Associations between Plasma Insulin-Like Growth Factor Proteins and C-Peptide and Quality of Life in Patients with Metastatic Colorectal Cancer

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Abstract

Objective: **Predictors of quality of life (QOL) in patients with metastatic colorectal cancer are lacking. The insulin-like growth factor (IGF) family of proteins is associated with QOL in noncancer populations. We sought to study whether these proteins are associated with QOL in patients with colorectal cancer.**

Method: **We used a cohort of 526 patients with metastatic colorectal cancer treated with combination chemotherapy. Plasma samples of IGF-I, IGF-II, IGF binding protein-3, and C-peptide were collected before initiation of chemotherapy. QOL was measured by the uniscale instrument and the Symptom Distress Scale at baseline and throughout treatment.**

Results: **Baseline plasma levels of IGF-I and IGF-II before initiation of chemotherapy were significantly associated with several important baseline QOL measures in patients with metastatic colorectal cancer. Patients with lower levels of IGF-I reported increased distress with regard to appearance, appetite, cough, and nausea intensity after adjustment for potential confounders. Similarly, decreased levels of IGF-II were predictive of worse quality related to appearance, appetite, fatigue, nausea frequency and intensity, pain frequency, and composite Symptom Distress Scale score. IGF binding protein-3 and C-peptide were not predictive of baseline QOL. Baseline biomarkers were not associated with subsequent changes in QOL during treatment. Higher body mass index was significantly associated with superior baseline QOL in several areas; nonetheless, the association of IGF-I and IGF-II with baseline QOL measures remained significant even after controlling for baseline body mass index.**

Conclusion: **Baseline plasma IGF-I and IGF-II are significantly associated with symptom distress. Whether this association is simply reflective of patient nutritional status and/or disease burden or represents an independent biological effect of IGFs on QOL remains uncertain. Nonetheless, these data suggest that molecular biomarkers may be useful predictors of QOL in cancer patients.**

Introduction

Colorectal cancer is the fourth most common cancer in the United States and the second leading cause of cancer-related deaths (1). Forty percent of patients will develop metastatic disease during the course of their disease, which generally is incurable. In these patients, treatment should be aimed at prolonging survival while maintaining and improving quality of life (QOL; ref. 2). Although the ability to directly measure QOL has improved (3), few studies have identified predictors of quality among patients with metastatic cancer (4).

Hyperinsulenima and the insulin-like growth factor (IGF) pathway may play a role in the development and pathogenesis of colorectal cancer (5). Insulin is a promoter of colorectal neoplasia in animal models (6), and elevated circulating insulin and C-peptide levels (an indicator of insulin production) have been prospectively associated to colon cancer risk (7-9). The actions of insulin may in part be regulated through the IGF system (5). IGF-I and IGF-II regulate cell proliferation and differentiation and inhibit apoptosis. The availability of free IGF-I and IGF-II for interaction with their receptor (primarily IGF-I receptor) is modulated by the IGF binding proteins (IGFBP), especially IGFBP-3. IGFBPs can have opposing actions to IGF-I and IGF-II in part by preventing a ligand-receptor interaction (10) as well as through direct inhibitory and apoptotic effects on target cells (11). In prospective studies, relatively high plasma IGF-I (12-14) and IGF-II (15, 16) and low IGFBP-3 (16) levels were associated with greater risk of colorectal cancer.

An association between IGF proteins and QOL has been reported in several settings. In a study of 270 healthy patients, Unden et al. showed that IGF-I levels correlated with social well-being, mental well-being, depression, self-esteem, social support, self-rated health, and coping in a subgroup of middle-aged subjects (17). In a small randomized study of 33 obese postmenopausal women on a diet and exercise program, Thompson et al. found that women treated with IGF-I with or without growth hormone, but not growth hormone alone or placebo, had significant improvements in depression and anxiety scores (18). In contrast, Trojan et al. did not observe

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any associations between IGF-I levels and QOL measurements among 112 patients with post–polio syndrome (19). The mechanism of the potential influence of the IGF proteins on QOL is unclear, although the IGF/growth hormone axis has been correlated with improved organ functions, such as those of the brain (20) and heart (21, 22) as well as bone density (23), which may lead to enhanced physical and psychological well-being. To our knowledge, no such studies have examined the relationship between this important family of proteins and QOL in cancer patients.

A randomized treatment trial of patients with metastatic colorectal cancer was recently reported comparing irinotecan-based and oxaliplatin-based combination therapies (24). During the trial, we prospectively collected plasma samples and self-reported measurements of QOL. The effect of the different chemotherapies on QOL (25) and the relationship between baseline IGF protein levels and treatment efficacy (26) will be reported separately. In this report, we will focus on the association between pretreatment plasma levels of these biomarkers and baseline QOL as well as changes in quality over the course of therapy.

Materials and Methods

Patient Population. Patients included in this study were drawn from a national, intergroup randomized trial of chemotherapy for metastatic colorectal cancer [North Central Cancer Treatment Group (NCCTG) 9741; ref. 24]. Full details of the treatment trial have been published previously (24). Briefly, patients were required to have histologically proven unresectable colorectal adenocarcinoma; a baseline Eastern Cooperative Oncology Group performance status of ≤ 2; and adequate renal, liver, and bone marrow function. Exclusion criteria included prior therapy for advanced disease, baseline peripheral neuropathy or central nervous system disease, uncontrolled or severe comorbid illnesses, and baseline of more than three loose stools per day. Patients signed informed consent for participation in the trial and were given the option of inclusion in this companion study of plasma biomarkers. All patients were required to participate in the QOL portion of the study.

Plasma Biomarkers. Blood samples were collected on study registration at respective institutions and sent to the Mayo Central Laboratory for Clinical Trials (Rochester, MN). Whole-blood samples were cooled and sent by overnight delivery to the laboratory. The stability of these biomarkers during the period of transport has been documented previously (27). Samples were centrifuged, divided, and frozen before use. IGF-I, IGF-II, IGFBP-3, and C-peptide levels were assayed in the laboratory of Dr. Michael Pollak using ELISAs with reagents provided by Diagnostic Systems Laboratory (Webster, TX). This methodology is more reproducible than and highly correlated ($r = 0.98$) with a RIA technique employed previously (28). Each patient had repeated measurements of each of biomarkers, with intraindividual correlations ranging from 0.98 to 0.99. Blinded quality control samples are included in each batch so that the mean intrapair coefficients can be assessed. In previous studies, the mean intrabatch coefficients of variation calculated from the quality-control samples were 7%, 5%, 9%, and 10%, respectively, for IGF-I, IGF-II, IGFBP-3, and C-peptide (9, 13, 29, 30).

The IGF ratio was defined as the molar ratio of the sum of IGF-I and IGF-II divided by IGFBP-3. The ratio serves as a surrogate for free or potentially bioavailable IGF-I.

QOL Instruments. Patients participating in the treatment trial were requested to complete several instruments measuring various aspects of patient QOL (Figs. 1 and 2). Protocol specifications were to obtain baseline QOL and then follow-up assessments every 12 weeks and at study completion for both instruments. The uniscale single-item instrument is a linear analogue measure of overall QOL that has been used in numerous clinical settings (31). It is valid and practical for patients with advanced colorectal cancer in community-based clinical trial settings (32). To obtain further details in other domains, the McCorkle and Young Symptom Distress Scale (SDS) was used (33). The SDS scale was developed for cancer patients and has been proven reliable and valid as well as prognostic for survival, although it has not been specifically tested in a cohort of only colorectal cancer patients (34-37). The SDS consists of 13 symptoms measuring degrees of distress related to appearance, appetite, breathing, bowel habits, cough, concentration, insomnia, fatigue, nausea frequency, nausea intensity, outlook, pain frequency, and pain intensity. For each symptom, five answers are possible (with a higher numerical response indicating a worse quality for that symptom). Due to reduced numbers of patient responses, the fourth and fifth lowest answers were collapsed into a single category. Each of the items was analyzed as separate individual constructs as well as a summated psychometrically validated scale, normalized to a scale of 0 to 100, with 0 being the worst QOL and 100 being the best QOL.

Statistical Analysis. In total, 1,379 patients enrolled in NCCTG 9741 after the incorporation of an amendment to collect blood samples for companion biomarker studies. Of this cohort, 526 patients provided blood samples for these analyses; ~80% of these patients completed at least portions of one of the two QOL. Baseline responses from the QOL instruments and changes in symptoms were studied in relationship to plasma levels of IGF-I, IGF-II, IGFBP-3, and C-peptide. Only patients who completed the baseline QOL instruments before

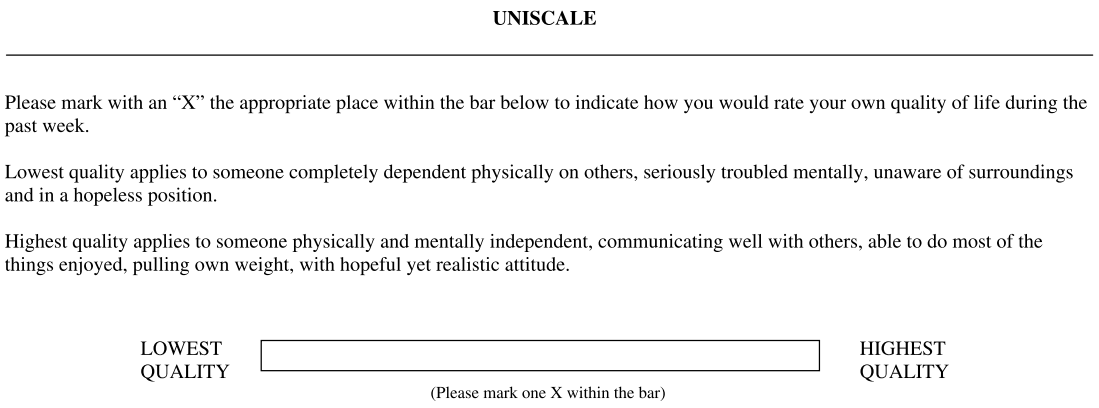

Figure 1. Uniscale instrument.

starting chemotherapy were included in the baseline analyses of the uniscale and SDS scores; patients with missing values at baseline were excluded from that particular symptom score. Changes in symptoms were reported as the maximum decline or improvement from the baseline measurement over the course of participation in the trial; only patients completing the baseline instruments and at least one additional QOL assessment for an individual construct were included in each analyses. Trends for significance were measured by linear regression, with the dependent and independent variables treated as continuous variables. To satisfy the normality assumption, C-peptide was log transformed when modeling. Additionally, we adjusted analyses for age, gender, baseline performance status, and body mass index (BMI). For studies on IGF-I and IGF-II, we adjusted for IGFBP-3 and vice versa. Multivariate models were tested for collinearity and did not meet Belsey-Kuh-Welch criteria for collinearity. Further, for changes in symptoms, we adjusted for treatment arm. All statistical analyses used the SAS program package version 8.02 (SAS Institute, Cary, NC). Ps < 0.05 were used to denote statistical significance; all Ps reported are two sided.

Results

Baseline Characteristics. We compared baseline characteristics of the overall cohort of patients who enrolled in the treatment trial with the subsets of patients participating in the

System Distress Scale Patient Form

Appearance				
My appearance has basically not changed	My appearance has gotten a little worse	My appearance is definitely worse than it used to be, but I am not greatly concerned about it	My appearance is definitely worse than it used to be, and I am concerned about it	My appearance has changed drastically from what it was
Appetite				
I have my normal appetite	My appetite is usually, but not always, good	I don't really enjoy my food like I used to	I have to force myself to eat my food	I cannot stand the thought of food
Bowel				
I have my normal bowel pattern	My bowel pattern occasionally causes me some discomfort	I frequently have discomfort from my present bowel pattern	I am usually in discomfort because of my present bowel pattern	My present bowel pattern has changed drastically from what was normal for me
Breathing				
I usually breathe normally	I occasionally have trouble breathing	I often have trouble breathing	I can hardly ever breathe as easily as I want	I almost always have severe trouble with my breathing
Concentration				
I have my normal ability to concentrate	I occasionally have trouble concentrating	I often have trouble concentrating	I usually have at least some difficulty concentrating	I just can't seem to concentrate at all
Cough				
I seldom cough	I have an occasional cough	I often cough	I often cough, and occasionally have severe coughing spells	I often have persistent and severe coughing spells
Fatigue				
I am usually not tired at all	I am occasionally rather tired	There are frequent periods when I am quite tired	I am usually very tired	Most of the time, I feel exhausted
Insomnia				
I sleep as well as I always have	I have occasional spells of sleeplessness	I frequently have trouble getting to sleep and staying asleep	I have difficulty sleeping almost every night	It is almost impossible for me to get a decent night's sleep
Nausea (1) *Frequency*				
I seldom feel any nausea at all	I am nauseous once in a while	I am often nauseous	I am usually nauseous	I suffer form nausea almost continually
Nausea (2) *Intensity*				
When I do have nausea, it is very mild	When I do have nausea, it is mildly distressing	When I have nausea, I feel pretty sick	When I have nausea, I feel very sick	When I have nausea, I am as sick as I could possibly be
Outlook				
I am not fearful or worried	I am a little worried about things	I am quite worried, but unafraid	I am worried and a little frightened about things	I am worried and scared about things
Pain (1) *Frequency*				
I almost never have pain	I have pain once in a while	I frequently have pain-several times a week	I am usually in some degree of pain	I am in some degree of pain almost constantly
Pain (2) *Intensity*				
When I do have pain, it is very mild	When I do have pain, it is mildly distressing	The pain I do have is usually fairly intense	The pain I have is usually very intense	The pain I have is almost unbearable

Figure 2. McCorkle and Young SDS (33).

Table 1. Baseline characteristics of subgroups of NCCTG 9741

	All patients (n = 1,379)	Patients with blood samples for biomarker studies (n = 526)	Patients with blood samples and completing uniscale instrument before starting chemotherapy (n = 413)
Age (y), median	61	61	61
Baseline performance status, %			
0-1	95	95	95
2	5	5	5
Gender, %			
Male	61	59	58
Female	38	41	42
Race, %			
Caucasian	85	86	88
African American	8	7	6
Other or unknown	7	7	6
Treatment arm, %			
FOLFOX	48	58	53
IFL	27	22	24
IROX	25	20	23
Overall survival (mo), median (95% confidence interval)	18.1 (17.1-18.8)	18.2 (17.2-19.6)	18.3 (17.2-19.9)

NOTE: Only patients randomized to IFL, FOLFOX, or IROX on trial N9741 after the inclusion of the amendment for participation in the blood biomarker studies. FOLFOX, infusional 5-fluorouracil, leucovorin, and oxaliplatin; IFL, irinotecan, bolus 5-fluorouracil, and leucovorin; IROX, irinotecan, and oxaliplatin.

biomarker studies and those completing QOL assessments (Table 1). We did not detect any appreciable differences between these subgroups. Further, patients experienced similar overall survival at a median follow-up of 20.4 months.

Correlations among Plasma Markers, BMI, and Performance Status. We examined the relationships among the IGF axis biomarkers, C-peptide, BMI, and baseline performance status (Table 2). We defined correlation coefficients of >0.6 as strong, between 0.3 and 0.6 as moderate, and <0.3 as weak or nonexistent (38). Using Spearman correlations, we found strong correlations among IGF-I, IGF-II, and IGFBP-3 but weak or no correlations for these proteins and either C-peptide, BMI, or performance status. C-peptide and BMI were marginally correlated with each other, whereas neither C-peptide nor BMI were associated with baseline performance status.

Effect of BMI. We examined the influence of initial BMI on baseline QOL. Whereas increasing BMI is predictive of worse QOL in noncancer populations (39, 40), lower BMI can also be predictive of increased cancer burden in patients (41, 42). In this cohort of patients with metastatic colorectal cancer, increasing baseline BMI was indeed predictive of improved perceptions of appearance, appetite, bowel function, and overall SDS score (Table 3). These findings remained unchanged after adjustment for age, gender, and baseline performance status. Baseline BMI was not predictive of subsequent changes in QOL while patients were treated on the clinical trial (Table 4).

Biomarkers and Baseline QOL. We examined the association between baseline plasma levels of IGF-I, IGF-II, IGFBP-3, and C-peptide and baseline measures of QOL. We limited these analyses to patients who completed a QOL assessment before starting chemotherapy to understand the predictive value of these proteins toward the well-being of patients at presentation with metastatic disease. For each individual construct in the SDS, there were between 312 and 418 patients included. The median values of these proteins based on their response to the instruments are presented in Table 5. For the total SDS and uniscale scores, patients were divided into quartiles based on their responses.

In unadjusted analyses, higher levels of IGF-I were significantly related with improved QOL related to appearance, appetite, breathing, bowel function, fatigue, nausea frequency and intensity, and uniscale and total SDS. After adjustments for age, gender, IGFBP-3, and baseline performance status, the associations with appearance, appetite, and nausea intensity remained statistically significant. Additionally, after multivariate regression, distress from cough symptoms was also associated with IGF-I. These relationships remained significant when BMI was added into the model.

Similarly, IGF-II levels were associated with perceptions of appearance, appetite, breathing, bowel function, concentration, fatigue, nausea frequency and intensity, pain frequency, and uniscale score and total SDS. Appearance, appetite, fatigue, nausea frequency and intensity, pain frequency, and total SDS remained significant after adjustment for the above-listed potential confounders. The IGF ratio, incorporating IGF-I and IGF-II and adjusted for IGFBP-3 binding, showed similar results to IGF-II, with positive associations to appearance, appetite, breathing, fatigue, nausea frequency and intensity, and SDS composite score.

In contrast, IGFBP-3 and C-peptide were not associated with any of individual constructs or cumulative scores particularly after adjustments for potential confounders.

We considered the possibility that the association between plasma IGF-I and IGF-II and baseline QOL measures may simply reflect either individual patient disease burden or nutritional status. We therefore repeated our analyses after excluding patients with a baseline BMI of <21 kg/m^2 or a baseline performance status of 2. Among the remaining 347 patients, the associations between plasma IGF-I and IGF-II and baseline QOL measures remained essentially unchanged, albeit attenuated due to decrease in sample size. In this ''healthier'' cohort, the adjusted test for trend remained significant between IGF-I and appearance (P = 0.02), appetite (P = 0.01), and cough (P = 0.05) and between IGF-II and appearance (P = 0.006), appetite (P = 0.002), fatigue (P = 0.04), nausea frequency (P = 0.001), nausea intensity (P = 0.04), and SDS composite (P = 0.005).

Biomarkers and Change in QOL. We examined whether these baseline biomarkers would predict subsequent changes in QOL during treatment for metastatic disease. As a primary analysis, we examined maximum decline in each of the QOL constructs from baseline, limiting the analyses only to patients

Table 2. Spearman correlations among baseline biomarkers, BMI, and performance status

	IGF-I	IGF-II	IGFBP-3	C-peptide	BMI	Performance status
IGF-I	—	0.62 (P < 0.001)	0.70 (P < 0.001)	0.22 (P < 0.001)	0.17 (P = 0.005)	−0.15 (P = 0.003)
IGF-II	—	—	0.87 (P < 0.001)	0.16 (P = 0.001)	0.09 (P = 0.06)	−0.11 (P = 0.03)
IGFBP-3	—	—	—	0.16 (P = 0.001)	0.06 (P = 0.2)	−0.09 (P = 0.06)
C-peptide	—	—	—	—	0.27 (P < 0.001)	0.003 (P = 0.95)
BMI	—	—	—	—	—	0.0003 (P = 0.99)

Table 3. Relationship between baseline QOL and BMI

QOL indicator	Response*	No. patients in unadjusted analyses	BMI (median)
Appearance	1	312	26.8
	2	57	25.2
	3	22	22.3
	4	16	24.0
	P_{trend} (unadjusted)		<0.0001
	P_{trend} (adjusted)		<0.0001
Appetite	1	233	26.9
	2	94	25.3
	3	60	25.5
	4	26	25.1
	P_{trend} (unadjusted)		0.008
	P_{trend} (adjusted)		0.01
Breathing	1	342	26.2
	2	53	25.6
	3	9	27.1
	4	3	33.8
	P_{trend} (unadjusted)		0.42
	P_{trend} (adjusted)		0.39
Fatigue	1	102	26.0
	2	184	26.3
	3	85	25.5
	4	39	25.5
	P_{trend} (unadjusted)		0.57
	P_{trend} (adjusted)		0.69
Insomnia	1	153	26.5
	2	142	25.9
	3	61	25.6
	4	56	25.5
	P_{trend} (unadjusted)		0.45
	P_{trend} (adjusted)		0.50
Nausea frequency	1	302	26.4
	2	80	25.7
	3	21	24.7
	4	4	24.9
	P_{trend} (unadjusted)		0.16
	P_{trend} (adjusted)		0.19
Bowel	1	222	23.6
	2	113	26.6
	3	29	24.3
	4	45	25.4
	P_{trend} (unadjusted)		0.02
	P_{trend} (adjusted)		0.02
Cough	1	247	26.4
	2	141	26.0
	3	11	25.5
	4	9	25.9
	P_{trend} (unadjusted)		0.37
	P_{trend} (adjusted)		0.31
Concentration	1	278	26.1
	2	106	26.4
	3	15	25.4
	4	11	25.5
	P_{trend} (unadjusted)		0.55
	P_{trend} (adjusted)		0.55
Nausea intensity	1	242	26.4
	2	65	25.9
	3	33	24.9
	4	12	26.6
	P_{trend} (unadjusted)		0.51
	P_{trend} (adjusted)		0.65
Outlook	1	91	26.6
	2	180	26.4
	3	46	26.4
	4	94	25.2
	P_{trend} (unadjusted)		0.07
	P_{trend} (adjusted)		0.10
Pain frequency	1	149	26.4
	2	154	26.2
	3	42	25.4
	4	64	25.4
	P_{trend} (unadjusted)		0.64
	P_{trend} (adjusted)		0.55
Pain intensity	1	206	26.6
	2	127	25.6
	3	39	26.2
	4	12	24.7
	P_{trend} (unadjusted)		0.18
	P_{trend} (adjusted)		0.21
Uniscale	1	102	25.4
	2	107	25.7
	3	108	27.4
	4	96	26.0
	P_{trend} (unadjusted)		0.08
	P_{trend} (adjusted)		0.09
SDS composite	1	90	27.4
	2	71	27.3
	3	96	25.6
	4	84	25.2
	P_{trend} (unadjusted)		0.005
	P_{trend} (adjusted)		0.008

NOTE: Variables added into linear regression models for adjusted P_{trend}: age, gender, and baseline performance status.
*For individual SDS constructs, 1-4 represent actual survey response (with 4 = 4 or 5); for uniscale and SDS composite, 1-4 represent quartiles.

with at least two measurements. None of the biomarkers nor BMI predicted declines in QOL as measured by the SDS composite and uniscale (Table 4). Similarly, there were no associations between baseline IGF-I, IGF-II, IGFBP-3, IGF ratio, C-peptide, or BMI and any of the individual SDS constructs ($P > 0.05$). Similarly, no associations with improvements in QOL were detected (data not shown). Finally, there were no relationships between the IGF proteins or C-peptide and either declines or improvements of at least 10 points in the uniscale or SDS composite score within the same patient, which have been considered to be clinically meaningful (ref. 43; $P > 0.05$, all χ^2).

Discussion

Using a cohort of patients with previously untreated metastatic colorectal cancer, we showed that lower levels of plasma IGF-I and IGF-II are associated with greater baseline symptom distress before initiation of chemotherapy. In contrast, baseline levels of IGFBP-3 and C-peptide were not associated with measures of QOL. None of the baseline biomarkers were associated with subsequent declines or improvements of symptoms while being treated with first-line chemotherapy. Finally, higher baseline BMI was associated with improved baseline QOL and diminished symptom distress.

Several potential mechanisms may explain these findings. IGF-I and IGF-II may have direct beneficial biological effects on patients with cancer that lead to improved indicators of QOL. Indirect support of this hypothesis is seen in patients with growth hormone deficiency treated with growth hormone replacement, where IGF-I levels increase and QOL improves (44, 45). Administration of recombinant IGF-I improved QOL in certain chronic disease states (46), although not others (47, 48). Conversely, plasma levels of IGF-I and IGF-II may be a reflection of disease burden and nutritional status that are a consequence of disseminated cancer. IGF-I, IGF-II, and C-peptide levels are influenced by malnutrition (49-52). Notably, our findings for IGF-I and IGF-II did not change after controlling for baseline BMI and did not change after excluding leaner patients and those with an impaired performance status. Further, although C-peptide levels have been associated with nutritional status (53, 54) C-peptide was not associated with any QOL measure in the current analysis.

Table 4. Association between biomarkers and mean maximum decline per patient of QOL symptoms

Biomarker	Quartile and tests of significance	Uniscale	SDS composite
IGF-I	1	14.3	5.9
	2	12.6	4.5
	3	11.1	3.8
	4	11.2	3.3
	P_{trend} (adjusted baseline only)	0.04	0.58
	P_{trend} (multivariate adjusted)	0.35	0.09
IGF-II	1	15.9	5.8
	2	10.7	4.1
	3	9.5	3.9
	4	13.2	3.6
	P_{trend} (adjusted baseline only)	0.08	0.73
	P_{trend} (multivariate adjusted)	0.39	0.48
IGFBP-3	1	14.6	4.7
	2	9.6	4.0
	3	11.7	4.9
	4	13.2	3.8
	P_{trend} (adjusted baseline only)	0.14	0.42
	P_{trend} (multivariate adjusted)	0.85	0.06
C-peptide	1	11.1	4.0
	2	14.2	4.0
	3	12.5	4.6
	4	11.3	4.7
	P_{trend} (adjusted baseline only)	0.72	0.03
	P_{trend} (multivariate adjusted)	0.74	0.07
IGF ratio	1	14.6	5.8
	2	12.4	4.6
	3	11.0	3.8
	4	11.2	3.3
	P_{trend} (adjusted baseline only)	0.04	0.57
	P_{trend} (multivariate adjusted)	0.12	0.58
BMI	1	10.6	5.1
	2	12.5	5.3
	3	10.9	3.0
	4	16.0	4.5
	P_{trend} (adjusted baseline only)	0.66	0.37
	P_{trend} (multivariate adjusted)	0.64	0.41

NOTE: Variables added into linear regression models for adjusted P_{trend}: IGF-I and IGF-II (IGFBP-3, age, gender, baseline performance status, baseline QOL measure, and treatment arm), IGFBP-3 (IGF-I, age, gender, baseline performance status, baseline QOL measure, and treatment arm), C-peptide, and BMI (age, gender, baseline performance status, baseline QOL measure, and treatment arm).

Preliminary results from this cohort of patients with metastatic colorectal cancer show that higher IGFBP-3 levels are associated with increased likelihood of tumor response to chemotherapy and longer time to progression and overall survival (26). In contrast, IGF-I was not correlated with response rate, but increased levels were correlated with prolonged time to progression and overall survival. We believe our data support these findings, in that higher IGF-I may be reflective of a ''better host'' (55, 56) who experiences superior indicators of QOL, whereas IGFBP-3 may have an independent effect beyond the state of the patient. This explanation is purely speculative and will require further study in colorectal cancer.

Our observation that increased BMI was associated with an improved QOL likely reflects the fact that cancer patients with lower BMIs may have suffered weight loss before diagnosis, which is predictive of worse outcomes in colorectal cancer (57). Additionally, other studies have shown that obese patients have fewer side effects from chemotherapy (58, 59), which may be a consequence of their improved QOL at baseline.

Several limitations should be noted in this study. Although baseline BMI was recorded in this study, we did not collect information on weight loss that may have occurred immediately before study enrollment. Thus, residual confounding by cachexia associated with the diagnosis of metastatic colorectal cancer cannot be excluded. In addition, both protein levels and QOL may be affected by other physical and psychological factors affecting on individual patients before enrollment in a clinical trial, such as morbidity from recent surgery and physical symptoms related to the location of metastases. Although inclusion of performance status in our regression model may partially adjust for such differences, such unaccounted factors may not be adequately controlled for in our analyses. Protein levels were only measured at the start of chemotherapy, and the effect of change over time of these growth factors on QOL could not be assessed. However, one study of women receiving chemotherapy for advanced breast cancer showed that IGF-I did not change on therapy, whereas IGFBP-3 only modestly decreased (60).

As with other QOL studies, missing data can bias results. In our primary analyses of baseline IGF proteins and C-peptide, we only included patients who completed the QOL

Table 5. Relationship between baseline QOL and median plasma biomarkers

QOL indicator	Response*	No. patients in unadjusted analyses	IGF-I	IGF-II	IGFBP3	IGF ratio	C-peptide
Appearance	1	312	179	845	3,749	24.1	3.30
	2	57	155	723	3,562	21.1	2.64
	3	22	122	590	3,003	16.8	2.08
	4	16	139	787	3,871	18.8	2.71
	P_{trend} (unadjusted)		0.001	<0.0001	0.02	0.0009	0.03
	P_{trend} (adjusted)		0.01†	0.0002†	0.79	0.0005†	0.12
Appetite	1	233	182	876	3,766	24.7	3.36
	2	94	150	785	3,654	20.4	2.59
	3	60	144	741	3,497	19.5	3.25
	4	26	135	692	3,510	18.4	2.30
	P_{trend} (unadjusted)		<0.0001	<0.0001	0.005	<0.0001	0.24
	P_{trend} (adjusted)		0.007†	0.0008†	0.72	0.0003†	0.28
Breathing	1	342	174	832	3,700	23.5	3.17
	2	53	162	788	3,779	21.8	2.60
	3	9	144	741	3,283	19.6	2.84
	4	3	56	475	2,117	8.1	2.32
	P_{trend} (unadjusted)		0.008	0.02	0.02	0.008	0.59
	P_{trend} (adjusted)		0.37	0.61	0.46	0.04†	0.56
Bowel	1	222	176	829	3,728	23.7	3.28
	2	113	172	858	3,831	23.8	2.71
	3	29	152	777	3,581	20.6	3.53
	4	45	147	746	3,562	19.9	2.75
	P_{trend} (unadjusted)		0.05	0.05	0.11	0.05	0.21
	P_{trend} (adjusted)		0.78	0.31	0.32	0.15	0.28

(Continued on the following page)

Table 5. Relationship between baseline QOL and median plasma biomarkers (Cont'd)

QOL indicator	Response*	No. patients in unadjusted analyses	IGF-I	IGF-II	IGFBP3	IGF ratio	C-peptide
Cough	1	247	176	836	3,697	23.8	3.21
	2	141	158	788	3,688	21.5	2.88
	3	11	144	772	3,435	19.6	2.18
	4	9	148	886	4,034	20.0	3.17
	P_{trend} (unadjusted)		0.06	0.32	0.67	0.06	0.47
	P_{trend} (adjusted)		0.01†	0.24	0.06	0.16	0.27
Concentration	1	278	174	827	3,740	23.5	3.07
	2	106	161	790	3,686	21.8	3.26
	3	15	168	860	3,581	22.6	2.24
	4	11	154	747	3,316	20.7	2.07
	P_{trend} (unadjusted)		0.21	0.05	0.19	0.21	0.25
	P_{trend} (adjusted)		0.61	0.13	0.48	0.54	0.30
Fatigue	1	102	192	886	3,915	25.8	3.15
	2	184	168	837	3,726	22.6	3.02
	3	85	155	747	3,505	21.2	2.65
	4	39	132	711	3,283	18.0	3.23
	P_{trend} (unadjusted)		0.0001	<0.0001	0.0002	0.0001	0.71
	P_{trend} (adjusted)		0.57	0.008†	0.06	0.006†	0.60
Insomnia	1	153	164	805	3,651	22.2	3.08
	2	142	174	858	3,701	23.4	2.83
	3	61	168	845	3,831	22.6	3.27
	4	56	175	745	3,374	23.6	2.91
	P_{trend} (unadjusted)		0.84	0.39	0.73	0.84	0.62
	P_{trend} (adjusted)		0.33	0.29	0.22	0.91	0.30
Nausea frequency	1	302	177	835	3,747	23.9	3.22
	2	80	153	779	3,539	20.6	2.90
	3	21	129	770	3,697	17.6	2.83
	4	4	93	521	2,207	12.9	1.03
	P_{trend} (unadjusted)		0.0005	<0.0001	0.006	0.0004	0.16
	P_{trend} (adjusted)		0.15	0.0004†	0.42	0.003†	0.20
Nausea intensity	1	242	184	845	3,760	23.3	3.32
	2	65	165	756	3,697	22.5	2.81
	3	33	130	727	3,505	25.0	2.61
	4	12	116	711	3,305	20.5	2.09
	P_{trend} (unadjusted)		0.0003	0.003	0.06	0.0002	0.02
	P_{trend} (adjusted)		0.01†	0.02†	0.48	0.005†	0.12
Outlook	1	91	172	805	3,542	24.1	2.00
	2	180	166	840	3,723	21.8	3.08
	3	46	186	809	3,786	22.2	2.87
	4	94	151	794	3,536	22.6	3.07
	P_{trend} (unadjusted)		0.72	0.45	0.90	0.71	0.78
	P_{trend} (adjusted)		0.53	0.10	0.38	0.99	0.23
Pain frequency	1	149	179	846	3,761	23.7	3.23
	2	154	161	809	3,681	22.3	2.92
	3	42	163	751	3,251	24.2	2.64
	4	64	168	808	3,777	18.2	3.14
	P_{trend} (unadjusted)		0.18	0.007	0.10	0.17	0.43
	P_{trend} (adjusted)		0.75	0.03†	0.19	0.06	0.80
Pain intensity	1	206	176	843	3,728	23.7	3.35
	2	127	165	799	3,654	22.3	2.61
	3	39	181	825	3,823	24.2	3.07
	4	12	133	829	3,597	18.2	2.27
	P_{trend} (unadjusted)		0.26	0.15	0.45	0.25	0.04
	P_{trend} (adjusted)		0.59	0.19	0.82	0.30	0.10
Uniscale	1	102	151	781	3,653	20.4	2.73
	2	107	174	855	3,688	23.5	3.35
	3	108	179	844	3,792	24.1	2.84
	4	96	176	827	3,720	23.8	3.26
	P_{trend} (unadjusted)		0.05	0.04	0.23	0.05	0.25
	P_{trend} (adjusted)		0.25	0.17	0.65	0.23	0.24
SDS composite	1	90	194	848	3,760	26.1	3.82
	2	71	180	902	3,817	24.3	3.18
	3	96	157	745	3,465	21.4	2.95
	4	84	137	751	3,681	18.7	2.64
	P_{trend} (unadjusted)		0.0002	0.0003	0.02	0.0002	0.14
	P_{trend} (adjusted)		0.06	0.001†	0.75	0.002†	0.42

NOTE: Variables added into linear regression models for adjusted P_{trend}: IGF-I and IGF-II (IGFBP-3, age, gender, and baseline performance status), IGFBP-3 (IGF-I, age, gender, and baseline performance status), and C-peptide (age, gender, and baseline performance status).
*For individual SDS constructs, 1-4 represent actual survey response (with 4 = 4 or 5); for uniscale and SDS composite, 1-4 represent quartiles.
† $P < 0.05$ after additional adjustment by baseline BMI.

instruments before starting chemotherapy. However, if sicker patients with reduced QOL did not complete the survey, our results would be biased toward the null and we find multiple positive associations. Additionally, no differences in survival were observed for patients who did or did not complete the QOL assessments and provided blood sample. Finally, multiple comparisons can lead to positive relationships by chance. In the baseline analyses, we examined

six markers against 15 QOL constructs (90 comparisons). By chance alone, one might anticipate four to five positive associations; however, we showed 22 significant associations. Moreover, no associations were found with either C-peptide or IGFBP-3, which could be expected by random chance.

We did not detect a difference in declines or improvements of QOL based on any of the protein levels. These analyses may be limited by differential completion of follow-up QOL assessments, which may have biased the results toward the null. However, other such longitudinal studies in cancer patients have also had decreasing compliance with completion of follow-up instruments and were able to show associations between outcome and changes in QOL (61-64). Moreover, because we measured IGF proteins only at baseline, we were not able to add potential changes in those levels in our longitudinal models.

There is a growing interest in the IGF pathway as a potential target for cancer therapy (65). Although these data cannot address the merits of such a strategy, we would advocate close observation of QOL when testing such agents.

Genetic variants in folate metabolism were recently shown to be associated with QOL indicators in patients with metastatic colorectal cancer (4). We believe that these findings, in conjunction with the current study, begin to provide a link between molecular biology and QOL research. There is a strong interest to identify molecular biomarkers and genetic polymorphisms to tailor drugs for individual patients. In addition to predicting prognosis and response to therapy, such biological markers may also allow clinicians to incorporate QOL considerations when deciding on a course of treatment.

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