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

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Background: **Insulin-like growth factor-I (IGF-I) is a potent mitogen for normal and neoplastic cells, whereas IGF-binding protein-3 (IGFBP-3) inhibits cell growth in many experimental systems. Acromegalics, who have abnormally high levels of growth hormone and IGF-I, have higher rates of colorectal cancer. We therefore examined associations of plasma levels of IGF-I and IGFBP-3 with the risk of colorectal cancer in a prospective case–control study nested in the Physicians' Health Study. *Methods:* Plasma samples were collected at baseline from 14 916 men without diagnosed cancer. IGF-I, IGF-II, and IGFBP-3 were assayed among 193 men later diagnosed with colorectal cancer during 14 years of follow-up and among 318 age- and smoking-matched control subjects. All *P* values are two-sided. *Results:* IGFBP-3 levels correlated with IGF-I levels ($r = .64$) and with IGF-II levels ($r = .90$). After controlling for IGFBP-3, age, smoking, body mass index (weight in kg/[height in m]^2), and alcohol intake, men in the highest quintile for IGF-I had an increased risk of colorectal cancer compared with men in the lowest quintile (relative risk [RR] = 2.51; 95% confidence interval [CI] = 1.15–5.46; *P* for trend = .02). After controlling for IGF-I and other covariates, men with higher IGFBP-3 had a lower risk (RR = 0.28; 95% CI = 0.12–0.66; *P* for trend = .005, comparing extreme quintiles). The associations were consistent during the first and the second 7-year follow-up intervals and among younger and older men. IGF-II was not associated with risk. *Conclusions:* Our findings suggest that circulating IGF-I and IGFBP-3 are related to future risk of colorectal cancer.**

Insulin-like growth factors (IGFs)-I and -II are mitogenic in normal and neoplastic cells and act by binding to cell-surface IGF receptors *(1–5).* Several studies suggest that IGF-I and IGF-II are important in the pathophysiology of colorectal carcinoma. IGF receptors are found in human colon cancers *(5),* and full-length messenger RNAs for IGFs have been detected in human tumor cells *(6–8).* Exogenous IGF-I and -II stimulate proliferation of human colorectal cancer cells *(9,10),* whereas blockade of the IGF-I receptor inhibits tumor cell growth *(11).* Individuals with acromegaly, a disease of somatic growth caused by increased growth hormone and IGF-I, have an increased incidence of colonic cancer *(12–14).*

IGF-binding protein-3 (IGFBP-3) binds more than 95% of the IGF in serum and influences cell proliferation by modulating access of IGFs to the IGF receptors *(15–17).* IGFBP-3 also apparently inhibits growth and induces apoptosis through IGF-independent mechanisms *(18,19).* Most circulating IGF-I and IGFBP-3 are synthesized in the liver, where expression of each is increased by growth hormone. There is considerable between-person variability in blood levels of IGF-I, IGF-II, and IGFBP-3 *(1,20).* Tissue IGF bioactivity is influenced by circulating IGF levels and by local expression of IGFs, IGFBPs, and IGFBP proteases *(21).* Some factors that regulate determinants of local IGF bioactivity may regulate circulating IGF-I levels in a parallel fashion *(22,23).* Although colonic tumors secrete IGF-II, which may stimulate neoplastic growth *(6,7,24,25),* the role of circulating IGF-II is poorly understood *(15).*

We previously reported a strong positive association between baseline plasma IGF-I levels and subsequent risk of prostate cancer *(26)* or premenopausal breast cancer *(27).* We therefore hypothesized that men with high plasma levels of IGF-I would have increased risk of colorectal cancer, men with high levels of IGFBP-3 would have lower risk, and men with high IGF-I and low IGFBP-3 would have the highest risk.

Subjects and Methods

Subjects

This is a prospective case–control study nested in the Physicians' Health Study, a randomized, double-blind, placebo-controlled trial of aspirin and β-carotene among 22 071 healthy U.S. male physicians, 40–84 years of age in 1982 *(28).* Men were excluded at baseline if they had a history of myocardial infarction, stroke, transient ischemic attack, cancer (except nonmelanoma skin cancer), current renal or liver disease, peptic ulcer, gout, or current use of a vitamin A or β-carotene supplement. Study participants completed two mailed questionnaires before being randomly assigned, additional questionnaires at 6 and 12 months, and questionnaires annually thereafter. Before participants were randomly assigned, we sent kits to all participants with instructions to have their blood drawn into vacutainer tubes containing EDTA. The participants fractionated the blood by centrifugation and returned the samples (by overnight courier) in plastic cryopreservation vials. Each kit included a cold pack to keep specimens cool until receipt at our laboratory the following morning. At this time, specimens were divided into aliquots and stored at −82 °C. During storage, precautions were taken so that no specimens thawed or warmed substantially. We received specimens from 14 916 (68%) of the randomly assigned physicians.

When participants reported a diagnosis of cancer, we requested medical records (including pathology reports); these records were reviewed by physicians of the Study End Points Committee. By December 1995, we had confirmed 193 diagnoses of colorectal cancer among those who provided adequate baseline plasma samples. For each case subject, we attempted to select two control subjects who had provided blood and had not reported a diagnosis of colorectal cancer at the time the diagnosis was reported by the case subject. Control subjects were matched for age (±1 year) and smoking status (never, past, or current). We, however, could identify a second control subject for only 125 case subjects, and so in total 318 men formed the control group.

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See "Notes" following "References."

Assays of IGF-I, IGF-II, and IGFBP-3

Plasma levels of IGF-I, IGF-II, and IGFBP-3 were assayed in the laboratory of M. N. Pollak at the Lady Davis Research Institute of the Jewish General Hospital and McGill University. Samples from case subjects and their matched control subjects were assayed in the same batch to minimize interassay variability, and aliquots from a pool of quality control plasma were inserted randomly. Laboratory personnel were unable to distinguish among case, control, and quality control samples. Plasma levels of IGF-I, IGF-II, and IGFBP-3 were assayed by enzyme-linked immunosorbent assay with reagents from Diagnostic Systems Laboratory (Webster, TX). The mean intra-assay coefficients of variation for IGF-I, IGF-II, and IGFBP-3 from the blinded quality control samples were 2.9%, 1.7%, and 3.2%, respectively.

Statistical Analyses

We compared baseline characteristics between case subjects and control subjects by paired *t* tests and χ^2 tests. We used analysis of covariance (ANACOVA) to compare the age- and IGF-I-adjusted levels of IGFBP-3 and age- and IGFBP-3-adjusted levels of IGF-I or IGF-II between case subjects and control subjects. Conditional logistic regression was used to estimate the age- and smoking-matched relative risks (RRs) and 95% confidence intervals (CIs) for the association of IGFs and IGFBP-3 with risk of developing colorectal cancer. All models presented in the paper were also adjusted for body mass index (BMI, weight in kg/[height in m]^2) and alcohol intake. Physical activity, multivitamin use, and aspirin use were not included in the models because they are not associated with IGF and IGFBP-3 levels or with cancer risk in these participants. Because IGFBP-3 levels were correlated with IGF-I ($r = .64$) and IGF-II ($r = .90$) and may have opposite effects on risk, it was necessary to simultaneously adjust for these factors in the models to assess their independent effects. We also assessed the molar ratios of IGF-I to IGFBP-3, IGF-II to IGFBP-3, and (IGF-I + IGF-II) to IGFBP-3 (for conversion, 1 ng/mL is 0.130 n*M* for IGF-I, 0.134 n*M* for IGF-II, and 0.036 n*M* for IGFBP-3). We used IGF-I, IGF-II, and IGFBP-3 as continuous variables in conditional logistic regression models to test for trend and to estimate the RRs associated with incremental change of IGF-I and IGFBP-3. We further stratified the multivariate-adjusted models by median age (<60 or ⩾60 years), follow-up interval (1–7 or 8–14 years), and tumor site (colon or rectum). We also assessed the adjusted RRs for the joint effect of IGF-I and IGFBP-3 (categorized into tertiles based on the distribution among control subjects) by using the lowest tertiles of both factors as the reference group. All *P* values are two-sided, and all the analyses used the SAS program package *(29)*.

Table 1. Baseline characteristics in a prospective study of colorectal cancer among men

Characteristic	Subjects		*P**
	Case (n = 193)	Control (n = 318)	
Mean age, y	59	59	—
Mean height, m	1.78	1.77	.23
Mean weight, kg	80.5	78.2	.01
Mean body mass index†	25.3	24.8	.06
Cigarette smoking			
Never, %	37	39	
Past, %	55	53	
Current, %	8	8	—
Aspirin use, % who use aspirin	51	53	.64
Alcohol intake			
<1 drink/wk, %	29	35	
1–6 drinks/wk, %	39	34	
7 to ⩾14 drinks/wk, %	32	31	.28
Exercise			
<1 time/wk, %	25	27	
1–4 times/wk, %	58	58	
⩾5 times/wk, %	17	15	.80
Multivitamin use			
Never, %	62	64	
Past, %	16	14	
Current, %	22	22	.76

*All *P* values are two-sided.
†Body mass index = weight in kg/(height in m)^2.

Results

Baseline characteristics are shown in Table 1. Case subjects were heavier and tended to have a higher BMI than control subjects, but no statistically significant difference was observed for other possible risk factors. Levels of IGF-I, IGF-II, and IGFBP-3 were normally distributed, with a wide range for case subjects and control subjects; among control subjects, the 5th and 95th percentiles were 111 and 292 ng/mL, respectively, for IGF-I and 2023 and 4148 ng/mL, respectively, for IGFBP-3. Among control subjects, IGF-I was positively correlated with IGF-II (Pearson correlation coefficient [*r*] = .50) and IGFBP-3 ($r = .64$) and inversely correlated with age ($r = -.30$) and alcohol intake ($r = -.17$). IGFBP-3 was inversely correlated with age ($r = -.35$) and highly correlated with IGF-II ($r = .90$). IGF-II was also inversely correlated with age ($r = -.23$). Besides age and alcohol intake, other variables listed in Table 1 were not correlated with IGF-I, IGF-II, and IGFBP-3.

Mean plasma levels of IGF-I, IGF-II, and IGFBP-3 were similar among case subjects and control subjects. However, when IGF-I levels were assessed relative to IGFBP-3 levels, controlling for age, case subjects consistently had higher levels of IGF-I than control subjects at each level of IGFBP-3 (Fig. 1). After controlling for age and IGFBP-3, the mean level of IGF-I was higher among case subjects (198.7 ng/mL) than among control subjects (186.8 ng/mL) ($P = .02$). Conversely, the mean level of IGFBP-3 was lower among case subjects (2959 ng/mL) than among control subjects (3066 ng/mL) ($P = .02$), controlling for age and IGF-I. This result suggests that the opposite effects of IGF-I and IGFBP-3 on cancer risk were masked by each other, perhaps because most of the circulating IGF is carried by IGFBP-3 as an IGF–IGFBP-3 complex. There was no statistically significant case–control difference in age- and IGFBP-3-controlled IGF-II levels (case subjects, 623 ng/mL; control subjects, 622 ng/mL; $P = .82$). The molar ratio between IGF-I and IGFBP-3 may reflect free biologically active IGF-I *(30)*. We observed a small but statistically significant difference in the molar ratio of IGF-I to IGFBP-3 after controlling for age (mean for case subjects = 0.23 versus mean for control subjects = 0.22; $P = .03$). No statistically significant differences were observed for molar ratios of IGF-II to IGFBP-3 and (IGF-I + IGF-II) to IGFBP-3.

Table 2, A, shows associations of IGF-I and IGFBP-3 with risk of colorectal cancer after adjustment for age, cigarette smoking, BMI, and alcohol intake. Similar but slightly weaker associations were observed in models controlling only for age and smoking status. In separate models including only IGF-I or IGFBP-3, IGF-I was positively but not statistically significantly associated with risk of colorectal cancer, with no obvious trend. Similarly, only men in the highest quintile of

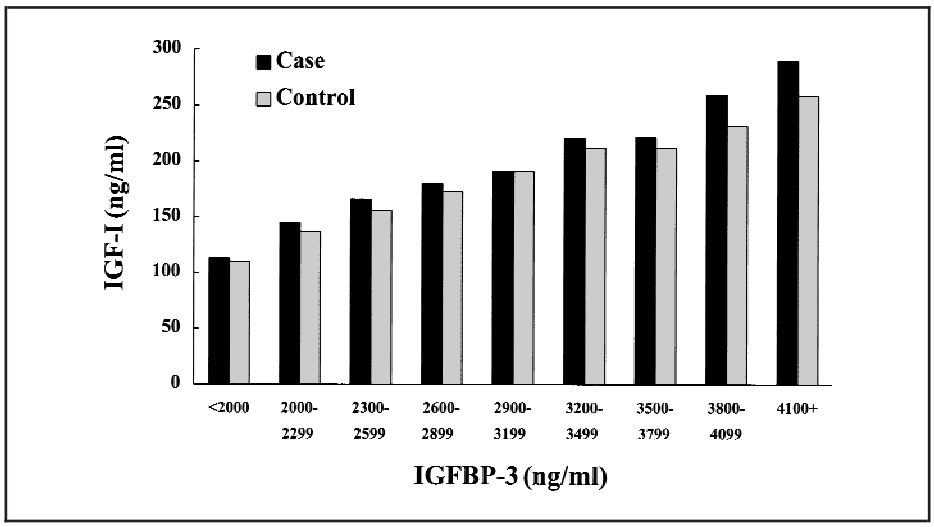

Fig. 1. Plasma levels of insulin-like growth factor-I (IGF-I) versus insulin-like growth factor-binding protein-3 (IGFBP-3), controlling for age, in a prospective study of colorectal cancer among men. After controlling for age and IGFBP-3, the mean level of IGF-I was higher among case subjects (198.7 ng/mL) than among control subjects (186.8 ng/mL) (two-sided $P = .02$ [analysis of covariance]).

IGFBP-3 had a statistically significantly lower risk (by 53%) than men in the lowest quintile. When IGF-I and IGFBP-3 were mutually adjusted in the same model to evaluate their independent effects, we found that IGF-I was positively and IGFBP-3 was inversely associated with risk of colorectal cancer, with statistically significant linear trends. An increase in IGF-I level of 100 ng/mL corresponded to a 69% increase in risk (RR = 1.69 per 100 ng/mL; 95% CI = 1.07–2.67). An increase in IGFBP-3 level of 1000 ng/mL corresponded to a 46% decrease in risk (RR = 0.54 per 1000 ng/mL; 95% CI = 0.34–0.84). Men with higher molar ratio of IGF-I to IGFBP-3 also had higher risk. The RRs for the highest four quintiles of the molar ratio compared with the lowest quintile were 0.93, 1.49, 1.38, and 1.67 (P for trend = .02). Plasma IGF-II levels, with or without adjustment for IGFBP-3, were not associated with risk.

To assess the possibility of an effect of preclinical disease on IGF levels, we stratified the analysis according to the follow-up interval, years 1–7 versus years 8–14 (Table 2, B). We found similar results in both periods. Indeed, the dose–response associations of IGF-I and IGFBP-3 with cancer risk were more apparent among case subjects diagnosed after 7 years of follow-up. Analyses of the associations among colon cancer and rectal cancer separately revealed no statistically significant differences. For colon cancer, the RR for the fifth versus the first quintile of IGF-I was 2.06 (95% CI = 0.85–5.00); for IGFBP-3, the RR was 0.39 (95% CI = 0.16–0.97). Because of

Table 2. Relative risk (RR) of colorectal cancer

A. RR of colorectal cancer according to quintiles of plasma levels of insulin-like growth factor-I (IGF-I) and insulin-like growth factor-binding protein-3 (IGFBP-3) in a prospective study of men

	Quintile						
	1 (referent)	2	3	4	5	Quintile 5, 95% CI*	P for trend†
IGF-I							
Mean, ng/mL (range)	115 (62–135)	156 (136–171)	183 (171–195)	212 (195–230)	273 (230–370)		
No. of case subjects	33	50	36	40	34		
No. of control subjects	63	64	64	64	63		
RR‡	1.00	1.68	1.30	1.51	1.36	0.72–2.55	.51
IGFBP-3							
Mean, ng/mL (range)	2161 (1398–2473)	2660 (2499–2809)	2996 (2817–3164)	3395 (3179–3596)	3984 (3598–5062)		
No. of case subjects	44	49	41	41	18		
No. of control subjects	63	64	64	64	63		
RR‡	1.00	1.26	1.03	1.04	0.47	0.23–0.95	.07
IGF-I and IGFBP-3							
RR for IGF-I§	1.00	1.89	1.66	2.14	2.51	1.15–5.46	.02
RR for IGFBP-3§	1.00	1.08	0.77	0.69	0.28	0.12–0.66	.005

B. RR§ of colorectal cancer according to quintiles (as in A) of IGF-I and IGFBP-3 stratified by follow-up years in a prospective study of men

	Quintile						
Follow-up	1 (referent)	2	3	4	5	Quintile 5, 95% CI*	P for trend†
≤7 y (88 case subjects)							
IGF-I	1.00	2.15	2.01	2.44	1.96	0.59–6.46	.16
IGFBP-3	1.00	0.64	0.89	0.82	0.26	0.07–0.99	.11
>7 y (105 case subjects)							
IGF-I	1.00	1.63	1.36	1.81	2.71	0.93–7.94	.06
IGFBP-3	1.00	1.58	0.74	0.61	0.31	0.10–0.98	.02

*95% CI = 95% confidence interval.

†All P values are two-sided.

‡Adjusted for age, cigarette smoking, body mass index (weight in kg/[height in m]^2), and alcohol intake.

§Adjusted for age, cigarette smoking, body mass index, alcohol intake, and IGF-I or IGFBP-3.

the small number of case subjects, we analyzed rectal cancer by tertiles: the RR for the highest versus the lowest tertile was 2.33 for IGF-I (95% CI = 0.47–11.44) and 0.11 for IGFBP-3 (95% CI = 0.02–0.78).

Men under the age of 60 years had statistically significantly higher levels of IGF-I and IGFBP-3 than older men. In the control group, younger men had higher levels of IGF-I than older men (196 ± 53 ng/mL [mean ± standard deviation] versus 171 ± 59 ng/mL [$P<.001$]), and younger men had higher levels of IGFBP-3 than older men (3173 ± 627 ng/mL [mean ± standard deviation] versus 2768 ± 624 ng/mL [$P<.0001$]). However, the positive association between IGF-I and risk was similar among men in both age groups. An increase in IGF-I of 100 ng/mL corresponded to an 82%–92% increase in risk (for younger men, RR = 1.92 per 100 ng/mL [95% CI = 1.02–3.62]; for older men, RR = 1.82 per 100 ng/mL [95% CI = 0.91–3.67]). The inverse association between IGFBP-3 and risk was also similar in the two age groups. An increase in IGFBP-3 of 1000 ng/mL corresponded to a 49%–51% decrease in risk (for younger men, RR = 0.51 per 1000 ng/mL [95% CI = 0.27–0.94]; for older men, RR = 0.49 per 1000 ng/mL [95% CI = 0.24–1.00]). Among participants in the overall Physicians' Health Study or in this nested case–control study, treatment with aspirin or β-carotene had no effect on the incidence of colorectal cancer *(28,31)*. The apparent association between IGF-I and IGFBP-3 and colorectal cancer was similar in different treatment groups.

Assessment of the combined effect of IGF-I and IGFBP-3 in association with colorectal cancer risk showed a fourfold increase in risk among men in the highest tertile of IGF-I and lowest tertile of IGFBP-3 compared with men in the lowest tertiles of both IGF-I and IGFBP-3 (Table 3). Elevated IGF-I levels were associated with increased risk only when IGFBP-3 levels were low, which suggests a possible interaction ($P_{\text{interaction}} = .09$).

Table 3. Relative risk (RR)* of colorectal cancer according to tertiles of insulin-like growth factor-I (IGF-I) and insulin-like growth factor-binding protein-3 (IGFBP-3) in a prospective study of men

	IGFBP-3		
IGF-I	Tertile 1	Tertile 2	Tertile 3
Tertile 1			
RR	1.00	2.24	0.87
95% CI†	(referent)	(1.10–4.56)	(0.21–3.57)
No. of case subjects/No. of control subjects	43/72	28/25	4/9
Tertile 2			
RR	1.54	1.30	0.50
95% CI†	(0.78–3.07)	(0.67–2.53)	(0.21–1.19)
No. of case subjects/No. of control subjects	21/30	27/44	9/32
Tertile 3			
RR	4.15	1.61	0.94
95% CI†	(1.13–15.19)	(0.81–3.17)	(0.49–1.80)
No. of case subjects/No. of control subjects	8/4	25/37	28/65

*Adjusted for age, cigarette smoking, body mass index (weight in kg/[height in m]^2), and alcohol intake.
†95% CI = 95% confidence interval.

Discussion

Our prospective data support the hypothesis that high prediagnostic IGF-I and low IGFBP-3 levels are independently associated with increased risk of colorectal cancer. Men with high levels of IGF-I and low levels of IGFBP-3 had the highest risk. Our findings suggest that circulating IGF-I and IGFBP-3 levels have stronger associations with colorectal cancer than most factors yet described. Although familial colon cancer syndromes are associated with higher risk of colorectal neoplasia, they are relevant to only a relatively small number of individuals. The relatively large study size, prospective design, unbiased selection of control subjects, high follow-up rate, and collection of blood samples before diagnosis are major strengths of this investigation. Furthermore, the consistency of associations throughout the duration of the follow-up indicates that they are likely to precede rather than be a consequence of the cancer. We also carefully controlled for age, a strong confounding factor, in assessing the association of IGF-I and IGFBP-3 with colorectal cancer risk. Our results among men are strikingly consistent with findings in women in the Nurses' Health Study (Giovannucci E, Pollak MN, Platz EA, Willett WC, Stampfer MJ, Majeed N, et al.: unpublished results).

We had only a single baseline plasma sample to characterize long-term levels of circulating IGF-I and IGFBP-3. Circulating IGF-I, IGF-II, and IGFBP-3 are mainly synthesized by the liver and are secreted as soon as they are synthesized *(2,20)*. The half-life for circulating IGFs carried by IGFBPs (mainly by IGFBP-3) is between 12 and 15 hours, but it is only 10 and 12 minutes for the free peptides *(32)*. However, plasma levels of IGF-I and IGFBP-3 determined by the enzyme-linked immunosorbent assay are generally reliable and not affected by the methods of blood sample collection *(26)*. Single measures of IGF-I and IGFBP-3 have shown reasonable correlation with numerous physiologic parameters (age, sex, adolescent rate of growth [height], and age at puberty), thus supporting the usefulness of the measure *(30,33,34)*. We observed a correlation of .65 for repeated measurements of IGF-I over an 8-week period *(26)*, a correlation similar to that of the measurements of blood pressure and plasma cholesterol. Since any misclassification of true circulating levels is likely to be independent of disease status, our results may underestimate the true associations of long-term IGF-I and IGFBP-3 levels with colorectal cancer risk.

Our results are biologically plausible. Individuals with high IGF bioactivity may have an increased proliferation rate of normal or partially transformed epithelial cells, which may favor the accumulation of the molecular alterations that occur in colorectal carcinogenesis *(35,36)*. At later stages of colorectal carcinogenesis, IGF physiology also may be important, because IGFs are potent stimulators of proliferation of cultured colorectal carcinoma cells and blockade of the IGF-I receptor inhibits growth of human colorectal cancer cells *(9,11)*. In advanced colorectal cancer, local production of IGF-II is common *(7)* and may render systemic sources of IGF-I irrelevant. IGF-I may also induce the expression of vascular endothelial growth factor, which can promote the progression of cancer by regulating the development of new blood vessels *(37)*.

IGFBP-3 was originally considered, mainly in its role as a binding protein, to protect circulating IGFs and deliver them to specific target tissues. At the tissue level, IGFBP-3 may regulate the interaction of IGF-I with its receptor by inhibit-

ing or augmenting the interaction *(20)*. Recently, IGFBP-3 was also identified as an apoptosis-inducing agent, acting at least in part through IGF-independent pathways. *In vitro*, IGF-I can partially prevent this effect by binding to IGFBP-3 *(18,38)*.

Patients with acromegaly have increased colonic epithelial cell proliferation *(39)* and are at increased risk of colorectal cancer *(12–14)*. In this condition, serum levels of both IGF-I and IGFBP-3 were elevated in men, but the increase in molar ratio of IGF-I to IGFBP-3 is not as dramatic as the very high absolute IGF-I levels relative to nonacromegalics *(40)*. The concomitant increase in IGFBP-3 and IGF-I may explain why acromegalics have a modest rather than an extreme increase in risk of colorectal cancer.

One small case–control study that did not measure IGFBP-3 found no statistically significant difference in serum IGF-I levels between 29 case subjects with colorectal cancer and 159 tumor-free control subjects *(41)*. However, since the growth hormone/IGF-I axis can be perturbed in patients with cancer, IGF-I and IGFBP-3 levels in patients with advanced cancer may not reflect values early in carcinogenesis. Prediagnostic IGF-II levels were not statistically significantly associated with subsequent risk in our study. In another small case–control study (with 23 case subjects), circulating levels of IGF-I were not associated with colorectal cancer, but elevated levels of IGF-II and IGFBP-2 and -3 were observed in case subjects *(42)*. Colorectal tumor cells frequently overexpress IGF-II *(6–8)*, and IGF-II and IGFBP-3 are highly correlated ($r = .90$ in our study). Thus, it is possible that, in advanced cancer, elevated levels of IGF-II originate from the tumor and result in a compensatory increase in circulating IGFBP-3.

Both IGF-I and IGFBP-3 decline with age after adolescence *(30,33,43)*. In one study *(43)*, 40% of healthy elderly adults (age 60–88 years) had IGF-I levels of less than 100 ng/mL. It has been suggested that this change and a decline in immune function may play an important role in aging-related tumorigenesis and that treatment with growth hormone or IGF-I might reverse the immune deficits in humans and primates *(43,44)*. In our study, only about 7% of the participants who were age 60 years and older had IGF-I levels that were less than 100 ng/mL. Our results showed that, although both IGF-I and IGFBP-3 levels decrease with age, IGF-I levels are higher among case subjects than among control subjects at each level of IGFBP-3, independent of age. The inverse association of IGFBP-3 with cancer risk is also independent of age and IGF-I. Furthermore, the associations of IGF-I and IGFBP-3 with risk were consistent among younger and older men. Since older men had statistically significantly lower levels of IGF-I than younger men, older men might be at even higher risk if their IGF-I levels were increased to levels equivalent to those at a younger age. This finding and a similar finding from our study of circulating IGF-I levels and risk of prostate cancer *(26)* raise concern that administration of growth hormone or IGF-I over long periods, as proposed for elderly men to delay the effects of aging *(44)*, may be associated with increased risk of neoplasia. Further work is needed to confirm these results, to better understand the determinants of circulating levels of IGF-I and IGFBP-3, to evaluate the feasibility of identifying individuals with high risk of colorectal cancer based on circulating IGF-I and IGFBP-3 levels, and to investigate potential lifestyle or pharmacologic approaches to decreasing IGF-I bioactivity in high-risk populations.

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NOTES

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