

Association of Dietary Patterns With Cancer Recurrence and Survival in Patients With Stage III Colon Cancer

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EPIDEMIOLOGICAL AND SCIENTIFIC research indicates that diet and other lifestyle factors have a significant influence on the risk of developing colon cancer.^{1,2} However, the influence of diet and other lifestyle factors on the outcome of patients with established colon cancer is largely unknown. Patients diagnosed with cancer are highly motivated to seek information about diet, physical activity, dietary supplement use, and nutritional complementary therapies.³⁻⁶ Two randomized controlled trials of patients with early stage breast cancer have provided mixed results on the impact of dietary changes after diagnosis and breast cancer outcomes.^{7,8} In contrast, few studies have assessed the influence of diet on colon cancer recurrence and survival.

Factor analysis has been used to examine overall dietary patterns beyond individual foods and nutrients and the risk of several cancers.⁹⁻¹² Specific dietary patterns have been associ-

Context Dietary factors have been associated with the risk of developing colon cancer but the influence of diet on patients with established disease is unknown.

Objective To determine the association of dietary patterns with cancer recurrences and mortality of colon cancer survivors.

Design, Setting, and Patients Prospective observational study of 1009 patients with stage III colon cancer who were enrolled in a randomized adjuvant chemotherapy trial (CALGB 89803) between April 1999 and May 2001. Patients reported on dietary intake using a semiquantitative food frequency questionnaire during and 6 months after adjuvant chemotherapy. We identified 2 major dietary patterns, prudent and Western, by factor analysis. The prudent pattern was characterized by high intakes of fruits and vegetables, poultry, and fish; the Western pattern was characterized by high intakes of meat, fat, refined grains, and dessert. Patients were followed up for cancer recurrence or death.

Main Outcome Measures Disease-free survival, recurrence-free survival, and overall survival by dietary pattern.

Results During a median follow-up of 5.3 years for the overall cohort, 324 patients had cancer recurrence, 223 patients died with cancer recurrence, and 28 died without documented cancer recurrence. A higher intake of a Western dietary pattern after cancer diagnosis was associated with a significantly worse disease-free survival (colon cancer recurrences or death). Compared with patients in the lowest quintile of Western dietary pattern, those in the highest quintile experienced an adjusted hazard ratio (AHR) for disease-free survival of 3.25 (95% confidence interval [CI], 2.04-5.19; *P* for trend <.001). The Western dietary pattern was associated with a similar detriment in recurrence-free survival (AHR, 2.85; 95% CI, 1.75-4.63) and overall survival (AHR, 2.32; 95% CI, 1.36-3.96), comparing highest to lowest quintiles (both with *P* for trend <.001). The reduction in disease-free survival with a Western dietary pattern was not significantly modified by sex, age, nodal stage, body mass index, physical activity level, baseline performance status, or treatment group. In contrast, the prudent dietary pattern was not significantly associated with cancer recurrence or mortality.

Conclusions Higher intake of a Western dietary pattern may be associated with a higher risk of recurrence and mortality among patients with stage III colon cancer treated with surgery and adjuvant chemotherapy. Further studies are needed to delineate which components of such a diet show the strongest association.

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ated with the development of colorectal cancer in case-control and cohort studies.¹³⁻¹⁸ In 2 large prospective cohort studies, increasing consumption of a Western diet (characterized by higher intakes of red and processed meats, sweets and desserts, french fries, and refined grains) was associated with a significantly increased risk of colon cancer whereas a prudent diet (higher intakes of fruits, vegetables, legumes, fish, poultry, and whole grains) was nonsignificantly associated with a reduced risk.^{13,16}

We therefore examined the influence of 2 distinct dietary patterns, Western and prudent, on cancer recurrence and survival in a large cohort of stage III colon cancer patients enrolled in a clinical trial of postoperative adjuvant chemotherapy sponsored by the National Cancer Institute (NCI).¹⁹ Within this trial, we prospectively collected extensive data on dietary and supplement intake, height, weight, physical activity, medication use, smoking, and family history that were updated during the conduct of the trial. Moreover, because data on pathological stage, performance status, postoperative treatment, and follow-up were carefully captured in this trial, the simultaneous effect of disease characteristics and the use of adjuvant therapy could be assessed.

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 comparing therapy with weekly fluorouracil and leucovorin to therapy with weekly irinotecan, fluorouracil, and leucovorin (CALGB 89803).¹⁹ Between April 1999 and May 2001, 1264 patients were enrolled in the treatment trial. A self-administered questionnaire capturing diet and lifestyle habits was given to patients midway through their adjuvant therapy (4 months following surgical resection), and 6 months after completion of adjuvant therapy (14 months af-

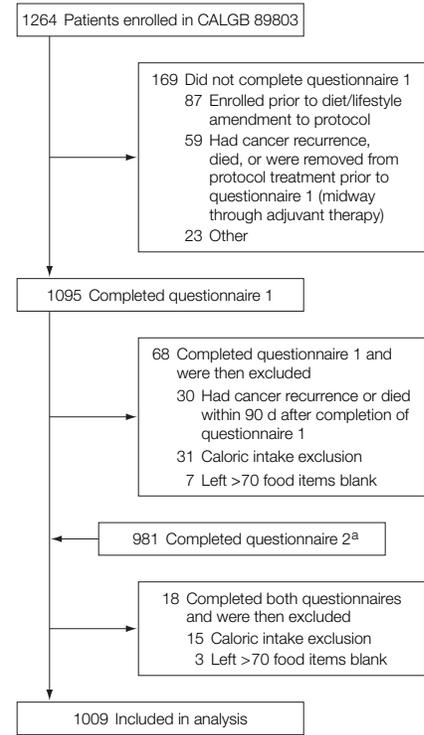
ter surgical resection). As an amendment to the protocol, a survey of diet and lifestyle was activated after the first 87 patients were enrolled; therefore, only the subsequent 1177 patients were offered the diet and lifestyle companion study. The FIGURE illustrates the adherence with completion of the questionnaires and derivation of the final sample size of 1009 patients for this study. To be included in these analyses, patients had to have completed at least questionnaire 1, reported realistic caloric intake, and have less than 70 blank items (of 131) on the food frequency questionnaires (the median number of missing items was 1 for the first questionnaire and 0 for the second questionnaire). Race or ethnicity was self-reported and recorded in the hospital database at each participating center. These data were reported by each participating center to the CALGB Statistical Center.

Patients in the treatment trial (and thus this companion study) were eligible if they underwent a complete surgical resection of the primary tumor within 56 days of study entry, had regional lymph node metastases (stage III colon cancer), but no evidence of distant metastases. Moreover, patients were required to have a baseline Eastern Cooperative Oncology Group performance status of 0 to 2 (ambulatory)²⁰ and have adequate bone marrow, renal, and hepatic function. All patients signed informed consent, approved by each site's institutional review board.

Dietary Assessment

Patients in these analyses completed semiquantitative food frequency questionnaires (SFFQ) developed, tested, and refined by Willett et al.^{21,22} Patients completed the SFFQ in the middle of their adjuvant chemotherapy course and approximately 6 months after the completion of adjuvant therapy. The questionnaire included 131 food items, vitamin and mineral supplements, and open-ended sections for other supplements and foods not specifically listed. Our ques-

Figure. Derivation of Cohort Size



CALGB indicates Cancer and Leukemia Group B.

^aTo be included for these analyses, patients only had to complete questionnaire 1. However, if they did go on to complete questionnaire 2 and had caloric intake exclusion or more than 70 items blank, they were not included in the analyses.

tionnaire was modified to inquire on average food intake during the immediate past 3 months. We inquired about the exact breakfast cereal, multivitamin supplement, margarine, and vegetable oil used for frying or baking. For each food, a commonly used unit or portion size (eg, 1 egg or slice of bread) was specified, and participants were asked how often, on average over the past 3 months, they consumed that amount of each food. There were up to 9 possible responses, which ranged from never to 6 or more times per day. We computed nutrient intakes by multiplying the frequency of consumption of each food by the nutrient content of the specified portions, using composition values from Department of Agriculture sources supplemented with other data, includ-

ing the components of specific vitamins and breakfast cereals.²³ We included supplements to total intake of specific nutrients. All nutrient values were energy-adjusted using the residuals method.²⁴ We have previously validated this SFFQ among cancer patients receiving chemotherapy.²⁵

Determination of Dietary Patterns

To identify dietary patterns, we applied factor analysis to data from the SFFQ in each cohort. Food items on the questionnaires were grouped into 39 predefined food groups (TABLE 1), as previously reported.^{9,10,13,16} Food items similar in nutrient profile were combined (eg, spinach, iceberg or head let-

tuce, and romaine or leaf lettuce were combined into “green leafy vegetables”). Certain food items were not combined if their nutrient profile was unique (eg, pizza). Patients who completed the first questionnaire were included in these analyses. The median time from study entry (which had to be within 8 weeks of surgery) to completion of the first questionnaire was 3.5 months (95% range, 2.5-5.0 months). Only patients who did not experience recurrence or die before the first questionnaire were included in these analyses. To avoid biases due to declining health immediately before recurrence or death, we also excluded from analyses patients who experienced either event within 90 days following the dietary assessment (Figure). We updated dietary exposures based on the results of the second questionnaire using cumulative averaging as previously described,²⁶ but weighted proportional to the time between the first and the second questionnaire and then the time between the second questionnaire and the disease-free survival period. For example, if a patient completed the first questionnaire at 4 months, the second questionnaire at 14 months, and had a cancer recurrence at 30 months, the total time between the first questionnaire and cancer recurrence was 26 months and 38% of that time was between the first and the second questionnaire and 62% of that time was between the second questionnaire and the recurrence. We therefore calculated the intake of total fruit as follows: total fruit = (total fruit at first questionnaire × 0.38) + [(total fruit at first questionnaire + total fruit at second questionnaire)/2] × 0.62}.

Factor analysis (principal component) was conducted using the factor procedure in SAS software (version 9.1, SAS Institute Inc, Cary, North Carolina). The factors were rotated by an orthogonal transformation (Varimax rotation function in SAS). Factor analysis aggregates correlated variables. The obtained factors are linear combinations of the included variables, explaining as much variation in the original vari-

Table 1. Pearson Correlation Coefficients for the Relationship Between Food Intake and Factors Representing Dietary Patterns^a

Food Grouping	Pattern 1 (Prudent Diet)	Pattern 2 (Western Diet)
Vegetables ^b	0.72	
Leafy vegetables	0.71	
Yellow vegetables	0.67	
Cruciferous vegetables	0.65	
Legumes	0.56	
Fruit	0.55	
Light salad dressing	0.48	
Tomatoes	0.46	0.36
Garlic	0.39	
Fish	0.46	
Poultry	0.37	
Fruit juice	0.35	
Whole grains	0.32	
Low-fat mayonnaise	0.31	
Wine	0.19	
Tea	0.16	
Diet beverages ^a		
High-fat dairy		0.67
Low-fat dairy		0.64
Refined grains		0.60
Condiments		0.51
Red meat		0.53
Sweets and desserts		0.53
Margarine		0.50
Processed meat		0.45
Potatoes	0.17	0.45
Regular mayonnaise		0.35
Butter		0.33
French fries	-0.16	0.37
Eggs		0.30
Snacks ^c		0.36
Nuts		0.30
Coffee		0.29
Sugar beverages	-0.15	0.29
Beer		0.22
Cream soup or chowder	0.16	0.25
Pizza		0.26
Regular salad dressing	0.19	0.19
Liquor ^a		

^aWith the orthogonal rotation used, correlation coefficients are identical to the factor loading matrix; to simplify data presentation, loadings with absolute values of less than 0.15 are not shown.

^bVegetables other than yellow, cruciferous, or green leafy vegetables.

^cPotato or corn chips, crackers, or popcorn.

ables as possible. We retained 2 factors, based on an eigenvalue of more than 1.5 and the interpretability of the derived factors, and we labeled these 2 factors as the prudent and Western patterns, as previously described.^{9,10,13,27-30} These terms have been extensively reported in the literature and thus were retained for consistency with other studies. The individual scores for the 2 patterns represent the values estimated for each participant based on their intake of foods and the factor loadings of the foods (ie, correlations with the patterns). Determinations of dietary pattern scores were blinded to patient and tumor characteristics and survival end points.

The validity and reproducibility of the dietary pattern scores were previously examined in a cohort of 127 healthy men.⁹ The Pearson correlation coefficient for a comparison between 2 food frequency questionnaires (administered 1 year apart) and diet records (corrected for week-to-week variation in the diet records) ranged from 0.45 to 0.74 for the prudent and Western dietary patterns, respectively.

Study End Points

In this ancillary study, the primary end point was disease-free survival, defined as time from the completion of SFFQ to tumor recurrence, occurrence of a new primary colon tumor, or death from any cause. In addition, we defined recurrence-free survival as the time from the completion of the first questionnaire to tumor recurrence or occurrence of a new primary colon tumor. For recurrence-free survival, patients who died without known tumor recurrence were censored at last documented evaluation by treating physician. Finally, overall survival was defined as the time from the completion of the first questionnaire to death from any cause.

Statistical Analyses

In the treatment trial (comparing 2 chemotherapy regimens), there was no statistical difference in either disease-free or overall survival between the treat-

ment groups.¹⁹ Therefore, data for patients in both treatment groups were combined and analyzed according to quintiles of each dietary pattern. Cox proportional hazards regression³¹ was used to determine the simultaneous impact of other variables potentially associated with outcome. We used time-varying covariates to adjust for total calories, physical activity, and body mass index (calculated as weight in kilograms divided by height in meters squared) with updating from the second questionnaire. Other covariates (including age at study entry, sex, number of positive lymph nodes, baseline performance status, presence of bowel perforation or obstruction at time of surgery, smoking history, treatment group, and weight change between the first and second questionnaire) were also entered into the model as fixed covariates. Covariates with missing variables were coded with indicator variables in adjusted models. We tested for linear trends across quintiles of dietary pattern by assigning each participant the median value for the quintile and modeling this value as a continuous variable, consistent with prior studies.^{10,29,30} The Cox regression models were tested for and met the assumption of proportionality. A level of significance of less than .05 was considered statistically significant. All *P* values are 2-sided and were not adjusted for multiple comparisons.

The sample size for the cohort was determined by the clinical trial comparing 2 chemotherapy regimens for patients with stage III colon cancer. However, in a post hoc calculation of power based on the known sample size and number of events for disease-free survival for these analyses, we had 80% power to detect hazard ratios (HRs) of 0.6 (protective) or 1.7 (detrimental) and 95% power to detect HRs of 0.5 and 2.0, comparing the highest with the lowest quintiles.

Patient registration and clinical data collection were managed and analyses were conducted by the CALGB Statistical Center. All analyses were based on the study database that was frozen on March 7, 2007.

RESULTS

Baseline Characteristics

Study participants were drawn from a multicenter study of postoperative adjuvant chemotherapy in patients with stage III colon cancer who underwent a curative-intent surgical resection. We identified 2 major dietary patterns with the factor analysis procedure. The first pattern (prudent) was characterized by high intakes of fruits, vegetables, whole grains, legumes, poultry, and fish and the second pattern (Western) was characterized by refined grains, processed and red meats, desserts, high-fat dairy products, and french fries (Table 1). For both patterns, the higher scores (and thus higher quintile) are indicative of higher intake of that particular diet. Of note, prudent and Western patterns were not correlated (Spearman correlation coefficient $r=0.02$).

Higher prudent pattern scores were detected in patients who were more physically active (both at the first and second questionnaire), had lower body mass index 6 months after adjuvant therapy (second questionnaire) and less likely to currently smoke cigarettes. Females also tended to have a more prudent dietary pattern. Higher Western pattern scores were seen in men, whites, and past or current smokers. Physical activity levels recorded 6 months after adjuvant therapy did not correlate with the Western dietary pattern, although patients with higher Western pattern scores were relatively more active than those with lower Western pattern scores during adjuvant therapy (first questionnaire). In contrast, other characteristics, particularly tumor characteristics known to predict prognosis, did not vary significantly by quintiles of either dietary pattern scores (TABLE 2 and TABLE 3). Similarly, weight change between the first and second questionnaire was not significantly associated with either pattern.

Western Dietary Pattern and Cancer Recurrence or Death

The median follow-up from the time of completion of the first questionnaire was 5.3 years. In total, 324 of the 1009

patients included in this analysis had cancer recurrence, 223 patients died with cancer recurrence, and 28 died without documented cancer recurrence.

The predefined, primary study end point of this analysis was disease-free survival (cancer recurrence or death from any cause). Higher intake of a

Western dietary pattern among patients who survived without disease progression 3 months after completion of the first questionnaire was as-

Table 2. Baseline Characteristics of 1009 Patients by Quintile for Prudent Dietary Pattern^a

	Prudent Pattern Quintile ^b					P Value ^c
	1 (n = 201)	2 (n = 202)	3 (n = 202)	4 (n = 202)	5 (n = 202)	
Physical activity, median (range), MET h/wk						
Questionnaire 1	2.5 (0 to 114.2)	3.9 (0 to 112.7)	5.6 (0 to 114.6)	6.5 (0 to 124.6)	6.7 (0 to 125.2)	<.001
Questionnaire 2	3.8 (0 to 80.7)	6.8 (0 to 95.0)	7.7 (0 to 91.3)	10.7 (0 to 106.7)	11.6 (0 to 108.8)	<.001
Male	129 (64)	114 (56)	115 (57)	115 (57)	93 (46)	.008
Age, median (range), y	57 (21 to 83)	62 (29 to 85)	61 (24 to 82)	63 (27 to 82)	60 (28 to 81)	.10 ^d
Race						
White	174 (87)	182 (90)	175 (87)	188 (93)	178 (88)	.12
Black	17 (8)	17 (8)	12 (6)	9 (4)	12 (6)	
Other	10 (5)	3 (2)	15 (7)	5 (3)	12 (6)	
Body mass index, median (range) ^e						
Questionnaire 1	27.5 (15.7 to 49.4)	27.7 (17.6 to 47.4)	26.8 (17.5 to 49.9)	27.7 (16.3 to 51.8)	27.3 (17.2 to 46.3)	.41 ^d
Questionnaire 2	28.6 (16.4 to 50.2)	28.5 (18.9 to 46.7)	28.5 (16.7 to 54.5)	28.8 (16.8 to 51.8)	27.5 (17.6 to 48.2)	.08 ^d
Weight change, median (range), kg ^f	2.7 (-20.9 to 57.2)	3.4 (-40 to 45)	2.3 (-14.1 to 49.1)	2.7 (-10.9 to 42.7)	2.3 (-15.5 to 40.0)	.16 ^d
Baseline performance status						
Fully active	143 (71)	152 (75)	164 (81)	158 (78)	147 (73)	.17
Ambulatory but restricted in physically strenuous activity ^g	58 (29)	50 (25)	38 (19)	44 (22)	55 (27)	
Invasion through bowel wall by T stage						
T1-2 ^h	20 (10)	29 (14)	27 (13)	27 (13)	33 (16)	.41
T3-4 ⁱ	166 (83)	161 (80)	164 (80)	161 (79)	151 (75)	
T stage unknown	15 (7)	12 (6)	14 (7)	17 (8)	18 (9)	
Positive lymph nodes						
1-3 (N1)	126 (63)	127 (63)	125 (62)	139 (69)	137 (68)	.39
>4 (N2)	75 (37)	75 (37)	77 (38)	63 (31)	65 (32)	
Clinical bowel abnormality						
Perforation	7 (3.5)	9 (4.5)	11 (5.4)	10 (5.0)	6 (3.0)	.65
Obstruction	42 (21)	47 (24)	44 (22)	46 (23)	43 (22)	.97
Postoperative carcinoembryonic antigen level >5 ng/dL	16 (8.0)	15 (7.4)	11 (5.5)	11 (5.5)	16 (7.9)	.72
Grade of differentiation						
Well	10 (5)	14 (7)	14 (7)	12 (6)	6 (3)	.48
Moderate	132 (66)	139 (69)	140 (69)	136 (67)	151 (75)	
Poor	53 (26)	45 (22)	43 (21)	48 (24)	39 (19)	
Unknown	6 (3)	4 (2)	5 (3)	6 (3)	6 (3)	
Treatment group						
Fluorouracil plus leucovorin	106 (53)	104 (51)	103 (51)	92 (46)	106 (52)	.69
Irinotecan, fluorouracil, and leucovorin	95 (47)	98 (49)	99 (49)	110 (54)	86 (48)	
Smoking status						
Current	32 (16)	21 (10)	14 (7)	9 (4)	8 (4)	<.001
Past	91 (45)	97 (48)	96 (48)	99 (49)	85 (42)	
Never	78 (39)	84 (42)	92 (45)	94 (47)	109 (54)	

Abbreviation: MET, metabolic equivalent tasks.

^aValues are expressed as number (percentage) unless otherwise indicated. Age, performance status, and postoperative carcinoembryonic antigen level based on patient's status at initiation of chemotherapy (entry into the treatment trial).

^bFor both patterns, the higher scores (and thus higher quintile) are indicative of higher intake of that particular diet.

^cThe χ^2 test was used unless otherwise noted.

^dThe Wilcoxon rank sum was used.

^eCalculated as weight in kilograms divided by height in meters squared.

^fChange in weight between questionnaire 1 (within 4 mo of surgery) and questionnaire 2 (around 6 mo after completion of chemotherapy).

^gSome persons able to carry out light work but others unable to carry out any work activities ($\geq 50\%$ of waking hours).

^hLevel of invasion through the bowel wall not beyond the muscle layer.

ⁱLevel of invasion through the bowel wall beyond the muscle layer.

sociated with a significant increase in the risk of cancer recurrence or mortality (TABLE 4), and this relationship remained largely unchanged after adjusting for other predictors of cancer recurrence. Compared with patients in the lowest Western dietary pattern quintile, those in the highest quintile experienced a multivariate-adjusted HR for recurrence or death of 3.25 (95% confidence interval [CI], 2.04-5.19; *P* for trend <.001). Even if patients in the

Table 3. Baseline Characteristics of 1009 Patients by Quintile for Western Dietary Pattern^a

	Western Pattern ^b					<i>P</i> Value ^c
	1 (n = 201)	2 (n = 202)	3 (n = 202)	4 (n = 202)	5 (n = 202)	
Physical activity, median (range), MET h/wk						
Questionnaire 1	3.3 (0 to 119.9)	3.7 (0 to 82.7)	4.7 (0 to 112.7)	6.7 (0 to 125.2)	6.2 (0 to 114.6)	.006
Questionnaire 2	8.0 (0 to 89.9)	6.5 (0 to 95.0)	7.8 (0 to 108.8)	8.4 (0 to 88.4)	7.5 (0 to 106.7)	.97
Male	73 (36)	103 (51)	104 (51)	131 (65)	156 (77)	<.001
Age, median (range), y	59 (33 to 74)	59 (21 to 80)	62 (26 to 82)	60 (29 to 81)	62 (28 to 83)	.77 ^d
Race						
White	155 (77)	185 (92)	177 (88)	185 (92)	195 (97)	<.001
Black	26 (13)	9 (4)	15 (7)	11 (5)	4 (2)	
Other	20 (10)	8 (4)	10 (5)	6 (3)	3 (1)	
Body mass index, median (range) ^e						
Questionnaire 1	26.4 (17.2 to 49.4)	28.0 (17.5 to 49.9)	27.0 (16.3 to 46.2)	27.5 (18.9 to 46.3)	27.5 (15.7 to 51.8)	.12 ^d
Questionnaire 2	27.5 (16.2 to 50.9)	28.7 (17.6 to 48.9)	28.0 (16.4 to 46.9)	28.4 (16.3 to 48.2)	28.8 (17.6 to 54.5)	.15 ^d
Weight change, median (range), kg ^f	2.3 (-47.2 to 20.0)	2.3 (-13.6 to 49.1)	3.2 (-40 to 57.3)	2.7 (-35.9 to 42.7)	3.2 (-15.5 to 17.7)	.09 ^d
Baseline performance status						
Fully active	150 (75)	157 (78)	146 (72)	158 (78)	152 (75)	.85
Ambulatory but restricted in physically strenuous activity ^g	51 (25)	45 (22)	56 (28)	44 (22)	50 (25)	
Invasion through bowel wall by T stage						
T1-2 ^h	23 (11)	37 (18)	28 (14)	25 (13)	23 (11)	.27
T3-4 ⁱ	163 (81)	153 (76)	164 (81)	162 (80)	161 (80)	
T stage unknown	15 (8)	12 (6)	10 (5)	15 (7)	18 (9)	
Positive lymph nodes						
1-3 (N1)	136 (68)	138 (68)	125 (62)	136 (67)	120 (59)	.24
>4 (N2)	65 (32)	64 (32)	77 (38)	66 (33)	82 (41)	
Clinical bowel abnormality						
Perforation	9 (4.5)	7 (3.5)	12 (6.0)	4 (2.0)	10 (5.0)	.33
Obstruction	46 (23)	31 (15)	44 (22)	56 (28)	48 (24)	.06
Postoperative carcinoembryonic antigen level >5 ng/dL	12 (6.0)	14 (6.9)	13 (6.4)	15 (7.4)	15 (7.4)	.97
Grade of differentiation						
Well	14 (7)	10 (5)	16 (8)	8 (4)	8 (4)	.24
Moderate	143 (71)	151 (75)	133 (66)	136 (67)	135 (67)	
Poor	39 (19)	35 (17)	50 (25)	50 (25)	54 (27)	
Unknown	5 (3)	6 (3)	2 (1)	8 (4)	5 (2)	
Treatment group						
Fluorouracil plus leucovorin	115 (57)	105 (52)	95 (47)	96 (48)	100 (50)	.25
Irinotecan, fluorouracil, and leucovorin	86 (43)	97 (48)	107 (53)	106 (52)	102 (50)	
Smoking status						
Current	8 (4)	8 (4)	19 (9)	22 (11)	27 (13)	<.001
Past	75 (37)	103 (51)	90 (45)	95 (47)	104 (51)	
Never	118 (59)	91 (45)	93 (46)	85 (42)	71 (36)	

Abbreviation: MET, metabolic equivalent tasks.

^a Values are expressed as number (percentage) unless otherwise indicated. Age, performance status, and postoperative carcinoembryonic antigen level based on patient's status at initiation of chemotherapy (entry into the treatment trial).

^b For both patterns, the higher scores (and thus higher quintile) are indicative of higher intake of that particular diet.

^c The χ^2 test was used unless otherwise noted.

^d The Wilcoxon rank sum was used.

^e Calculated as weight in kilograms divided by height in meters squared.

^f Change in weight between questionnaire 1 (within 4 mo of surgery) and questionnaire 2 (around 6 mo after completion of chemotherapy).

^g Some persons able to carry out light work but others unable to carry out any work activities ($\geq 50\%$ of waking hours).

^h Level of invasion through the bowel wall not beyond the muscle layer.

ⁱ Level of invasion through the bowel wall beyond the muscle layer.

highest quintile of Western dietary pattern were excluded, the adjusted *P* for trend was .001.

To isolate the influence of Western dietary pattern on cancer recurrence, we used the end point of recurrence-free survival and confirmed that higher intake of a Western dietary pattern conferred a significantly increased risk in cancer recurrence (*P* for trend <.001; Table 4). Patients in the highest quintile of Western dietary pattern were 2.9 times more likely to recur than those in the lowest quintile. Similarly, we observed a significantly higher overall mortality with increasing Western dietary pattern (adjusted *P* for trend <.001).

To address the possibility that changes in dietary habits could reflect occult cancer or impending death, we excluded patients who developed cancer recurrence or died within 90 days of completing the first questionnaire in our primary analyses. To further address this issue, we repeated the Cox proportional hazard models after excluding patients who developed cancer recurrence or died within 180 days of completing the SFFQ (n=965) and our results remained largely unchanged in this subset. Patients in the highest quintile of Western dietary

pattern had an adjusted HR for cancer recurrence or death of 3.58 (95% CI, 2.19-5.85), with an adjusted *P* for trend across quintiles of less than .001. Moreover, the adjusted linear tests for trend for cancer recurrence (recurrence-free survival) and overall mortality (overall survival) were both less than .001. Alternatively, not imposing this restriction and starting the disease-free survival from completion of SFFQ (n=1035), the adjusted HR is 3.29 (95% CI, 2.09-5.17; *P* for trend <.001), comparing the highest with the lowest quintiles.

Prudent Dietary Pattern and Cancer Recurrence or Death

We similarly examined the association of prudent dietary pattern (categorized by high intakes of fruits, vegetables, whole grains, legumes, poultry, and fish) on cancer recurrence and mortality (TABLE 5). In contrast to the Western dietary pattern, the prudent dietary pattern was not significantly related to patient outcome. The adjusted HR comparing the highest and lowest quintiles of prudent dietary pattern was 1.20 (95% CI, 0.83-1.75) for disease-free survival (*P* for trend=.78). Similarly, no relationship was seen for recurrence-free survival

(*P* for trend=.84) or overall survival (*P* for trend=.54) across intakes of the prudent dietary pattern.

Stratified Analyses by Potential Effect Modifiers

In light of the significant relationship of Western dietary pattern to cancer recurrence and mortality, we examined the associations with Western dietary pattern across strata of other potential predictors of patient outcome (TABLE 6). The effect of the Western dietary pattern was not significantly modified by age, sex, body mass index, level of physical activity, baseline performance status, number of positive lymph nodes, or treatment group.

As prudent and Western dietary patterns are not correlated, we considered simultaneous effect of Western and prudent diets on disease-free survival. When we added the prudent diet into the multivariate model for the Western diet, we continued to observe a significantly worse outcome with increasing intake of Western dietary pattern (*P* for trend for disease-free survival <.001). Furthermore, the prudent dietary pattern did not modify the effect of the Western dietary pattern (*P* for interaction=.69).

Table 4. Associations Between Colon Cancer Recurrence and Mortality and the Western Dietary Pattern^a

	Western Dietary Pattern by Quintile ^b					<i>P</i> for Trend
	1 (n = 201)	2 (n = 202)	3 (n = 202)	4 (n = 202)	5 (n = 202)	
Cancer recurrence or death from any cause (disease-free survival)						
No. of events/person-time at risk ^c	71/795	57/808	73/772	68/768	83/759	
Energy-adjusted only	1[Reference]	0.95 (0.66-1.36)	1.51 (1.06-2.15)	1.75 (1.19-2.58)	3.28 (2.12-5.07)	<.001
Multivariate adjusted ^d	1[Reference]	0.98 (0.68-1.43)	1.51 (1.05-2.17)	1.64 (1.09-2.46)	3.25 (2.04-5.19)	<.001
Cancer recurrence (recurrence-free survival)						
No. of events/person-time at risk ^c	68/795	51/808	68/769	61/768	76/759	
Energy-adjusted only	1[Reference]	0.86 (0.59-1.25)	1.41 (0.98-2.02)	1.54 (1.03-2.30)	2.82 (1.79-4.43)	<.001
Multivariate adjusted ^d	1[Reference]	0.92 (0.63-1.36)	1.42 (0.98-2.07)	1.44 (0.94-2.19)	2.85 (1.75-4.63)	<.001
Overall mortality						
No. of events/person-time at risk ^c	57/916	35/920	51/867	53/842	55/860	
Energy-adjusted only	1[Reference]	0.74 (0.48-1.15)	1.39 (0.93-2.09)	1.81 (1.17-2.80)	2.61 (1.59-4.30)	<.001
Multivariate adjusted ^d	1[Reference]	0.74 (0.48-1.17)	1.38 (0.90-2.11)	1.66 (1.04-2.65)	2.32 (1.36-3.96)	<.001

^aMedian follow-up of patients 5.3 years from completion of questionnaire 1; 5.6 years from trial entry.

^bFor both patterns, the higher scores (and thus higher quintile) are indicative of higher intake of that particular diet.

^cDoes not account for energy adjustment.

^dAdjusted for sex, age, depth of invasion through bowel wall (T1-2 vs T3-4), number of positive lymph nodes (1-3 vs ≥4), presence of clinical perforation at time of surgery, presence of bowel obstruction at time of surgery, baseline performance status (0 vs 1-2), treatment group, weight change between first and second questionnaire, time-varying body mass index, time-varying physical activity level, and time-varying total calories.

COMMENT

In a cohort of patients with stage III colon cancer treated with surgery and adjuvant chemotherapy surviving without cancer recurrence 3 months after the completion of a SFFQ, increasing consumption of a Western dietary pattern after diagnosis was associated with an increased risk of cancer recurrence or death. Compared with patients in the lowest level, those in the highest level of Western pattern intake experienced a tripling in risk of recurrence or death. In contrast, the prudent dietary pattern was not associated with survival outcomes after curative resection of stage III colon cancer.

Epidemiological and scientific research indicates that dietary factors are associated with the risk of developing colon cancer. Consumption of red meat,³²⁻³⁶ alcohol,^{37,38} calcium and vitamin D,³⁹⁻⁴⁴ vitamin E,⁴⁵⁻⁴⁷ and folic acid^{37,38,48,49} are among diet components that appear to influence the risk of developing the disease. Individual components of the diet interact with each other and confounding can make identification of a specific food or nutrient difficult. Pattern analysis may provide additional insight that takes into account the combined effects of foods. Specific dietary patterns have

been associated with risk of colon cancer.¹²⁻¹⁶

Few studies have assessed the relationship between diet and colon cancer recurrence and survival. In one small study of colon cancer patients, Slattery et al⁵⁰ observed an improved survival with increasing consumption of calories, fat, and protein. By contrast, higher fiber intake was associated with a decreased survival. Among 148 patients with colorectal cancer, Dray et al⁵¹ reported improved survival with increasing consumption of calories. Unfortunately, both of these studies were limited by their small samples size, heterogeneous patient population that included all stages of disease, inability to adjust for cancer treatment, and limited capacity to adjust for other prognostic factors. Ultimately, the positive relationship between energy intake and cancer survival observed in both of these studies may have reflected the inclusion of patients with more advanced disseminated (stage IV) cancer whose caloric intake was compromised by their burden of cancer.

There are several advantages to this cohort of stage III colon cancer patients treated within a NCI-sponsored clinical trial. First, all patients had lymph

node–positive cancer, reducing the impact of heterogeneity by disease stage. Second, treatment and follow-up care were standardized, and the date and nature of recurrence were prospectively recorded. Detailed information on other prognostic variables were all routinely collected at study entry. Finally, we updated dietary data to reflect changes in diet that may occur after patients completed adjuvant therapy and have recovered from treatment effects.

Our observation that the Western dietary pattern but not the prudent pattern are associated with cancer recurrence and mortality is consistent with most risk studies primarily showing a relationship between the Western pattern and development of colon cancer.^{12-14,16,52} Moreover, consistent with other studies, the Western and prudent patterns were not correlated in our cohort. Western dietary patterns are positively correlated with levels of serum insulin, C-peptide, and leptin.⁵³ Both insulin and insulinlike growth factors have been associated with enhanced tumor growth and antiapoptosis.⁵⁴ Following resection of stage III colon cancer, increasing Western pattern intake may facilitate a milieu that allows residual microscopic disease to proliferate and spread.

Table 5. Associations Between Colon Cancer Recurrence and Mortality and the Prudent Dietary Pattern^a

	Prudent Dietary Pattern by Quintile ^b					P for Trend
	1 (n = 201)	2 (n = 202)	3 (n = 202)	4 (n = 202)	5 (n = 202)	
Cancer recurrence or death from any cause (disease-free survival)						
No. of events/person-time in years at risk ^c	79/743	79/765	71/763	53/839	70/751	
Energy-adjusted only	1[Reference]	1.05 (0.77-1.44)	0.99 (0.71-1.37)	0.71 (0.50-1.01)	1.08 (0.76-1.51)	.59
Multivariate adjusted ^d	1[Reference]	1.17 (0.85-1.63)	1.07 (0.76-1.52)	0.81 (0.55-1.18)	1.20 (0.83-1.75)	.78
Cancer recurrence (recurrence-free survival)						
No. of events/person-time in years at risk ^c	73/740	68/765	67/763	52/839	64/751	
Energy-adjusted only	1[Reference]	0.98 (0.70-1.36)	1.00 (0.71-1.41)	0.75 (0.52-1.08)	1.04 (0.73-1.49)	.86
Multivariate adjusted ^d	1[Reference]	1.07 (0.76-1.51)	1.05 (0.74-1.51)	0.83 (0.57-1.23)	1.13 (0.77-1.67)	.84
Overall mortality						
No. of events/person-time in years at risk ^c	63/852	58/869	44/872	34/942	52/852	
Energy-adjusted only	1[Reference]	0.99 (0.69-1.42)	0.79 (0.53-1.17)	0.57 (0.37-0.87)	1.05 (0.71-1.55)	.60
Multivariate adjusted ^d	1[Reference]	1.18 (0.81-1.71)	0.94 (0.62-1.43)	0.72 (0.46-1.13)	1.32 (0.86-2.04)	.54

^aMedian follow-up of patients 5.3 years from completion of questionnaire 1; 5.6 years from trial entry.

^bFor both patterns, the higher scores (and thus higher quintile) are indicative of higher intake of that particular diet.

^cDoes not account for energy adjustment.

^dAdjusted for sex, age, depth of invasion through bowel wall (T1-2 vs T3-4), number of positive lymph nodes (1-3 vs ≥ 4), presence of clinical perforation at time of surgery, presence of bowel obstruction at time of surgery, baseline performance status (0 vs 1-2), treatment group, weight change between first and second questionnaire, time-varying body mass index, time-varying physical activity level, and time-varying total calories.

Patients who enroll in randomized controlled trials may differ from the population at large. To participate, patients must meet eligibility criteria, be selected as an appropriate candidate, and be motivated to participate. However, we did observe reasonable variability in dietary intake among participants. Moreover, because the study included patients across North America, as well as both community and academic centers, our findings should reflect the general population of stage III patients.

We cannot completely exclude the possibility that higher intake of a Western dietary pattern may be reflective of other predictors of poor prognosis. However, we did not observe any significant association between diet and predictors associated with cancer recurrence or survival (extent of invasion into bowel wall, number of posi-

tive lymph nodes, clinical bowel perforation or obstruction, preoperative carcinoembryonic antigen levels, grade of tumor differentiation). Given that patients were enrolled in a clinical trial, they all initiated fluorouracil-based adjuvant chemotherapy after surgery, thus cancer treatment was standardized. Moreover, the detrimental effect of a high intake Western diet remained largely unchanged across the number of positive lymph nodes and baseline performance status. We recently reported that regular physical activity improved outcomes in this cohort,^{55,56} however, the relationship between the Western dietary pattern and outcome was similar across levels of physical activity.

We considered the possibility that sick patients (with undetected cancer recurrences and limited survival) may have altered their diet to one that may

be less healthy to increase nutritional intake. To minimize this bias, we excluded recurrences or deaths within 90 days of the physical activity assessment in the primary analysis. Furthermore, we continue to see an association even when we extended this restriction to exclude events 6 months after dietary assessment. Finally, because all patients were followed up in a clinical trial with prescribed follow-up visits and testing, we would expect few patients to have undetected recurrences over extended periods, given the relatively brief natural history of recurrent colon cancer.

Given that patients who have a high intake Western diet after cancer diagnosis may have had a similar diet before diagnosis, we cannot exclude the possibility that individuals preferring a Western diet acquire tumors that are biologically more aggressive. Nonethe-

Table 6. Subgroup Analyses of Multivariate-Adjusted Disease-Free Survival by Quintile of Western Dietary Pattern^a

	No. of Patients	Quintile of Western Dietary Pattern ^b					P for Interaction	P for Trend
		1	2	3	4	5		
Age, y								
< 61	516	1 [Reference]	1.26 (0.75-2.13)	1.53 (0.91-2.59)	1.31 (0.74-2.33)	2.63 (1.36-5.09)	.77	.007
≥ 61	493	1 [Reference]	0.82 (0.47-1.42)	1.28 (0.77-2.15)	2.05 (1.14-3.70)	3.65 (1.88-7.10)		<.001
Body mass index ^c								
≤ 25 (Underweight or normal weight)	331	1 [Reference]	0.53 (0.25-1.12)	1.12 (0.60-2.07)	1.03 (0.49-2.14)	2.90 (1.28-6.58)	.90	.002
> 25 (Overweight or obese)	678	1 [Reference]	1.20 (0.77-1.87)	1.64 (1.03-2.61)	1.79 (1.09-2.94)	2.82 (1.58-5.04)		<.001
Sex								
Male	568	1 [Reference]	1.14 (0.66-1.96)	1.72 (1.01-2.91)	1.96 (1.13-3.73)	3.37 (1.83-6.23)	.54	<.001
Female	441	1 [Reference]	0.97 (0.58-1.64)	1.36 (0.80-2.32)	1.20 (0.61-2.37)	3.56 (1.66-7.66)		.003
Physical activity								
Lower 2 quintiles	505	1 [Reference]	0.96 (0.59-1.59)	1.52 (0.92-2.50)	1.69 (0.95-2.99)	3.56 (1.90-6.66)	.17	<.001
Higher 3 quintiles	412	1 [Reference]	1.22 (0.60-2.45)	1.64 (0.86-3.11)	1.62 (0.82-3.23)	2.77 (1.26-6.08)		<.001
Baseline performance status								
0	763	1 [Reference]	1.00 (0.64-1.54)	1.74 (1.14-2.64)	1.59 (0.99-2.56)	2.75 (1.58-4.79)	.51	<.001
1-2	246	1 [Reference]	1.19 (0.57-2.45)	0.81 (0.39-1.68)	1.40 (0.63-3.08)	4.23 (1.76-10.2)		<.001
No. of positive lymph nodes								
1-3	655	1 [Reference]	0.90 (0.55-1.45)	1.33 (0.82-2.17)	1.47 (0.87-2.48)	2.65 (1.44-4.88)	.94	<.001
≥ 4	354	1 [Reference]	1.21 (0.67-2.21)	1.66 (0.94-2.95)	1.75 (0.90-3.40)	3.91 (1.85-8.29)		<.001
Treatment group								
Fluorouracil plus leucovorin	511	1 [Reference]	0.92 (0.63-1.36)	1.42 (0.98-2.07)	1.44 (0.94-2.20)	2.85 (1.75-4.63)	.47	<.001
Irinotecan, fluorouracil, and leucovorin	498	1 [Reference]	1.02 (0.59-1.75)	1.40 (0.83-2.36)	1.28 (0.72-2.28)	2.60 (1.37-4.91)		.001

^aAdjusted for sex, age, depth of invasion through bowel wall (T1-2 vs T3-4), number of positive lymph nodes (1-3 vs ≥4), presence of clinical perforation at time of surgery, presence of bowel obstruction at time of surgery, baseline performance status (0 vs 1-2), treatment group, weight change between first and second questionnaire, time-varying body mass index, time-varying physical activity level, and time-varying total calories.

^bFor both patterns, the higher scores (and thus higher quintile) are indicative of higher intake of that particular diet.

^cCalculated as weight in kilograms divided by height in meters squared.

less, as stated above, we did not observe any significant association between a Western dietary pattern and tumor-related characteristics associated with cancer recurrence. Moreover, the associations of a Western diet were largely unchanged across strata of other prognostic factors.

Diet was self-reported in this study. The SFFQ from this study has been extensively validated in healthy populations^{21,22} as well as a population of patients receiving cytotoxic chemotherapy.²⁵ Diet was recorded prior to any knowledge of colon cancer–related outcomes, thus reducing the likelihood of reporting biases.

Studies have shown an improved disease-free survival among patients who receive adjuvant chemotherapy following the surgical resection of stage III colon cancer. This is the first study, to our knowledge, in a potentially cured population of colon cancer survivors to address the effect of diet. Because this was an observational study, causality cannot and should not be drawn from these data. Nonetheless, the data suggest that a diet characterized by higher intakes of red and processed meats, sweets and desserts, french fries, and refined grains increases the risk of cancer recurrence and decreases survival. Further analyses are under way to better delineate specific nutrients or food groupings that may have the strongest association.

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