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Article

Body Mass Index and Weight Loss in Metastatic Colorectal Cancer in CALGB (Alliance)/SWOG 80405

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Abstract

Background: In nonmetastatic colorectal cancer, overweight and mild-to-moderately obese patients experience improved outcomes compared with other patients. Obesity's influence on advanced or metastatic colorectal cancer (mCRC) is relatively unexplored. **Methods:** We conducted a prospective body mass index (BMI) companion study in Cancer and Leukemia Group B (now Alliance)/SWOG 80405, a phase III metastatic colorectal cancer (mCRC) treatment trial. BMI was measured at trial registration. Primary and secondary endpoints were overall and progression-free survival, respectively. To minimize confounding by poor and rapidly declining health, we used Cox proportional hazards regression to adjust for known prognostic factors, comorbidities, physical activity, and weight loss during the 6 months prior to study entry. We also examined weight loss prior to enrollment as an independent predictor of patient outcome. All statistical tests were two-sided. **Results:** Among 2323 patients with mCRC, there were no statistically significant associations between BMI and overall or progression-free survival (adjusted $P_{trend} = .12$ and .40, respectively). Weight loss during the 6 months prior to study entry was associated with shorter overall and progression-free survival; compared with individuals with stable weight ±4.9%, individuals with weight loss greater than 15% experienced an adjusted hazard ratio of 1.52 for all-cause mortality (95% confidence interval [CI] = 1.26 to 1.84; $P_{trend} < .001$) and of 1.23 for disease progression or death (95% CI = 1.02 to 1.47; $P_{trend} = .006$). **Conclusions:** In this prospective study of patients with mCRC, BMI at time of first-line chemotherapy initiation was not associated with patient outcome. Weight loss prior to study entry was associated with increased risk of patient mortality and disease progression.

Obesity, defined as body mass index (BMI) no less than 30 kg/m^2, is a risk factor for colorectal cancer (CRC), the second leading cause of cancer-related death in the United States (1–6). However, the relationship between BMI and patient outcome after CRC diagnosis is less clear (7). A growing body of evidence suggests that the association between BMI and nonmetastatic CRC survival is U- or J-shaped, wherein overweight and class I obese patients (BMI 25–35 kg/m^2) experience the most favorable outcomes (8–12). The association of high BMI with both increased CRC risk and improved nonmetastatic CRC outcome is referred to as the BMI paradox (13) and runs contrary to a large body of literature suggesting that factors associated with energy excess increase CRC mortality and disease recurrence (14–19). The influence of BMI on patients with advanced and metastatic colorectal cancer (mCRC) is relatively unexplored (7).

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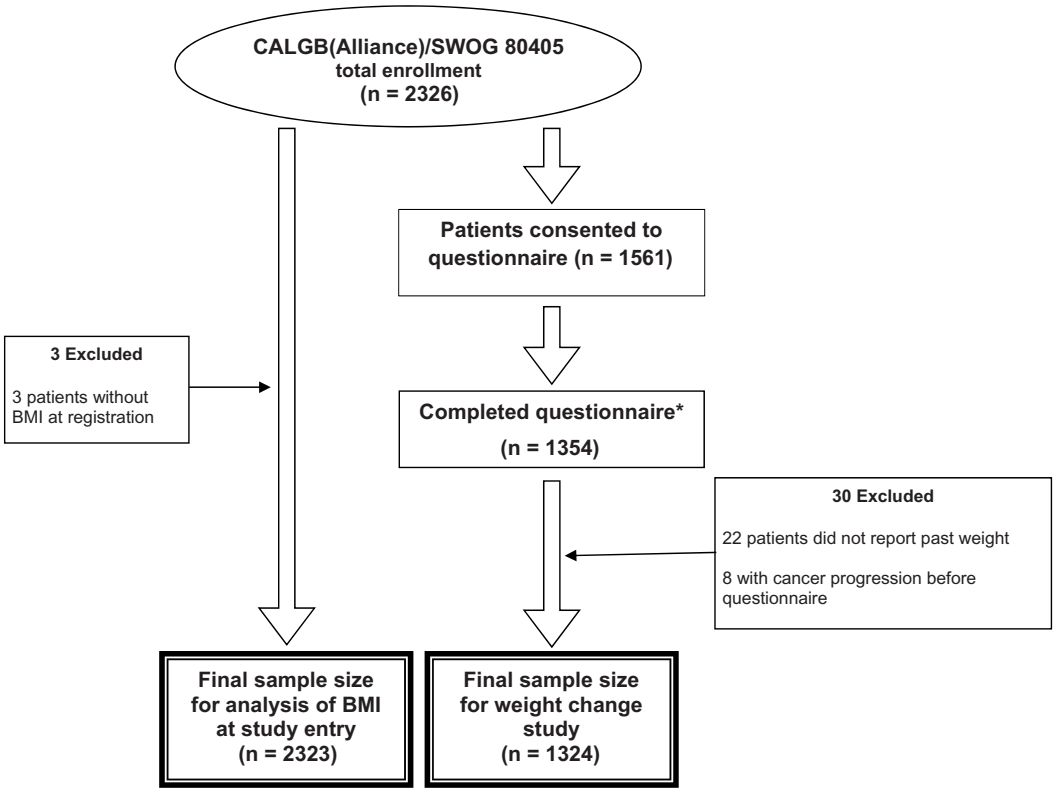

Figure 1. Derivation of the study cohort.

CALGB = Cancer and Leukemia Group B (now Alliance for Clinical Trials in Oncology); BMI = body mass index. *A voluntary questionnaire administered within 4 weeks after initiating chemotherapy for metastatic disease was used to collect data on weight change over the prior 6 months, asking patients their weight at time of questionnaire completion and 6 months prior.

In the current study, we examined associations of BMI with cancer progression and survival in patients with mCRC within a large National Cancer Institute (NCI)-sponsored clinical trial of systemic therapy. Among patients enrolled in this trial, we prospectively collected data on BMI, weight change, cancer progression, and mortality. Moreover, because data on *KRAS* status, performance status, treatment, and follow-up were carefully captured in the trial, the simultaneous effect of disease characteristics and the use of systemic therapies could be assessed.

Methods

Study Population

Subjects were participants of an NCI-sponsored phase III trial of first-line therapy for advanced or metastatic colorectal adenocarcinoma, receiving irinotecan, 5-fluorouracil, and leucovorin (FOLFIRI) or oxaliplatin, 5-fluorouracil, and leucovorin (mFOLFOX6) combined with cetuximab, bevacizumab, or a combination of cetuximab and bevacizumab (Cancer and Leukemia Group B [CALGB, now part of the Alliance for Clinical Trials in Oncology]/SWOG 80405; ClinicalTrials.gov identifier NCT00265850) (20). The clinical trial design of CALGB/SWOG 80405 underwent substantial changes during enrollment (Supplementary Methods, available online). Figure 1 demonstrates derivation of the cohort.

Eligibility requirements for the trial and this companion study included a baseline Eastern Cooperative Oncology Group performance status of 0 to 1 (21) and adequate bone marrow, renal, and hepatic function. Patients signed written informed consent approved by each site's institutional review board. The study was performed in accord with an assurance filed with and approved by the US Department of Health and Human Services.

Assessment of BMI and Weight Change

Height and weight were measured by clinical staff at time of trial registration. BMI at study entry was calculated by dividing this weight in kilograms by squared height in meters squared.

Given the prognostic significance of weight loss in CRC (7) and its potential to confound associations between BMI and patient outcome, we also conducted analyses of weight change prior to study entry. Weight change data were captured using a self-reported questionnaire completed within 4 weeks after initiating trial therapy, soliciting weight at questionnaire completion and 6 months prior. Percent weight change was defined as weight at questionnaire completion minus weight 6 months prior divided by weight 6 months prior.

We also considered that the relationship between BMI at study entry and patient outcome might suffer confounding by disease-related weight loss despite efforts to control for weight change. Therefore, we performed secondary analyses examining associations of outcome with BMI at an earlier time point, approximately 6 months prior to study entry, to reduce the impact of cancer-related weight loss. BMI prior to study entry was

Table 1. Baseline characteristics by voluntary questionnaire completion

Portion of study cohort Patient deaths/At risk	Questionnaire complete (1154/1354)	Questionnaire not complete (819/972)	All patients combined (1973/2326)
Baseline characteristics			
BMI, median (IQR), kg/m^2	27.1 (24.0–31.3)	26.9 (23.3–30.9)	27.1 (23.7–31.2)
Male, No. (%)	799 (59.0)	556 (57.2)	1355 (58.3)
Age, median (IQR), y	59.1 (51.1–67.6)	59.3 (51.3–67.4)	59.1 (51.2–67.6)
Race, No. (%)			
White	1154 (85.2	742 (76.3)	1896 (81.5)
Black	142 (10.5)	136 (14.0)	278 (12.0)
Other	40 (3.0)	57 (5.9)	97 (4.2)
Unknown	18 (1.3)	37 (3.8)	55 (2.4)
Performance status, No. (%)*			
ECOG 0	828 (61.2)	533 (54.8)	1361 (58.5)
ECOG 1	525 (38.8)	437 (45.0)	962 (41.4)
ECOG 2	1 (0.1)	2 (0.2)	3 (0.1)
Planned chemotherapy, No. (%)			
FOLFIRI	310 (22.9)	220 (22.6)	530 (22.8)
mFOLFOX6	1044 (77.1)	752 (77.4)	1796 (77.2)
Prior adjuvant chemotherapy, No. (%)			
No	1177 (86.9)	815 (83.8)	1992 (85.6)
Yes	177 (13.1)	157 (16.2)	334 (14.4)
Primary tumor unresected at study entry, No. (%)			
No	1066 (78.7)	729 (75.0)	1795 (77.2)
Yes	288 (21.3)	243 (25.0)	531 (22.8)
Prior radiation therapy, No. (%)			
No	1239 (91.5)	882 (90.7)	2121 (91.2)
Yes	115 (8.5)	90 (9.3)	205 (8.8)
Assigned targeted-treatment arm, No. (%)			
Bevacizumab	518 (38.3)	379 (39.0)	897 (38.6)
Cetuximab	515 (38.0)	382 (39.3)	897 (38.6)
Bevacizumab + cetuximab	321 (23.7)	211 (21.7)	532 (22.9)
KRAS, No. (%)†			
Wild-type	829 (61.2)	470 (48.4)	1299 (55.8)
Mutant	257 (19.0)	160 (16.5)	417 (17.9)
Indeterminate/Missing	268 (19.8)	342 (35.2)	610 (26.2)
Primary tumor location, No. (%)			
Left colon	469 (34.6)	316 (32.5)	785 (33.7)
Right or transverse colon	785 (58.0)	551 (56.7)	1336 (57.4)
Missing	100 (7.4)	105 (10.8)	205 (8.8)

*Baseline performance status categories: Eastern Cooperative Oncology Group (ECOG) 0 is fully active; ECOG 1 is restricted in physically strenuous activity but ambulatory and able to carry out light work; ECOG 2 is ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours. BMI = body mass index; FOLFIRI = 5-fluorouracil, leucovorin, and irinotecan; IQR = interquartile range; mFOLFOX6 = 5-fluorouracil, leucovorin, and oxaliplatin.

†Although *KRAS* eligibility criteria for inclusion in the clinical trial's primary analysis was based on examination of exon 2 codons 12 and 13 using the Scorpion method (20), our covariate analysis supplemented this data with *KRAS* data from the Alliance A151425 Project (a collaboration with Genentech) (22) and Merck BEAMing technology (23–25).

calculated using weight and height data from the questionnaire, which asked for each patient's weight 6 months prior to questionnaire completion. Of patients enrolled in the trial, 68% consented to the questionnaire, of which 86% completed the questionnaire (Figure 1). Compared with individuals who did not complete the questionnaire, patients who completed the questionnaire were more likely to be white and have better performance status and less likely to have indeterminate or missing *KRAS* status but did not differ in other tumor or patient characteristics, including BMI (Table 1).

Study Endpoints

Our study's predetermined primary endpoint was overall survival (OS), defined as time from BMI assessment to death from any cause. We also assessed progression-free survival (PFS), defined as time from BMI measurement to death from any cause or progression of disease (per RECIST 1.0) (26).

Statistical Analyses

For this companion study, patient data from all treatment arms were included. Data were analyzed according to predefined categories of BMI (<21, 21–24.9, 25–29.9, 30–34.9, and ≥35 kg/m2) and percent change in weight (loss >15%, loss 10.1%–15%, loss 5%–10%, stable ±4.9%, and gain ≥5%), based on prior studies (5,8,27–29). Cox proportional hazards regression (30) was used to adjust for potential confounders. Model adjustments are detailed in table and figure legends. For purposes of model adjustment, physical activity was assessed by the voluntary questionnaire, as described and validated previously (31–36). Considering the potential for declining health to cause weight

loss and confound assessments of BMI, we adjusted models examining BMI further for comorbidities and weight change during the 6 months prior to study entry as proxies for poor or rapidly declining health; models examining the impact of weight change on patient outcome were also further adjusted for comorbidities. To measure comorbidities, participants were asked questions regarding 18 comorbid conditions (Supplementary Methods, available online). For all covariates, missing variables were coded as the median value for continuous variables or major category for categorical variables.

We tested for linear trends across discrete categories of BMI and weight change by assigning each participant the median value for his or her category and modeling this value as a continuous variable, consistent with prior studies (14,17,19, 37–39). Subgroup exploratory analyses were conducted to explore effects of BMI and weight change across strata of other known and potential predictors of patient outcome. For BMI, tests for trend and interaction used normal BMI (21–24.9 kg/m^2) as the reference group and excluded patients in the lowest BMI category (<21 kg/m^2), given that underweight patients may be more likely to have poor or rapidly declining health. Although prior studies suggest a U-shaped association between BMI and survival, we used restricted cubic splines to test for nonlinearity, and results were not statistically significant, making an assumption of linear trend across BMI categories reasonable. For analyses of weight loss, tests for trend and interaction used the category of minimal weight change (change <5%) as the reference group and excluded individuals with weight gain greater than 5%. The proportionality of hazards assumption was tested and satisfied using time-dependent covariates in the model. Data collection was conducted by the Alliance Statistics and Data Center. Data analyses were performed using SAS Version 9.4 (SAS Institute Inc, Cary, NC) on a dataset locked on January 18, 2018. Data quality was ensured by review of data by the Alliance Statistics and Data Center and by the study chairperson following Alliance policies. *P* value less than .05 was considered statistically significant. All *P* values are 2-sided and not adjusted for multiple comparisons.

Results

Associations of BMI With Overall and Progression-Free Survival

Baseline characteristics are displayed by BMI category in Table 2. Compared with individuals with normal BMI (21–24.9 kg/m^2), morbidly obese individuals (≥35 kg/m^2) were more likely to be female, to have received adjuvant chemotherapy, and to receive FOLFIRI. Individuals with high BMI were more likely to have comorbidities and were less physically active.

Median follow-up for patients included in the analysis of BMI measured at study entry was 5.98 years. During follow-up, 1926 of the 2323 patients experienced cancer progression; 1726 of these patients died. An additional 244 died without documented cancer progression.

BMI was not statistically significantly associated with OS (Table 3). Compared with individuals with normal BMI of 21–24.9 kg/m^2, individuals with morbid obesity (BMI 35 kg/m^2) experienced an adjusted hazard ratio (HR) for mortality of 0.89 (95% confidence interval [CI] = 0.76 to 1.05; P_{trend} = .15). These findings remained largely unchanged after further adjustment for weight change, physical activity, and comorbidities (P_{trend} = .12). Similarly, BMI was not statistically significantly associated with PFS (adjusted P_{trend} = .40). The absence of a statistically significant association between BMI and OS persisted when analyses of BMI at study entry were restricted to patients who completed the self-reported questionnaire and when analyses were further adjusted for race (P_{trend} for OS = .09; P_{trend} for PFS = .33).

In exploratory subgroup analyses examining associations of BMI with survival across strata of various factors, we compared OS of individuals with BMI no less than 35 kg/m^2 to those with BMI of 21–24.9 kg/m^2, adjusting for covariates including weight change and comorbidity (Figure 2). The absence of a statistically significant association between BMI and OS appeared consistent across most strata of patient, disease, and treatment characteristics.

Based on a prior study of BMI in mCRC (40), we performed a post hoc analysis comparing OS and PFS in patients with BMI less than 28 kg/m^2 at study entry to patients with BMI at least 28 kg/m^2, adjusting for covariates as in our primary analysis. Unlike the prior study, we excluded patients with BMI less than 21 kg/m^2 given that underweight patients may be more likely to have poor or rapidly declining health. Compared with individuals with a BMI of at least 28 kg/m^2, patients with a BMI less than 28 kg/m^2 experienced adjusted hazard ratios for mortality of 1.12 (95% CI = 1.02 to 1.23; P_{trend} = .02). There was no statistically significant association between a BMI less than 28 kg/m^2 and PFS (adjusted HR = 1.06, 95% CI = 0.97 to 1.17; P_{trend} = .19).

Associations of Weight Loss With Overall and Progression-Free Survival

Baseline characteristics by category of self-reported weight change during the 6 months prior to study entry (Table 4) demonstrated that, compared with individuals with stable weight, individuals with weight loss tended to have poorer performance status and be less physically active and were less likely to have received FOLFIRI, prior adjuvant chemotherapy or prior radiation therapy or have left-sided primary tumors.

Patients who completed the questionnaire (n = 1324) were included in analyses of weight change, comparing each patient's weight reported at time of questionnaire completion to their weight 6 months prior. Median follow-up for patients included in analyses of weight change was 6.05 years. During follow-up, 1142 of the 1324 patients included in this analysis experienced cancer progression; 1026 of these patients died. An additional 106 died without documented cancer progression.

Weight loss during the 6 months prior to study entry was associated with shorter OS (Table 5). Compared with individuals reporting stable weight (±4.9%), individuals reporting weight loss greater than 15% experienced an adjusted hazard ratio for all-cause mortality of 1.52 (95% CI = 1.26 to 1.84; P_{trend} < .001). These findings persisted despite adjusting further for physical activity and comorbidities (P_{trend} < .001). Similarly, greater weight loss was associated with shorter PFS, even after adjusting for potential confounders including BMI, physical activity, and comorbidities (adjusted HR = 1.23, 95% CI = 1.02 to 1.47; P_{trend} = .006). Our results remained statistically significant after further adjustment for race (P_{trend} for OS < .001; P_{trend} for PFS = .006).

In exploratory subgroup analyses, the association of weight loss with shorter OS appeared consistent across strata of disease and patient characteristics, including sex (data not shown). Tests for interaction between weight loss and each of these characteristics were not statistically significant, with the

Table 2. Baseline characteristics by BMI at study entry (n = 2323; median follow-up = 5.98 years)

Characteristics	BMI category, kg/m^2				
	<21	21–24.9	25–29.9	30–34.9	≥35
Patient deaths/At risk	215/248	449/532	697/823	390/463	219/257
Baseline characteristics					
BMI, median (IQR), kg/m^2	19.5 (18.3–20.2)	23.3 (22.1–24.2)	27.2 (26.1–28.4)	32.1 (31.0–33.3)	38.9 (36.5–42.4)
Male, No. (%)	120 (48.4)	307 (57.7)	524 (63.7)	277 (59.8)	126 (49.0)
Age, median (IQR), y	57.7 (49.3–66.4)	59.3 (51.5–68.5)	60.2 (52.1–68.7)	58.5 (51.2–66.8)	57.6 (49.3–63.8)
Race, No. (%)					
White	184 (74.2)	435 (81.8)	673 (81.8)	389 (84.0)	213 (82.9)
Black	36 (14.5)	49 (9.2)	102 (12.4)	53 (11.4)	38 (14.8)
Other/Unknown	28 (11.3)	48 (9.0)	48 (5.8)	21 (4.5)	6 (2.3)
Performance status, No. (%)*					
ECOG 0	119 (48.0)	291 (54.7)	508 (61.7)	295 (63.7)	146 (56.8)
ECOG 1	127 (51.2)	241 (45.3)	315 (38.3)	168 (36.3)	110 (42.8)
ECOG 2	2 (0.8)	—	—	—	1 (0.4)
Planned chemotherapy, No. (%)					
FOLFIRI	47 (19.0)	102 (19.2)	189 (23.0)	114 (24.6)	78 (30.4)
mFOLFOX6	201 (81.0)	430 (80.8)	634 (77.0)	349 (75.4)	179 (69.6)
Prior adjuvant chemotherapy, No. (%)					
No	229 (92.3)	475 (89.3)	714 (86.8)	373 (80.6)	199 (77.4)
Yes	19 (7.7)	57 (10.7)	109 (13.2)	90 (19.4)	58 (22.6)
Primary tumor unresected at study entry, No. (%)					
No	169 (68.1)	426 (80.1)	642 (78.0)	358 (77.3)	199 (77.4)
Yes	79 (31.9)	106 (19.9)	181 (22.0)	105 (22.7)	58 (22.6)
Prior radiation therapy, No. (%)					
No	231 (93.1)	485 (91.2)	756 (91.9)	411 (88.8)	235 (91.4)
Yes	17 (6.9)	47 (8.8)	67 (8.1)	52 (11.2)	22 (8.6)
Assigned targeted-treatment arm, No. (%)					
Bevacizumab	111 (44.8)	212 (39.8)	297 (36.1)	181 (39.1)	94 (36.6)
Cetuximab	83 (33.5)	188 (35.3)	341 (41.4)	180 (38.9)	104 (40.5)
Bevacizumab + cetuximab	54 (21.8)	132 (24.8)	185 (22.5)	102 (22.0)	59 (23.0)
KRAS, No. (%)					
Wild-type	139 (56.0)	289 (54.3)	453 (55.0)	258 (55.7)	158 (61.5)
Mutant	46 (18.5)	99 (18.6)	154 (18.7)	75 (16.2)	43 (16.7)
Indeterminate/Missing	63 (25.4)	144 (27.1)	216 (26.2)	130 (28.1)	56 (21.8)
Primary tumor location, No. (%)					
Right or transverse colon	80 (32.3)	172 (32.3)	284 (34.5)	158 (34.1)	89 (34.6)
Left colon	145 (58.5)	315 (59.2)	467 (56.7)	265 (57.2)	143 (55.6)
Multiple/Missing	23 (9.3)	45 (8.5)	72 (8.7)	40 (8.6)	25 (9.7)
Diabetes, No. (%)					
No	228 (91.9)	481 (90.4)	697 (84.7)	362 (78.2)	180 (70.0)
Yes	20 (8.1)	51 (9.6)	126 (15.3)	101 (21.8)	77 (30.0)
Questionnaire completed, No. (%)	125 (50.4)	302 (56.8)	498 (60.5)	275 (59.4)	153 (59.5)
Physical activity, median (IQR), MET h/w†	3.2 (0.6–14.7)	4.6 (0.7–15.0)	3.9 (0.8–14.0)	3.0 (0.4–9.6)	2.0 (0.2–7.5)
Percent weight change, No. (%)†					
Loss ≥5%	96 (38.7)	202 (38.0)	322 (39.1)	159 (34.3)	89 (34.6)
Stable ±4.9%	22 (8.9)	89 (16.7)	164 (19.9)	106 (22.9)	59 (23.0)
Gain ≥5%	7 (2.8)	11 (2.1)	12 (1.5)	10 (2.2)	5 (1.9)
Missing	123 (49.6)	230 (43.2)	325 (39.5)	188 (40.6)	104 (40.5)
Comorbidity, No. (%)†					
None	88 (35.5)	237 (44.5)	327 (39.7)	167 (36.1)	70 (27.2)
Any	37 (14.9)	65 (12.2)	171 (20.8)	108 (23.3)	83 (32.3)
Missing	123 (49.6)	230 (43.2)	325 (39.5)	188 (40.6)	104 (40.5)

*Baseline performance status categories: Eastern Cooperative Oncology Group (ECOG) 0 is fully active; ECOG 1 is restricted in physically strenuous activity but ambulatory and able to carry out light work; ECOG 2 is ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours. BMI = body mass index; FOLFIRI = 5-fluorouracil, leucovorin, and irinotecan; IQR = interquartile range; MET h/w = metabolic equivalent task hours per week; mFOLFOX6 = 5-fluorouracil, leucovorin, and oxaliplatin.

†Measured by voluntary questionnaire. Among patients who completed the questionnaire, 4 patients were missing data on physical activity, and 22 patients were missing data on weight change.

Table 3. Associations of BMI at study entry with mortality and disease progression in patients with advanced or metastatic colorectal cancer (n = 2323)

Variable	BMI category, kg/m²*					
	<21	21–24.9	25–29.9	30–34.9	≥35	P_{trend}†
Median BMI (IQR), kg/m²	19.5 (18.3–20.2)	23.3 (22.1–24.2)	27.2 (26.1–28.4)	32.1 (31.0–33.3)	38.9 (36.5-42.4)	—
OS						
Event /total	215/248	449/532	697/823	390/463	219/257	
Unadjusted HR (95% CI)	1.20 (1.02 to 1.41)	1 (Referent)	0.91 (0.81 to 1.03)	0.87 (0.76 to 0.99)	0.88 (0.75 to 1.04)	.08
Adjusted 1 HR (95% CI)‡	1.18 (1.00 to 1.39)	1 (Referent)	0.92 (0.82 to 1.04)	0.89 (0.77 to 1.02)	0.89 (0.76 to 1.05)	.15
Adjusted 2 HR (95% CI)§	1.15 (0.98 to 1.35)	1 (Referent)	0.92 (0.82 to 1.04)	0.89 (0.78 to 1.02)	0.88 (0.74 to 1.04)	.12
PFS						
Event/total	230/248	492/532	778/823	431/463	239/257	
HR (95% CI)						
Unadjusted HR (95% CI)	1.15 (0.98 to 1.35)	1 (Referent)	0.96 (0.86 to 1.08)	0.92 (0.81 to 1.05)	0.96 (0.83 to 1.12)	.45
Adjusted 1 HR (95% CI)‡	1.14 (0.97 to 1.33)	1 (Referent)	0.97 (0.87 to 1.09)	0.93 (0.81 to 1.06)	0.96 (0.82 to 1.12)	.42
Adjusted 2 HR (95% CI)§	1.12 (0.95 to 1.31)	1 (Referent)	0.97 (0.86 to 1.09)	0.93 (0.81 to 1.06)	0.94 (0.80 to 1.11)	.40

*BMI was calculated using height and weight measured in clinic at time of trial registration, dividing weight in kilograms by height in meters squared. BMI = body mass index; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FOLFIRI = 5-fluorouracil, leucovorin, and irinotecan; HR = hazard ratio; IQR = interquartile range; MET h/w = metabolic equivalent task-hours per week; mFOLFOX6 = 5-fluorouracil, leucovorin, and oxaliplatin; OS = overall survival; PFS = progression-free survival.

†Tests for trend excluded patients in lowest BMI category (<21 kg/m²), given that underweight patients may be more likely to have poor or rapidly declining health. P values are 2-sided.

‡Adjusted 1: Adjusting for age (continuous years), sex (female, male), ECOG performance status (0, 1, or 2), planned chemotherapy (FOLFIRI, mFOLOFOX6), prior adjuvant chemotherapy (yes, no), prior radiation therapy (yes, no), assigned targeted-treatment arm (bevacizumab, cetuximab, bevacizumab + cetuximab), *KRAS* (wild-type, mutant, indeterminate/missing), and primary tumor location (right/transverse colon, left colon, multiple/missing).

§Adjusted 2: Adjusting for all above plus percent weight change (loss ≥5 %, stable ±4.9%, gain ≥5%, missing because of incomplete questionnaire), physical activity (0–2.9 MET h/w, 3–8.9, 9–17.9, ≥18, missing because of incomplete questionnaire), and comorbidity (none, any, missing because of incomplete questionnaire). Of the patients, 970 did not complete the voluntary questionnaire collecting information on weight change, physical activity, and comorbidities. Among patients who completed the questionnaire, 4 patients were missing data on physical activity, and 22 patients were missing data on weight change; missing values were replaced with the majority category.

exception of diabetes ($P_{interaction}$ = .02), wherein the association of weight loss with shorter OS appeared more robust among diabetic patients. Compared with stable weight (±4.9%), weight loss greater than 15% was associated with a hazard ratio for all-cause mortality of 1.38 (95% CI = 1.12 to 1.70) among nondiabetic patients, whereas the hazard ratio among diabetic patients was 2.63 (95% CI = 1.72 to 4.01). We also tested for interactions of weight loss with BMI but found no statistically significant interaction ($P_{interaction}$ = .43).

Associations of BMI Prior to Study Entry With Overall and Progression-Free Survival

Considering that assessment of BMI at study entry might suffer confounding by disease-related weight loss despite efforts to control for weight loss and declining health, we performed secondary analyses of BMI approximately 6 months prior to study entry. However, BMI prior to study entry demonstrated no statistically significant association with OS or PFS (Table 6). Exploratory subgroups analyses demonstrated no statistically significant interactions between BMI prior to study entry and other factors (data not shown).

Discussion

In this prospective study of patients with previously untreated mCRC enrolled in an NCI-sponsored, randomized trial of systemic therapy, BMI was not associated with all-cause mortality (OS) or disease progression (PFS). In subgroup analyses of OS, we found no statistically significant interactions between BMI and other predictors of patient outcome. In contrast, weight loss during the 6 months prior to study entry was associated with increased risk of mortality and disease progression independent of other predictors of patient outcome.

Prior studies suggest that overweight and class I obese BMI are associated with reduced mortality and disease recurrence in nonmetastatic CRC (8–12). BMI was investigated in mCRC in a prior study by Renfro et al. (40) pooling 25 trials that found BMI less than 28 kg/m² to be associated with increased risk of disease progression and mortality. In contrast, our results suggest that BMI is not associated with mCRC outcome, although our post hoc analysis suggested that BMI less than 28 kg/m² may be associated with shorter OS. The difference in our primary results from those of Renfro et al. may stem from our adjustment for comorbidities, physical activity, and weight change, although adjustment for these parameters minimally attenuated point estimates between our adjusted and unadjusted models. Further, the difference may be related to our exclusion of patients with BMI less than 21 kg/m², which we performed to reduce confounding by poor or rapidly declining health in patients of lower weight but was not performed in the prior study. The difference between our results may also stem from heterogeneity across trials included in the prior analysis or its higher statistical power. Based on the results of our post hoc analysis, we cannot exclude an OS advantage for patients with BMI of at least 28 kg/m², although such post hoc analyses should be considered hypothesis-generating.

Interpretation of our findings must account for the inability of BMI to differentiate adipose tissue from muscle mass (41). Measures of adiposity other than BMI, such as cross-sectional imaging, generally show greater adiposity to be associated with increased CRC patient mortality (42,43). Furthermore, sarcopenia is associated with inferior outcomes in CRC and other malignancies (43–48). The association of inferior CRC outcome with

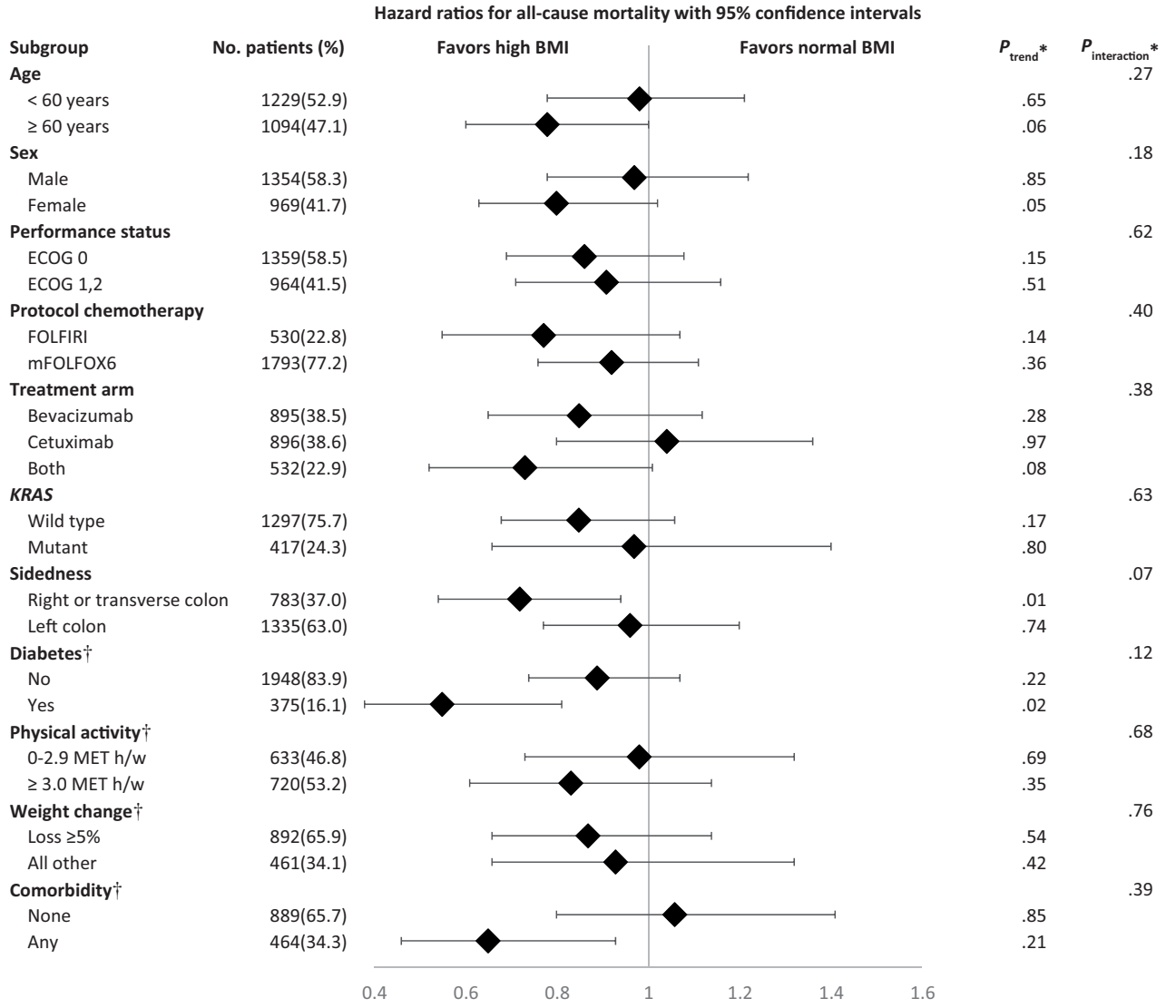

Figure 2. Multivariable hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality across strata of patient, treatment, and disease characteristics. The forest plot displays hazard ratios for all-cause mortality comparing patients with morbidly obese BMI (≥35 kg/m^2) to patients with normal BMI (21–24.9 kg/m^2); other levels of BMI were still included in the model, adjusting with Cox proportional hazards regression for age (continuous years), sex (female, male), ECOG performance status (0, 1, or 2), planned chemotherapy (FOLFIRI, mFOLOFOX6), prior adjuvant chemotherapy (yes, no), prior radiation therapy (yes, no), assigned targeted-treatment arm (bevacizumab, cetuximab, bevacizumab + cetuximab), KRAS (wild-type, mutant, indeterminate/missing), primary tumor location (right/transverse colon, left colon, multiple/missing), physical activity (0–2.9, 3–8.9, 9–17.9, ≥18 MET h/w, missing), percent weight change (loss ≥5%, stable ±4.9%, gain ≥5%), and comorbidity (none, any). BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; FOLFIRI = 5-fluorouracil, leucovorin, and irinotecan; MET h/w = metabolic equivalent task-hours per week; mFOLFOX6 = 5-fluorouracil, leucovorin, and oxaliplatin. *Tests for trend and interaction used categories of BMI (<21, 21–24.9, 25–29.9, 30–34.9, ≥35 kg/m^2) but excluded patients in the lowest BMI category (<21 kg/m^2), given that underweight patients may be more likely to have poor or rapidly declining health. *P* values are 2-sided.

†Measured by voluntary questionnaire.

increasing adiposity and decreasing muscle likely explains the BMI paradox, wherein patients with BMI 25–35 kg/m^2 experience superior outcomes (43). The mechanism linking sarcopenia to adverse patient outcome is unclear but may be mediated by tumor-instigated catabolism (49), proteolytic effects of chemotherapy (45,47), inflammation (50), altered mitochondrial function (51), or insulin resistance (52–54).

To our knowledge, our study is also the first to investigate an association between weight loss and patient outcomes in mCRC. Our study's association of weight loss with shorter OS is consistent with studies of stage I–III CRC (28,55–57), wherein weight loss was associated with increased all-cause mortality, CRC-specific mortality (28,55,57), and disease recurrence (56), although the latter was not replicated in a similar cohort (8). Although such findings may be due to weight loss caused by relatively aggressive disease, weight loss may also drive poor outcomes by increasing risk of sarcopenia (28), which may reduce survival through multiple mechanisms as discussed above. Another potential explanation for our finding is lead-time bias, because patients enrolled at a time later in their disease course might be expected to have greater weight loss as well as shorter survival (58).

Table 4. Baseline characteristics by categories of weight change (n = 1324, median follow-up = 6.05 y)

Characteristics	Percent weight change category, %				
	Loss >15	-15 to -10.1	-10 to -5	Stable ±4.9	Gain ≥5
Patient deatds/At risk	170/195	233/264	328/382	365/438	36/45
Baseline characteristics					
Percent weight change, median (IQR), %†	−18.5 (-21.8 to -16.8)	−11.9 (-13.2 to -11.0)	−7.2 (-8.6 to -6.1)	−2.0 (-3.7–0.0)	9.3 (7.1–17.0)
Female, No. (%)	95 (48.7)	101 (38.3)	158 (41.4)	169 (38.6)	17 (37.8)
Age, median (IQR), y	57.2 (49.7–66.4)	58.4 (50.6–68.0)	59.3 (51.2–67.4)	59.7 (51.5–67.9)	58.7 (48.2–65.8)
Body mass index, median (IQR), kg/m^2	26.5 (22.8–30.0)	26.5 (23.7–30.6)	27.2 (24.0–31.2)	28.1 (25.0–32.4)	26.3 (23.1–30.9)
Race, No. (%)					
White	156 (80.0)	222 (84.1)	345 (90.3)	378 (86.3)	33 (73.3)
Black	23 (11.8)	31 (11.7)	26 (6.8)	48 (11.0)	5 (11.1)
Other/Unknown	16 (8.2)	11 (4.2)	11 (2.9)	12 (2.7)	7 (15.6)
Performance status, No. (%)*					
ECOG 0	96 (49.2)	143 (54.2)	233 (61.0)	310 (70.8)	30 (66.7)
ECOG 1	99 (50.8)	121 (45.8)	148 (38.7)	128 (29.2)	15 (33.3)
ECOG 2			1 (0.3)		
Planned chemotherapy, No. (%)					
FOLFIRI	39 (20.0)	56 (21.2)	70 (18.3)	117 (26.7)	14 (31.1)
mFOLFOX6	156 (80.0)	208 (78.8)	312 (81.7)	321 (73.3)	31 (68.9)
Prior adjuvant chemotherapy, No. (%)					
No	186 (95.4)	251 (95.1)	337 (88.2)	346 (79.0)	33 (73.3)
Yes	9 (4.6)	13 (4.9)	45 (11.8)	92 (21.0)	12 (26.7)
Primary tumor unresected at study entry, No. (%)					
No	144 (73.8)	207 (78.4)	312 (81.7)	340 (77.6)	37 (82.2)
Yes	51 (26.2)	57 (21.6)	70 (18.3)	98 (22.4)	8 (17.8)
Prior radiation therapy, No. (%)					
No	188 (96.4)	255 (96.6)	357 (93.5)	376 (85.8)	37 (82.2)
Yes	7 (3.6)	9 (3.4)	25 (6.5)	62 (14.2)	8 (17.8)
Assigned targeted-treatment arm, No. (%)					
Bevacizumab	74 (37.9)	88 (33.3)	144 (37.7)	183 (41.8)	19 (42.2)
Cetuximab	74 (37.9)	103 (39.0)	139 (36.4)	168 (38.4)	18 (40.0)
Bevacizumab + Cetuximab	47 (24.1)	73 (27.7)	99 (25.9)	87 (19.9)	8 (17.8)
KRAS, No. (%)					
Wild-type	114 (58.5)	157 (59.5)	239 (62.6)	274 (62.6)	27 (60.0)
Mutant	43 (22.1)	47 (17.8)	69 (18.1)	86 (19.6)	5 (11.1)
Indeterminate/Missing	38 (19.5)	60 (22.7)	74 (19.4)	78 (17.8)	13 (28.9)
Primary tumor location, No. (%)					
Right or transverse colon	76 (39.0)	102 (38.6)	139 (36.4)	130 (29.7)	11 (24.4)
Left colon	101 (51.8)	141 (53.4)	220 (57.6)	276 (63.0)	32 (71.1)
Multiple/Missing	18 (9.2)	21 (8.0)	23 (6.0)	32 (7.3)	2 (4.4)
Diabetes, No. (%)†					
No	158 (81.0)	213 (80.7)	333 (87.2)	359 (82.0)	38 (84.4)
Yes	37 (19.0)	51 (19.3)	49 (12.8)	79 (18.0)	7 (15.6)
Physical activity, median (IQR), MET h/w †	2.0 (0.2–8.4)	2.9 (0.5–7.9)	4.3 (0.5–13.9)	4.9 (0.9–15.9)	6.7 (1.7–16.0)
Comorbidity, No. (%)†					
None	124 (63.6)	171 (64.8)	260 (68.1)	286 (65.3)	32 (71.1)
Any	71 (36.4)	93 (35.2)	122 (31.9)	152 (34.7)	13 (28.9)

*Baseline performance status categories: Eastern Cooperative Oncology Group (ECOG) 0 is fully active; ECOG 1 is restricted in physically strenuous activity but ambulatory and able to carry out light work; ECOG 2 is ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours. FOLFIRI = 5-fluorouracil, leucovorin, and irinotecan; IQR = interquartile range; MET h/w = metabolic equivalent task-hours per week; mFOLFOX6 = 5-fluorouracil, leucovorin, and oxaliplatin.

†Measured by voluntary questionnaire. Among patients who completed the questionnaire and reported prior weight, 2 patients were missing data for physical activity.

To our knowledge, our study is also the first in mCRC to suggest an interaction between weight loss and diabetes as predictors of shorter PFS. Although our test for interaction was exploratory and hypothesis generating, meta-analyses have shown diabetes to be associated with shorter CRC-specific survival (16,59). Diabetes may reduce physiologic reserve or increase chemotherapy side effects such as peripheral neuropathy, prompting dose reduction or regimen change, consistent with prior studies reporting less aggressive CRC treatment in diabetic patients (60,61). A prior analysis of our study cohort demonstrated an association between diabetes and at least grade 3 hypertension, but no other adverse events (62). Diabetes was not associated with FOLFOX dose intensity. However, among patients initially treated with FOLIRI, patients with diabetes were less likely to receive FOLFOX second line. Alternatively, the interaction between diabetes and weight loss

Table 5. Associations of weight change with mortality and disease progression in patients with advanced or metastatic colorectal cancer (n = 1324)

Variable	Percent weight change category* (%)					P_{trend}†
	Loss >−15	−15 to −10.1	−10 to −5.1	Stable ±4.9	Gain ≥5	
Median weight change (IQR), %	−18.5 (−21.8 to −16.8)	−11.9 (−13.2 to −11.0)	−7.2 (−8.6 to −6.1)	−2.0 (−3.7–0.0)	9.3 (7.1–17.0)	
OS						
Event/total	170/195	233/264	328/382	365/438	36/45	
Unadjusted HR (95% CI)	1.65 (1.37 to 1.98)	1.44 (1.22 to 1.69)	1.18 (1.02 to 1.38)	1 (Referent)	0.98 (0.70 to 1.38)	<.001
Adjusted 1 HR (95% CI)‡	1.55 (1.28 to 1.87)	1.40 (1.18 to 1.66)	1.15 (0.99 to 1.34)	1 (Referent)	0.99 (0.70 to 1.40)	<.001
Adjusted 2 HR (95% CI)§	1.52 (1.26 to 1.84)	1.37 (1.15 to 1.63)	1.15 (0.99 to 1.34)	1 (Referent)	1.01 (0.71 to 1.42)	<.001
PFS						
Event/total	182/195	253/264	360/382	409/438	44/45	
Unadjusted HR (95% CI)	1.26 (1.06 to 1.50)	1.28 (1.10 to 1.50)	1.02 (0.88 to 1.17)	1 (Referent)	1.08 (0.79 to 1.47)	<.001
Adjusted 1 HR (95% CI)‡	1.24 (1.03 to 1.48)	1.28 (1.09 to 1.50)	1.02 (0.88 to 1.18)	1 (Referent)	1.10 (0.81 to 1.51)	.003
Adjusted 2 HR (95% CI)§	1.23 (1.02 to 1.47)	1.25 (1.07 to 1.48)	1.02 (0.88 to 1.17)	1 (Referent)	1.14 (0.83 to 1.56)	.006

*Weight loss was measured by voluntary questionnaire completed within 4 weeks of chemotherapy initiation. The questionnaire solicited patient weight at time of questionnaire completion and patient weight 6 months prior. BMI = body mass index; CI = confidence interval; FOLFIRI = 5-fluorouracil, leucovorin, and irinotecan; HR = hazard ratio; IQR = interquartile range; mFOLFOX6 = 5-fluorouracil, leucovorin, and oxaliplatin; OS = overall survival; PFS = progression-free survival.

†Tests for trend excluded the last category for weight gain ≥5%. *P* values are 2-sided.

‡Adjusted 1: Adjusting for age (continuous years), sex (female, male), performance status (0, 1, or 2), planned chemotherapy (FOLFIRI, mFOLOFOX6), prior adjuvant chemotherapy (yes, no), prior radiation therapy (yes, no), assigned targeted-treatment arm (bevacizumab, cetuximab, bevacizumab + cetuximab), *KRAS* (wild-type, mutant, indeterminate/missing), and primary tumor location (right/transverse colon, left colon, multiple/missing).

§Adjusted 2: Adjusting for all above and physical activity (0–2.9, 3–8.9, 9–17.9, ≥18 MET h/w, missing) and comorbidity (none, any). Among patients who completed the questionnaire and reported prior weight, 2 patients were missing data for physical activity and were replaced with the majority category.

Table 6. Associations of BMI prior to treatment with mortality and disease progression in patients with advanced or metastatic colorectal cancer (n = 1324)

Variable	BMI category,* kg/m^2					P_{trend}†
	<21	21–24.9	25–29.9	30–34.9	≥35	
Median BMI (IQR), kg/m^2	19.6 (18.8–20.1)	23.4 (22.2–24.1)	27.4 (26.3–28.8)	32.2 (31.2–33.3)	38.4 (36.4-42.1)	—
OS						
Event/total	57/66	183/209	395/471	271/325	226/253	—
Unadjusted HR (95% CI)	1.16 (0.86 to 1.57)	1 (Referent)	0.88 (0.74 to 1.05)	0.87 (0.72 to 1.04)	1.02 (0.84 to 1.24)	.55
Adjusted 1 HR (95% CI)‡	1.05 (0.78 to 1.42)	1 (Referent)	0.88 (0.74 to 1.06)	0.83 (0.69 to 1.01)	0.99 (0.81 to 1.20)	.95
Adjusted 2 HR (95% CI)§	1.09 (0.80 to 1.48)	1 (Referent)	0.88 (0.73 to 1.05)	0.81 (0.67 to 0.98)	0.92 (0.75 to 1.12)	.42
PFS						
Event/total	63/66	193/209	449/471	303/325	240/253	—
Unadjusted HR (95% CI)	1.06 (0.80 to 1.41)	1 (Referent)	0.90 (0.76 to 1.07)	0.88 (0.74 to 1.06)	0.98 (0.81 to 1.19)	.93
Adjusted 1 HR (95% CI)‡	1.03 (0.77 to 1.37)	1 (Referent)	0.90 (0.76 to 1.07)	0.87 (0.72 to 1.04)	0.97 (0.80 to 1.17)	.84
Adjusted 2 HR (95% CI)§	1.02 (0.75 to 1.37)	1 (Referent)	0.88 (0.75 to 1.05)	0.84 (0.70 to 1.01)	0.91 (0.75 to 1.11)	.43

*BMI prior to treatment was calculated using height and weight data from a voluntary questionnaire completed within 4 weeks after initiation of trial therapy. On the questionnaire, patients reported their weight 6 months prior to questionnaire completion. BMI = body mass index; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FOLFIRI = 5-fluorouracil, leucovorin, and irinotecan; HR = hazard ratio; IQR = interquartile range; mFOLFOX6 = 5-fluorouracil, leucovorin, and oxaliplatin; OS = overall survival; PFS = progression-free survival.

†Tests for trend excluded patients in the lowest BMI category (<21 kg/m^2), given that underweight patients may be more likely to have poor or rapidly declining health. *P* values are 2-sided.

‡Adjusted 1: Adjusting for age (continuous years), sex (female, male), ECOG performance status (0, 1, or 2), planned chemotherapy (FOLFIRI, mFOLOFOX6), prior adjuvant chemotherapy (yes, no), prior radiation therapy (yes, no), assigned targeted-treatment arm (bevacizumab, cetuximab, bevacizumab + cetuximab), *KRAS* (wild-type, mutant, indeterminate/missing), and primary tumor location (right/transverse colon, left colon, multiple/missing).

§Adjusted 2: Adjusting for all above as well as percent weight change (loss ≥5 %, stable ±4.9%, gain ≥5%), physical activity (0–2.9, 3–8.9, 9–17.9, ≥18 MET h/w), and comorbidity (none, any). Among patients who completed the questionnaire and reported prior weight, 2 were missing data on physical activity and were replaced with the majority category.

may be mediated by hyperinsulinemia, because insulin and insulin-like growth factors have been implicated in CRC aggressiveness and treatment resistance (63).

Conducting a prospective cohort study nested within an NCI-sponsored clinical trial offers several advantages. First, all patients had advanced disease at baseline, reducing the impact of heterogeneity related to disease stage. Second, treatment and follow-up were standardized, allowing dates and nature of disease progression or mortality to be collected prospectively and accurately. Finally, detailed information on prognostic variables was collected at baseline, allowing adjustment for potential confounders.

Our study has several notable limitations. First, our study is observational and cannot exclude unmeasured confounding. However, our results were adjusted for known and potential predictors of patient outcome, including tumor characteristics, disease treatments, physical activity, and comorbidities. Second, patients enrolled in clinical trials may differ from the general population. Such patients must satisfy eligibility criteria, be selected

for the study, and be motivated to participate. However, this cohort, drawn from a large NCI-sponsored trial, included patients from representative community and academic centers throughout North America. Third, our adjustment for markers of poor or declining health were limited because a portion of our cohort did not complete the voluntary questionnaire, which inquired about weight loss, physical activity, and comorbidities. However, we would expect any residual confounding to have biased results of our BMI analysis away from the null. Interpretation of our weight change analysis is also limited by the self-reported nature of our weight change data, which can be especially biased in obese patients (64). This limitation does not apply to our analysis of BMI at time of study entry, which used measurements collected in clinic. Finally, interpretation of our findings is limited because BMI does not differentiate between muscle and adipose tissue. Future studies should aim to assess muscle and adipose tissue as independent prognostic predictors of mCRC outcome.

In summary, this prospective study of patients with mCRC embedded in a randomized, phase III clinical trial demonstrated no statistically significant association between BMI and patient mortality or disease progression. In contrast, weight loss during the 6 months prior to study entry was associated with reduced mortality and disease progression after adjusting for potential confounders. Although our study's observational nature precludes inferences of causality, our findings offer potentially prognostic information for clinical practice. Further studies are needed to confirm our findings.

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Notes

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