Impact of Body Mass Index and Weight Change After Treatment on Cancer Recurrence and Survival in Patients With Stage III Colon Cancer: Findings From Cancer and Leukemia Group B 89803

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ABSTRACT

Purpose

Obesity is a risk factor for the development of colon cancer. However, the influence of body mass index (BMI) on the outcome of patients with established colon cancer remains uncertain. Moreover, the impact of change in body habitus after diagnosis has not been studied.

Patients and Methods

We conducted a prospective, observational study of 1,053 patients who had stage III colon cancer and who were enrolled on a randomized trial of adjuvant chemotherapy. Patients reported on height and weight during and 6 months after adjuvant chemotherapy. Patients were observed for cancer recurrence or death.

Results

In this cohort of patients with stage III cancer, 35% of patients were overweight (BMI, 25 to 29.9 kg/m²), and 34% were obese (BMI ≥ 30 kg/m²). Increased BMI was not significantly associated with a higher risk of colon cancer recurrence or death (*P* trend = .54). Compared with normal-weight patients (BMI, 21 to 24.9 kg/m²), the multivariate hazard ratio for disease-free survival was 1.00 (95% CI, 0.72 to 1.40) for patients with class I obesity (BMI, 30 to 34.9 kg/m²) and 1.24 (95% CI, 0.84 to 1.83) for those with class II to III obesity (BMI ≥ 35 kg/m²) after analysis was adjusted for tumor-related prognostic factors, physical activity, tobacco history, performance status, age, and sex. Similarly, after analysis was controlled for BMI, weight change (either loss or gain) during the time period between ongoing adjuvant therapy and 6 months after completion of therapy did not significantly impact on cancer recurrence and/or mortality.

Conclusion

Neither BMI nor weight change was significantly associated with an increased risk of cancer recurrence and death in patients with colon cancer.

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INTRODUCTION

Prospective cohort studies support the relationship between adiposity and the risk of developing colon cancer.¹⁻¹² The mechanism by which obesity influences the incidence of colorectal neoplasia remains uncertain. Elevated glucose and insulin levels appear to promote the growth of adenomatous and malignant lesions in the bowel.¹³⁻¹⁵ Both body mass index (BMI) and visceral adiposity are critical determinants of insulin resistance and of hyperinsulinemia.¹⁶⁻¹⁸

Recent studies have examined the association between obesity and the risk of cancer recurrence in patients who were diagnosed with colon can-

cer. In a large, randomized trial of adjuvant chemotherapy for stages II to III colon cancer (INT 0089), obesity (BMI ≥ 30 kg/m²) was associated with a 24%, nonstatistically significant, poorer disease-free survival (DFS) compared with normal-weight women (BMI, 21 to 24.9 kg/m²).¹⁹ Among patients enrolled on two National Surgical Adjuvant Breast and Bowel Project (NSABP) adjuvant chemotherapy trials for colon cancer, very obese patients (BMI ≥ 35 kg/m²) experienced a 27% statistically significant increase in cancer recurrence or death compared with normal-weight participants.²⁰ However, because neither study updated anthropometric data after completion of adjuvant therapy, the impact

Fig 1. Derivation of cohort sizes.

of change in weight after recovery from all treatments could not be assessed. Among women who received adjuvant therapy for breast cancer, weight gain after completion of therapy has been associated with an increased risk of recurrence in some,^{21,22} though not all, studies.²³

We therefore examined the influence of body habitus on outcome among patients who participated in a large National Cancer Institute (NCI)–sponsored clinical trial of adjuvant chemotherapy for stage III colon cancer. As part of this trial, we prospectively assessed weight and other covariates at study baseline and approximately 6 months after completion of postoperative chemotherapy, and we monitored patients thereafter for cancer recurrence. Because patient eligibility, cancer treatment, and follow-up were rigorously defined by the trial, we were able to examine directly the influence of body habitus and weight gain on patient outcome while we minimized confounding by other disease and treatment characteristics.

PATIENTS AND METHODS

Study Population

Patients in this prospective cohort study were participants in the NCI-sponsored Cancer and Leukemia Group B (CALGB) adjuvant therapy trial for stage III colon cancer that compared therapy with weekly fluorouracil (FU) and leucovorin to weekly irinotecan, FU, and leucovorin (CALGB 89803).²⁴ Between April 1999 and May 2001, 1,264 patients were enrolled on the treatment trial. A self-administered questionnaire that

captured diet and lifestyle habits was given to patients midway through their adjuvant therapy (4 months after surgery) and again 6 months after completion of adjuvant therapy (14 months after surgery). After the first 87 patients were enrolled, the protocol was amended to include a survey of diet and lifestyle; only the subsequent 1,177 patients were eligible for this companion study. Figure 1 illustrates the compliance with completion of the questionnaires and derivation of the final sample sizes for both evaluation of BMI at the time of questionnaire one (Q1), BMI at time of questionnaire two (Q2), and weight change.

Patients in the treatment trial were eligible if they underwent a complete surgical resection of the primary tumor within 56 days of study entry and had regional lymph node metastases (stage III colon cancer) but had no evidence of distant metastases. Moreover, patients were required to have a baseline Eastern Cooperative Oncology Group performance status of 0 to 2²⁵ and to have adequate bone marrow, renal, and hepatic function. All patients signed informed consent, which was approved by each site's institutional review board.

Determination of Height, Weight, and BMI

In the initial study questionnaire, Q1 (during adjuvant therapy and approximately 4 months after surgery) and the follow-up questionnaire, Q2 (6 months after adjuvant therapy), patients self-reported their weight. Patients also reported their height on Q1. We compared the weight and height recorded at cancer treatment facilities (at study entry) with the patient self-reports on Q1, and we found correlations of 0.91 and 0.92 (both $P < .0001$), respectively. For consistency, we utilized self-reported weight and height for all analyses, though analyses with the weight from the treatment center did not change the associations reported. We calculated BMI (kg/m^2) by dividing the patient's squared height (meters) into the

weight (kilograms). For the primary analysis of BMI, we used cumulative averaging to determine a patient's BMI as follows:

$$\left\{ \text{BMI at Q1} \times \frac{\text{time from Q1 to Q2}}{\text{total DFS time}} \right\} + \left\{ \frac{(\text{BMI at Q1} + \text{BMI at Q2})}{2} \times \frac{\text{time from Q2 to total DFS time}}{\text{total DFS time}} \right\}$$

BMI categories were created on the basis of WHO classifications and prior analyses.^{19,26} Change in weight was calculated by subtracting the patient's weight at Q2 from the weight at Q1 for patients that completed both Q1 and Q2 ($n = 836$).

Study End Points

In analyses of BMI, the primary end point was DFS, which was defined as the time from the completion of Q1 to tumor recurrence, occurrence of a new primary colon tumor, or death from any cause. We defined recurrence-free survival (RFS) as the time from the completion of Q1 to tumor recurrence or occurrence of a new primary colon tumor. For RFS, patients who died without known tumor recurrence were censored at last documented evaluation by the treating provider. Overall survival (OS) was defined as the time from the completion of Q1 to death from any cause. For analyses of weight change, all end points began at the time of completion of Q2. To avoid biases caused by declining health and possible weight changes immediately before recurrence or death, we excluded patients who had either a cancer recurrence or who died within 90 days of Q1 (for BMI analyses) or Q2 (for weight change analyses).

Statistical Analyses

During interim analysis of the treatment trial, it was determined that no difference in either DFS or OS would be observed between the treatment arms.²⁷ Data for patients in both treatment arms were combined and analyzed in BMI and weight-change categories. Cox proportional hazards regression²⁸ was used to determine the simultaneous impact of potential confounders. We conducted our primary analyses by using cumulative averaging of BMI and physical activity. Other potential confounders also were entered into the model as fixed covariates. Covariates with missing variables were coded with indicator variables in adjusted models. Because we observed a quadratic shape to the relationship between BMI and outcomes, we modeled BMI + BMI,² similar to prior reports.²⁰ A level of significance less than .05 was considered statistically significant. All P values were two-sided and were not adjusted for multiple comparisons.

Patient registration and clinical data collection were managed by the CALGB Statistical Center, and all analyses were based on the study database that was frozen on May 19, 2006.

RESULTS

Baseline Characteristics

Study participants were drawn from a multicenter study of post-operative adjuvant chemotherapy in patients with stage III colon cancer who underwent a curative-intent surgical resection. Within our cohort, 35% of patients were overweight (BMI, 25 to 29.9 kg/m²), and 34% were obese (BMI ≥ 30 kg/m²). Table 1 represents baseline patient characteristics according to updated BMI and weight change between the Q1 and Q2. Underweight (BMI < 21 kg/m²) patients were less likely to be men but were more likely to be current smokers, whereas overweight (BMI, 25 to 29.9 kg/m²) and obese (BMI ≥ 30 kg/m²) patients were more likely to be men, be younger, be less physically active, have well- to moderately differentiated tumors, have less extension through bowel wall, and have greater weight change. There were no significant differences in the number of positive lymph nodes, the number of lymph nodes sampled or node ratio, clinical bowel perforation at time of surgery, race, or treatment arm on the basis of BMI.

We did not observe any consistent linear trends in baseline characteristics by weight change between Q1 and Q2. Although the num-

ber of positive lymph nodes, smoking status, and treatment arm all appeared to differ significantly according to categories of weight change, the relations that emerged were principally U-shaped and had comparable values at the extreme categories of weight change.

Impact of BMI on Cancer Recurrences or Death

After a median follow-up from completion of Q1 of 5.3 years, 369 of the 1,053 eligible patients experienced cancer recurrence, and 261 patients died. We did not observe any statistically significant differences in DFS, RFS, and OS with increasing BMI (Table 2 and Fig 2). Compared with normal-weight patients (BMI, 21 to 24.9 kg/m²), the multivariate hazard ratio for cancer recurrence or death (DFS) was 1.00 (95% CI, 0.72 to 1.40) for patients with WHO class I obesity (BMI, 30 to 34.9 kg/m²) and was 1.24 (95% CI, 0.84 to 1.83) for those with class II to III obesity (BMI ≥ 35 kg/m²). We conducted our primary analyses with cumulative averaging of BMI, and we utilized data from both Q1 and Q2. However, when we repeated our analysis with only baseline BMI, the results were similar; the hazard ratio for DFS in patients with a BMI of 30 to 34.9 kg/m² was 1.05 (95% CI, 0.75 to 1.48) and was 1.29 (95% CI, 0.86 to 1.91) for patients with a BMI of ≥ 35 kg/m² compared with patients who had a BMI of 21 to 25 kg/m².

We examined whether the influence of BMI on patient outcome was significantly modified by any baseline patient or disease characteristics. Among men, the hazard ratio for DFS in those with a BMI of 30 to 34.9 kg/m² was 1.04 (95% CI, 0.66 to 1.63) and was 1.41 (95% CI, 0.83 to 2.41) in those who had a BMI ≥ 35 kg/m² compared with normal-weight men. Among women, the hazard ratio for DFS in those with a BMI of 30 to 34.9 kg/m² was 1.07 (95% CI, 0.64 to 1.80) and was 1.11 (95% CI, 0.61 to 2.02) in those with a BMI of ≥ 35 kg/m² compared with normal-weight women. The P value for the interaction between sex and BMI was not significant ($P = .31$). Beyond sex, the effect of BMI on DFS was not significantly different for patients who exercised regularly compared with those who were relatively sedentary ($P_{\text{interaction}} = .98$). Similarly, the relation between BMI and DFS was not modified by age ($P_{\text{interaction}} = .82$), baseline performance status ($P_{\text{interaction}} = .86$), number of positive lymph nodes ($P_{\text{interaction}} = .92$), or treatment arm ($P_{\text{interaction}} = .29$).

Impact of Weight Change on Cancer Recurrence or Death

In addition, we examined patient outcome according to change in weight as measured from Q1 to Q2. To minimize any potential bias by an undetected cancer recurrence or other life-threatening condition, we excluded recurrence or death that occurred within 90 days of completion of Q2. As listed in Table 3, neither weight loss or weight gain was significantly associated with DFS, RFS, or OS. If we did not exclude recurrence or death that occurred within the first 90 days, greater weight loss between Q1 and Q2 was associated with a poorer outcome (hazard ratio for DFS, 1.87; 95% CI, 1.02 to 3.41 for patients who experienced a weight loss of ≥ 5 kg compared with patients who had a weight change < 2 kg; P trend = .007). In addition, weight change was not associated with outcome even among baseline BMI subgroups (data not shown).

We tested whether more extremes of weight gain (10 or 20 kg) would impact DFS. Patients who gained 10 or more kilograms ($n = 391$) had an adjusted hazard ratio for DFS of 1.11 (95% CI, 0.60 to 2.32) compared with those who maintained weight within 2 kilograms. Similarly, the adjusted hazard ratio for patients who gained 20 or more kilograms ($n = 135$) was 1.11 (95% CI, 0.63 to 1.95). We did not detect any interactions between weight gain and

Table 1. Baseline Characteristics by Initial Body Mass Index and Weight Change After Completion of Therapy

Characteristic	Body Mass Index (kg/m ²)					P*	Weight Change Between Q1 and Q2 (kg)					P*
	< 21	21-24.9	25-29.9	30-34.9	≥ 35		> 5 Loss	2.1-5 Loss	± 2	2-4.9 Gain	≥ 5 Gain	
No. of patients	68	258	369	236	122		47	42	105	104	538	
% of total cohort	6	25	35	22	12		6	5	13	12	64	
Body mass index, kg/m ²	19.7	23.4	27.4	32.2	37.8	< .0001						
Median weight change, kg	5	6	7	8	10	.02	-9	-4	0	3	12	< .0001
Age, years	64	63	61	60	55	< .0001	59	60	59	62	60	.82
Sex, % male	38	47	66	60	46	< .0001	64	60	59	49	56	.43
Ethnicity, %						.19						.89
White	89	90	88	90	82		92	86	92	92	88	
Black	7	6	6	8	11		6	9	4	4	8	
Other	4	4	6	2	7		2	5	4	4	4	
Baseline performance status, %						.04						.08
0	63	75	79	76	71		62	71	82	79	76	
1-2	37	25	21	24	29		38	29	18	21	24	
Smoking status, %						.05						.006
Current	15	12	10	4	5		6	17	9	12	6	
Past	43	40	48	48	48		49	26	42	55	46	
Never	42	48	42	48	47		45	57	49	33	48	
Number of positive nodes (%)						.18						.04
1-3	63	66	62	64	75		66	52	78	66	68	
≥ 4	37	34	38	36	25		34	48	22	34	32	
Median No. of nodes examined	11	13	12	12	13	.27	12	13	12	14	12	.40
Ratio of No. of positive lymph nodes to No. of examined nodes	0.25	0.25	0.25	0.22	0.17	.09	0.21	0.32	0.17	0.23	0.22	.11
T stage extent through bowel wall, %						.01						.40
T1-2	21	10	12	16	21		17	5	16	15	16	
T3-4	79	90	88	84	79		83	95	84	85	87	
Bowel perforation, %	6	4	4	5	6	.84	2	0	4	5	4	.65
Clinical bowel obstruction, %	30	26	22	15	29	.009	22	21	22	19	23	.97
Serum CEA ≥ 5 ng/mL	13	7	7	6	7	.29	2	5	1	8	5	.18
Grade of differentiation, %						.003						.22
Well	9	6	5	3	11		9	10	9	5	5	
Moderate	69	65	71	81	69		80	64	72	65	73	
Poor	22	29	24	16	20		11	26	19	30	22	
Treatment arm, %						.34						.002
IFL	46	47	52	52	44		53	71	61	53	46	
FU/LV	54	43	48	48	56		47	29	39	47	54	
Physical activity in MET, h/wk												
Q1	4.9	5.2	6.1	4.4	2.0	< .0001	5.7	4.2	8.1	6.4	4.0	.005
Q2	7.8	8.9	8.2	6.3	3.2	.0004	8.7	7.6	11.1	12.5	6.5	.02

NOTE. Q1 represents questionnaire one, which was administered during adjuvant therapy; Q2 represents questionnaire two, which was administered 6 months after completion of adjuvant therapy.

Abbreviations: CEA, carcinoembryonic antigen; IFL, irinotecan, bolus fluorouracil, and leucovorin; FU, fluorouracil; LV, leucovorin; MET, metabolic equivalent tasks.

*P values were obtained by two-sided χ^2 testing.

sex ($P_{\text{interaction}} = .22$), level of physical activity ($P_{\text{interaction}} = .09$), or initial BMI ($P_{\text{interaction}} = .84$).

We also considered change in BMI, as utilized in other analyses in breast cancer.²² The hazard ratio for DFS was 1.32 (95% CI, 0.73 to 2.38) for patients whose BMI decreased by 0.5 to 2.0 kg/m² and was 1.44 (95% CI, 0.59 to 2.54) for those whose BMI decreased by greater than 2.0 kg/m² compared with patients who maintained their BMI within 0.5 kg/m². Similarly, there were no significant differences in DFS for patients with BMI increases of 0.5 to 2.0 kg/m² (hazard ratio, 1.26; 95% CI, 0.81 to 1.94) nor for those with BMI increases of greater than 2.0 kg/m² (hazard ratio, 1.05; 95% CI, 0.65 to 1.69).

DISCUSSION

Among patients enrolled on an NCI-sponsored clinical trial of postoperative adjuvant chemotherapy for stage III colon cancer, we did

not observe any significant associations between BMI and cancer recurrence and mortality. Similarly, weight gain after completion of adjuvant therapy did not negatively impact survival for patients with stage III colon cancer.

In CALGB 89803, data on weight, smoking habits, physical activity, diet, and other factors were collected prospectively shortly after study initiation and approximately 6 months after the completion of therapy. Because such patient behavior and lifestyle habits may change over time, particularly in the period after adjuvant therapy, repeated measurements of diet, lifestyle, and anthropometric factors may reduce misclassification with time and may better reflect the influence of these factors on cancer recurrence and survival. By using updated assessments of body habitus, we did not find a statistically significant association between BMI and cancer recurrence or mortality. However, our results are similar to those of Dignam et al,²⁰ who reported adjusted hazard ratios of 1.06 (95% CI, 0.93 to 1.21) for patients with

Table 2. Cancer Recurrence and Mortality According to Body Mass Index

	Body Mass Index (kg/m ²)					
Recurrence and Mortality	< 21	21-24.9	25-29.9	30-34.9	≥ 35	P*
Disease-free survival†						
No. of events	27	90	117	85	50	
No. at risk	68	258	369	236	112	
Unadjusted HR	1.13	Reference	0.86	1.00	1.18	.86
Unadjusted 95% CI	0.73 to 1.73		0.66 to 1.14	0.75 to 1.35	0.84 to 1.67	
Adjusted HR‡	1.35	Reference	0.81	1.00	1.24	
Adjusted 95% CI	0.86 to 2.13		0.59 to 1.11	0.72 to 1.40	0.84 to 1.83	
Recurrence-free survival§						
No. of events	23	83	104	79	49	
No. at risk	68	258	369	236	112	
Unadjusted HR	1.04	Reference	0.83	1.01	1.25	.65
Unadjusted 95% CI	0.65 to 1.64		0.62 to 1.11	0.74 to 1.38	0.88 to 1.78	
Adjusted HR‡	1.22	Reference	0.75	0.97	1.27	
Adjusted 95% CI	0.75 to 1.98		0.54 to 1.03	0.69 to 1.37	0.85 to 1.89	
Overall mortality						
No. of events	17	69	85	60	30	
No. at risk	68	258	369	236	112	
Unadjusted HR	0.91	Reference	0.84	0.93	0.88	.63
Unadjusted 95% CI	0.53 to 1.54		0.61 to 1.15	0.66 to 1.31	0.58 to 1.36	
Adjusted HR‡	1.07	Reference	0.72	0.90	0.87	
Adjusted 95% CI	0.61 to 1.87		0.50 to 1.03	0.61 to 1.34	0.54 to 1.42	

Abbreviation: HR, hazard ratio.

*Likelihood-ratio test (two-sided) for the body mass index term for continuous functional form: BMI + BMI².

†Measured by cancer recurrence or death from any cause.

‡Analyses were adjusted for sex, age, depth of invasion through bowel wall (T1-2 v T3-4), number of positive lymph nodes (1-3 v ≥ 4), presence of clinical perforation at time of surgery, presence of bowel obstruction at time of surgery, baseline performance status (0 v 1-2), treatment arm, weight change between first and second questionnaire, smoking status at time of second questionnaire (current, past, and never), and physical activity level.

§Measured by cancer recurrence.

a BMI of 30 to 34.9 kg/m² and of 1.27 (95% CI, 1.05 to 1.53) for those with a BMI of 35 kg/m² or greater. In comparison, we found hazard ratios of 1.00 (95% CI, 0.72 to 1.40) and 1.24 (95% CI, 0.84 to 1.83), respectively. The difference in statistical significance between these two studies could be related to the power of each study (2,074 events in 4,288 patients in the study by Dignam et al compared with 369 events in 1,053 patients in this study). Additional, treatment in the two trials evaluated by Dignam et al required dose capping with a maximum

body surface area of 2.0 m²;²⁰ thus, the very obese patients in their analyses may have received suboptimal adjuvant therapy.

Obesity and sedentary lifestyle have been shown fairly consistently to increase the risk of developing colorectal cancer.^{29,30} Until recently, few studies had addressed whether these factors influence the outcomes of survivors of colorectal cancer. Because increased circulating levels of insulin and free insulin-like growth factor 1 have been associated with obesity and physical inactivity,^{14,31,32} and because both insulin and insulin-like growth factor 1 promote cell proliferation and inhibit apoptosis in colon cancer cells,³³⁻³⁶ one could hypothesize that such lifestyle factors may influence the risk of colon cancer recurrence by promoting growth of micrometastases through insulin-related growth factors.

We recently reported a beneficial association between physical activity and outcomes in colon cancer survivors with two prospective cohorts, including CALGB 89803.^{37,38} In both reports, BMI did not influence the benefits of exercise. Conversely, in this analysis, physical activity did not significantly modify the lack of association between BMI and DFS.

Three other recent studies have demonstrated that obesity may be associated with colon cancer recurrence and mortality.^{19,20,39} Haydon et al³⁹ found that waist circumference was the most predictive measure of adiposity, as a 20% increase in risk of disease recurrence or death was noted for every 10-cm increase in circumference.³⁹ Two other studies^{19,20} utilized height and weight data collected from NCI-sponsored cooperative group studies of adjuvant therapy in patients with stages II to III disease, though neither study could

Fig 2. Disease-free survival by body mass index (BMI).

Table 3. Impact of Weight Change on Recurrences and Survival

Recurrence and Survival	Weight Change (kg)					P	
	> 5 Loss	2.1-5 Loss	± 2	2-4.9 Gain	≥ 5 Gain	Weight Loss Trend	Weight Gain Trend
Disease-free survival*							
No. of events	14	11	20	22	126		
No. at risk	47	42	105	104	538		
Unadjusted HR	1.65	1.43	Reference	1.15	1.31	.02	.41
Unadjusted 95% CI	0.84 to 3.28	0.69 to 2.99		0.63 to 2.11	0.82 to 2.10		
Adjusted HR†	1.39	1.15	Reference	1.11	1.19	.13	.90
Adjusted 95% CI	0.69 to 2.79	0.54 to 2.44		0.60 to 2.06	0.73 to 1.94		
Recurrence-free survival‡							
No. of events	12	9	18	18	116		
No. at risk	47	42	105	104	538		
Unadjusted HR	1.55	1.29	Reference	1.04	1.34	.02	.34
Unadjusted 95% CI	0.75 to 3.22	0.58 to 2.87		0.54 to 2.00	0.81 to 2.19		
Adjusted HR†	1.35	1.04	Reference	1.00	1.17	.07	.98
Adjusted 95% CI	0.64 to 2.81	0.46 to 2.35		0.52 to 1.95	0.70 to 1.96		
Overall mortality							
No. of events	7	5	12	12	75		
No. at risk	47	42	105	104	538		
Unadjusted HR	1.29	1.11	Reference	1.07	1.30	.43	.60
Unadjusted 95% CI	0.51 to 3.29	0.39 to 3.14		0.48 to 2.38	0.71 to 2.39		
Adjusted†	1.13	0.89	Reference	0.97	1.23	.53	.85
Adjusted 95% CI	0.44 to 2.93	0.31 to 2.57		0.43 to 2.18	0.65 to 2.31		

Abbreviation: HR, hazard ratio.

*Measured by cancer recurrence or death from any cause.

†Analyses were adjusted for sex, age, depth of invasion through bowel wall (T1-2 v T3-4), number of positive lymph nodes (1-3 v ≥ 4), presence of clinical perforation at time of surgery, presence of bowel obstruction at time of surgery, baseline performance status (0 v 1-2), treatment arm, time between questionnaire one and questionnaire two, time-varying body mass index, smoking status at time of questionnaire two (current, past, and never), and physical activity level.

‡Measured by cancer recurrence.

account for other factors that could confound the results (eg, smoking and physical activity).

In contrast with studies of patients with early-stage breast cancer, weight gain after adjuvant therapy in this study did not significantly influence survival. One hypothesis of the negative impact of weight gain in women with breast cancer is that such gain will increase circulating estrogens. In the survivors of colon cancer, estrogen may be protective, as seen in a recent analysis of hormone replacement therapy in survivors of colorectal cancer.⁴⁰ Nonetheless, there was no interaction with sex and weight change in this study. In contrast, although weight loss did not affect outcomes in our primary analyses, weight loss was significantly associated with poorer outcomes when we included patients whose disease recurred or who died within 90 days of Q1. Such a result confirms the utility of restrictions in the analyses of factors that may be a result of, rather than the cause of, an outcome.

Patients who enroll on randomized trials may differ from the population at-large. However, the distribution of BMI in our cohort is similar to that of the general population.⁴¹ Compared with the National Health and Nutrition Examination Survey (NHANES), our cohort had similar prevalence of overweight status (BMI, 25 to 29.9 kg/m²; 34% in NHANES and 36% in CALGB 89803) and obesity (BMI ≥ 30 kg/m²; 30.5% in NHANES and 30.5% in CALGB 89803).

Several potential limitations for our study should be considered. In this study, we could only assess obesity by BMI and not other measures of body habitus, such as waist-hip ratio or waist circumference. In some studies, these measures were more predictive of the risk of developing colon cancer than BMI.^{3,4} Such measures of body hab-

itus may better distinguish abdominal adiposity, which has been correlated with serum insulin level. Another limitation is that we assessed weight change up to 6 to 8 months after the completion of adjuvant therapy. Whether longer follow-up of weight change would influence outcomes cannot be addressed in this study.

Although our study did not reach statistical significance, this is the second NCI-sponsored intergroup study of adjuvant chemotherapy for colon cancer to demonstrate an approximately 25% increased risk of cancer recurrence and survival in patients with resected colon cancer who had a BMI ≥ 35 kg/m² (class II to III obesity). Of greatest concern is the rising incidence of obesity in the United States in the last two decades.⁴¹ Patients enrolled on the study of Dignam et al²⁰ were diagnosed with colon cancer between 1989 and 1994, whereas those in this study were diagnosed between 1999 and 2001. In the Dignam study, 5.5% of patients were classified as class II to III obesity. One decade later, in this study, 11.6% of patients had class II to III obesity. Thus, if the 25% increase is the true relationship between class II to III obesity and cancer recurrence and mortality, an increasing trend in obesity will be an important prognostic factor. Future research is necessary to better understand the impact of obesity on survivors of colon cancer and whether interventions among obese survivors of colon cancer will improve overall outcomes.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Conception and design: Jeffrey A. Meyerhardt, Leonard B. Saltz, Charles S. Fuchs

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).