26 (26.5)	22 (22.2)	0.28
Advanced lesion‡	38 (38.4)	43 (43.9)	52 (52.5)	0.13

*Adenoma is >1 cm in size.
†Adenoma is either tubulovillous or villous.
‡Adenoma either tubulovillous or villous and/or >1 cm in size.

associations were shown for IGFBP-1, IGFBP-3, or IGF-I/IGFBP-3.

Our cross-sectional findings of a significantly greater proportion of adenomas with villous histology among participants in the highest tertile of IGF-I compared with lower tertiles are similar to what has been reported in several published studies, indicating that IGF-I levels might be associated with the presence of more advanced colorectal neoplasia (18, 21, 22). In contrast, we detected an ~50% lower odds of adenoma recurrence among men in the highest tertile of baseline IGF-I levels compared with those in the lowest tertile. To our knowledge, only one other small study has investigated the association between IGF-I, IGFBPs, and risk for colorectal adenoma recurrence (23). In that study of 66 acromegalic patients, no differences in baseline serum IGF-I were reported for those with and without an adenoma recurrence. Those results and the results of the current work are in opposition to the general mechanism of action proposed for IGF-I in the colon.

IGF-I has been established as having proliferative, antiapoptotic effects on colorectal lesions (1-3), and bioavailability of free IGF-I has been suggested as a potential mediator of the direct association between body size and risk for colorectal neoplasia (31). Our results do not support this hypothesis. In the current study, IGF-I/IGFBP-3 was used as a surrogate of bioavailable IGF-I (10), and a nonsignificant inverse trend was observed for adenoma recurrence, whereas for total measured IGF-I, a statistically significant inverse association was shown, particularly for adenomas with advanced features. Additionally, in this and other work, total IGF-I levels were similar among normal weight and overweight men, with a decrease among those with the highest body mass index (32-35), indicating that IGF-I may not be a mediator of the association between obesity and colorectal neoplasia. These data are consistent with the recognized suppression of the somatotropic axis in persons with metabolic syndrome (36), suggesting that the associated metabolic disturbances and inflammation may act as important determinants of adenoma development in polyp formers. Larger studies using more direct biochemical measures of inflammation and metabolic status, such as free IGF-I, C peptide, and adiponectin, may shed light on direct effects of IGF-I or indirect physiologic consequences of growth hormone deficiency, which is more common in the aging and obese population than high exposures to IGF-I.

Table 3. Crude and adjusted ORs (95% CIs) for baseline tertiles of plasma IGF biomarkers and colorectal adenoma recurrence

Biomarker	Recur/total	Crude OR (95% CI)	Adjusted* OR (95% CI)
IGF-I (mean, ng/mL)			
68.0 ± 22.8	62/100	1.00	1.00
116.4 ± 12.2	51/99	0.65 (0.37-1.14)	0.55 (0.29-1.01)
176.3 ± 35.5	45/99	0.51 (0.29-0.90)	0.49 (0.26-0.91)
P_{trend}		0.02	0.02
IGFBP-1 (mean, ng/mL)			
9.6 ± 3.9	49/100	1.00	1.00
27.0 ± 6.1	57/99	1.41 (0.81-2.47)	1.40 (0.75-2.65)
63.6 ± 21.0	53/99	1.20 (0.69-2.09)	0.82 (0.42-1.61)
P_{trend}		0.52	0.58
IGFBP-3 (mean, ng/mL)			
2,381.9 ± 544.0	55/100	1.00	1.00
3,622.6 ± 283.0	56/100	1.04 (0.60-1.82)	1.12 (0.59-2.12)
5,198.2 ± 1,047.2	48/99	0.77 (0.44-1.34)	1.17 (0.59-2.31)
P_{trend}		0.36	0.65
IGF-I/IGFBP-3			
0.07 ± 0.02	58/100	1.00	1.00
0.12 ± 0.01	52/99	0.80 (0.46-1.40)	0.71 (0.38-1.30)
0.19 ± 0.05	48/99	0.68 (0.39-1.19)	0.58 (0.31-1.08)
P_{trend}		0.18	0.08

*Models adjusted for age, calcium intake, previous polyp, number of adenomas at baseline, number of colonoscopies, and baseline IGF-I levels (except for IGF-I and IGF-I/IGFBP-3 ratio).

Table 4. Adjusted ORs (95% CIs) for baseline tertiles of plasma IGF biomarkers and nonadvanced and advanced colorectal adenoma recurrence

Biomarker	*n*	Nonadvanced recurrence	Adjusted* OR (95% CI)	Advanced recurrence	Adjusted* OR (95% CI)
IGF-I (mean, ng/mL)					
68.0 ± 22.8	100	36	1.00	23	1.00
116.4 ± 12.2	99	31	0.58 (0.29-1.14)	17	0.44 (0.19-1.02)
176.3 ± 35.5	99	32	0.56 (0.29-1.10)	12	0.34 (0.14-0.83)
P_{trend}			0.10		0.02
IGFBP-1 (mean, ng/mL)					
9.6 ± 3.9	100	31	1.00	15	1.00
27.0 ± 6.1	99	33	1.27 (0.64-2.54)	21	1.40 (0.56-3.47)
63.6 ± 21.0	99	35	0.93 (0.45-1.92)	17	0.49 (0.18-1.35)
P_{trend}			0.85		0.16
IGFBP-3 (mean, ng/mL)					
2381.9 ± 544.0	100	32	1.00	21	1.00
3622.6 ± 283.0	100	37	1.29 (0.64-2.60)	18	1.05 (0.43-2.54)
5198.2 ± 1047.2	99	30	1.19 (0.56-2.53)	14	1.30 (0.50-3.43)
P_{trend}			0.66		0.63
IGF-I/IGFBP-3 (mean, ng/mL)					
0.07 ± 0.02	100	35	1.00	20	1.00
0.12 ± 0.01	99	31	0.70 (0.36-1.38)	18	0.69 (0.30-1.62)
0.19 ± 0.05	99	33	0.66 (0.34-1.29)	14	0.43 (0.17-1.06)
P_{trend}			0.23		0.07

*Models adjusted for age, calcium intake, previous polyp, number of adenomas at baseline, number of colonoscopies, and baseline IGF-I levels (except for IGF-I and IGF-I/IGFBP-3 ratio).

Although speculative at this time, a potential alternative hypothesis to describe the apparent protective action of IGF-I in the postpolypectomy setting is an analogy to the role of transforming growth factor-β, which acts as a potent growth inhibitor in normal epithelium but has growth stimulatory activity in the presence of tumor-associated defects in transforming growth factor-β signaling (37). Work conducted by Ewton et al. in colon carcinoma cell lines supports a similar duality of function for IGF-I, where exposure is associated with a brief phase of proliferation, followed by induction of differentiation of intestinal epithelial cells, with concomitant growth arrest mediated via IGF-I induction of $p27^{kip1}$ (38). These data, along with previous work showing IGF-I as a strong differentiating factor in HT29-D4 colon carcinoma cells (39), suggest potential duality of function for IGF-I in the colon. Additionally, our results indicate that, in our study population, individuals with higher IGF-I levels may be a somewhat healthier group than those with lower concentrations. For example, participants in the highest tertile were slightly younger, had a lower body mass index, were less likely to have had a polyp before qualifying colonoscopy, were less likely to have diabetes, consumed more calcium, had lower glucose and triglyceride levels, and had a lower triglyceride/HDL ratio than those in the lowest tertile. Thus, perhaps, a cluster of healthier characteristics may have contributed to reduced risk for colorectal adenoma among those in the highest tertile of IGF-I levels.

The limitations of this study include the absence of a polyp-free control group. Much of the literature for IGF-I and colorectal lesions compares those with polyps to those without, but we were unable to make such comparisons. Nonetheless, the difference in our study design may in part explain some of the differences found in the current work compared with previous studies. Lesions detected in prior studies may have been present for a longer time period than the recurrent lesions found after a few years of follow-up in the current study. Therefore, IGF-I might have differential effects in short-term versus long-term development of colorectal neoplasia, although this is speculative. Another consideration is that the measured IGF-I levels in the current work are lower than those reported in some of the published literature. For example, among men in the Physician's Health Study, the mean IGF-I levels among colorectal cancer cases and controls were 198.7 and 186.8 ng/mL, respectively (10), whereas for the current work, the means were 128.8 and 112.4 ng/mL, respectively, for nonrecurrences and recurrences. Our highest tertile for IGF-I levels roughly corresponds with the middle quintile of the Physician's Health Study (10), the latter of which showed a modest increased risk for colorectal cancer of 1.30. Conversely, our measured IGF-I concentrations are quite similar to those of Schoen et al. from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, who reported levels of 117.1 ng/mL for controls, 126.3 ng/mL for the presence of nonadvanced adenomas, and 132.3 ng/mL for the presence of advanced adenomas (18). Therefore, an increased risk for colorectal neoplasia has been reported at the IGF-I concentrations shown in the current work, and it does not seem that our relatively lower levels explain the differences between our study and others. Another issue for the current study was a potential effect of the fiber intervention of the parent study. We analyzed the association between IGF-I levels and colorectal adenoma recurrence within each treatment group, and we did not detect differences in effect between the treatment groups. Furthermore, we created an interaction term between treatment group and IGF-I, which had no material effect on the models. Therefore, we do not believe that the fiber intervention had an effect on the results. The strengths of the study include the measured levels of several members of the IGF-I family and the availability of dietary data and biomarkers for evaluation of the association with circulating IGF-I levels.

In summary, the current study confirmed previous results demonstrating that circulating IGF-I is positively associated with higher-risk lesions when analyzed cross-sectionally. However, we found an inverse relation between IGF-I and odds of colorectal adenoma recurrence, which was unexpected. These results do not support IGF-I as a mediator of body size and risk for colorectal neoplasia. As discussed above, potential explanations for these findings include that IGF-I may have dual effects on the colon analogous to the action of transforming growth factor-β or that higher IGF-I levels may reflect an overall healthier metabolic state. Additional studies with more comprehensive measures of metabolic status and with larger sample sizes would help clarify these observations and perhaps identify modifiable risk factors for adenoma recurrence.

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