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ORIGINAL REPORT

Coffee Intake, Recurrence, and Mortality in Stage III Colon Cancer: Results From CALGB 89803 (Alliance)

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ABSTRACT

Purpose
Observational studies have demonstrated increased colon cancer recurrence in states of relative hyperinsulinemia, including sedentary lifestyle, obesity, and increased dietary glycemic load. Greater coffee consumption has been associated with decreased risk of type 2 diabetes and increased insulin sensitivity. The effect of coffee on colon cancer recurrence and survival is unknown.

Patients and Methods
During and 6 months after adjuvant chemotherapy, 953 patients with stage III colon cancer prospectively reported dietary intake of caffeinated coffee, decaffeinated coffee, and nonherbal tea, as well as 128 other items. We examined the influence of coffee, nonherbal tea, and caffeine on cancer recurrence and mortality using Cox proportional hazards regression.

Results
Patients consuming 4 cups/d or more of total coffee experienced an adjusted hazard ratio (HR) for colon cancer recurrence or mortality of 0.58 (95% CI, 0.34 to 0.99), compared with never drinkers (P_{trend} = .002). Patients consuming 4 cups/d or more of caffeinated coffee experienced significantly reduced cancer recurrence or mortality risk compared with abstainers (HR, 0.48; 95% CI, 0.25 to 0.91; P_{trend} = .002), and increasing caffeine intake also conferred a significant reduction in cancer recurrence or mortality (HR, 0.66 across extreme quintiles; 95% CI, 0.47 to 0.93; P_{trend} = .006). Nonherbal tea and decaffeinated coffee were not associated with patient outcome. The association of total coffee intake with improved outcomes seemed consistent across other predictors of cancer recurrence and mortality.

Conclusion
Higher coffee intake may be associated with significantly reduced cancer recurrence and death in patients with stage III colon cancer.

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INTRODUCTION

Mounting evidence supports an association between excess energy balance and increased risk of developing colon cancer.[1-4] Promotion of cancer by hyperinsulinemia has been proposed as the mechanism underlying this relationship,[5,6] and prospective studies find a significant association between a history of type 2 diabetes (T2D), elevated plasma insulin, and C-peptide, and subsequent colorectal cancer risk.[6-11] Beyond cancer risk, observational studies of patients with established colorectal cancer suggest that energy excess, as manifested by T2D, obesity, sedentary lifestyle, Western pattern diet, high dietary glycemic load, and high intake of sugar-sweetened beverages,

confers an increased risk of colon cancer recurrence and mortality.[12-17] Moreover, increased cancer mortality was observed among patients with stage I, II, and III colorectal cancer with elevated plasma C-peptide or low insulin-like growth factor binding protein-1.[15]

Insight into the role of other dietary factors may contribute to strategies to improve outcome in patients with colon cancer. Coffee is commonly consumed worldwide, and coffee consumption has been associated with decreased risk of T2D,[18-22] lower plasma C-peptide,[11,23] and increased plasma adiponectin, an endogenous insulin sensitizer.[24,25] In addition, some, but not all, studies demonstrate an inverse relationship between coffee consumption and risk of colorectal cancer.[26-28]

In light of evidence supporting a link between excess energy balance, hyperinsulinemia, and increased recurrence in patients with colon cancer, we prospectively examined the association of coffee intake with cancer recurrence and mortality in a cohort of patients with stage III colon cancer enrolled onto a National Cancer Institute–sponsored randomized clinical trial of adjuvant chemotherapy. In this trial, comprehensive data on diet and lifestyle were collected before any documentation of cancer recurrence. Moreover, because data on pathologic stage, performance status, postoperative treatment, and follow-up were carefully captured in this trial, the simultaneous effects of disease characteristics and adjuvant therapy use could be assessed.

PATIENTS AND METHODS

Study Population

Patients in this prospective cohort participated in the National Cancer Institute–sponsored Cancer and Leukemia Group B 89803 (CALGB 89803; now Alliance for Clinical Trials in Oncology) adjuvant therapy trial

for stage III colon cancer, comparing therapy with once per week fluorouracil and leucovorin with therapy with once per week irinotecan, fluorouracil, and leucovorin (ClinicalTrials.gov NCT000038350).[29] Between 1999 and 2001, 1,264 patients were enrolled. After 87 patients were enrolled, an amendment required patients to complete a self-administered semiquantitative food frequency questionnaire (FFQ) that captured diet and lifestyle habits midway through adjuvant therapy (4 months after surgery; questionnaire 1 [Q1]), and again, 6 months after completion of treatment (14 months after surgery; questionnaire 2 [Q2]).

Patients who underwent a complete surgical resection of the primary tumor within 56 days of trial entry, had regional lymph node metastases without evidence of distant metastases, had a baseline Eastern Cooperative Oncology Group performance status of 0 to 2,[30] and had adequate bone marrow, renal, and hepatic function were eligible. Patients were excluded if they reported significantly abnormal caloric intake (< 600 or $> 4,200$ calories/d for men; < 500 or $> 3,500$ calories/d for women), left more than 70 food items blank, or left blank one or more questions about caffeinated coffee, decaffeinated coffee, or nonherbal tea on Q1 or Q2. Finally, patients were excluded if they had cancer recurrence or death within 90 days of completing the questionnaire to avoid dietary assessment bias because of declining health, resulting in 953 eligible patients (Fig 1). We previously
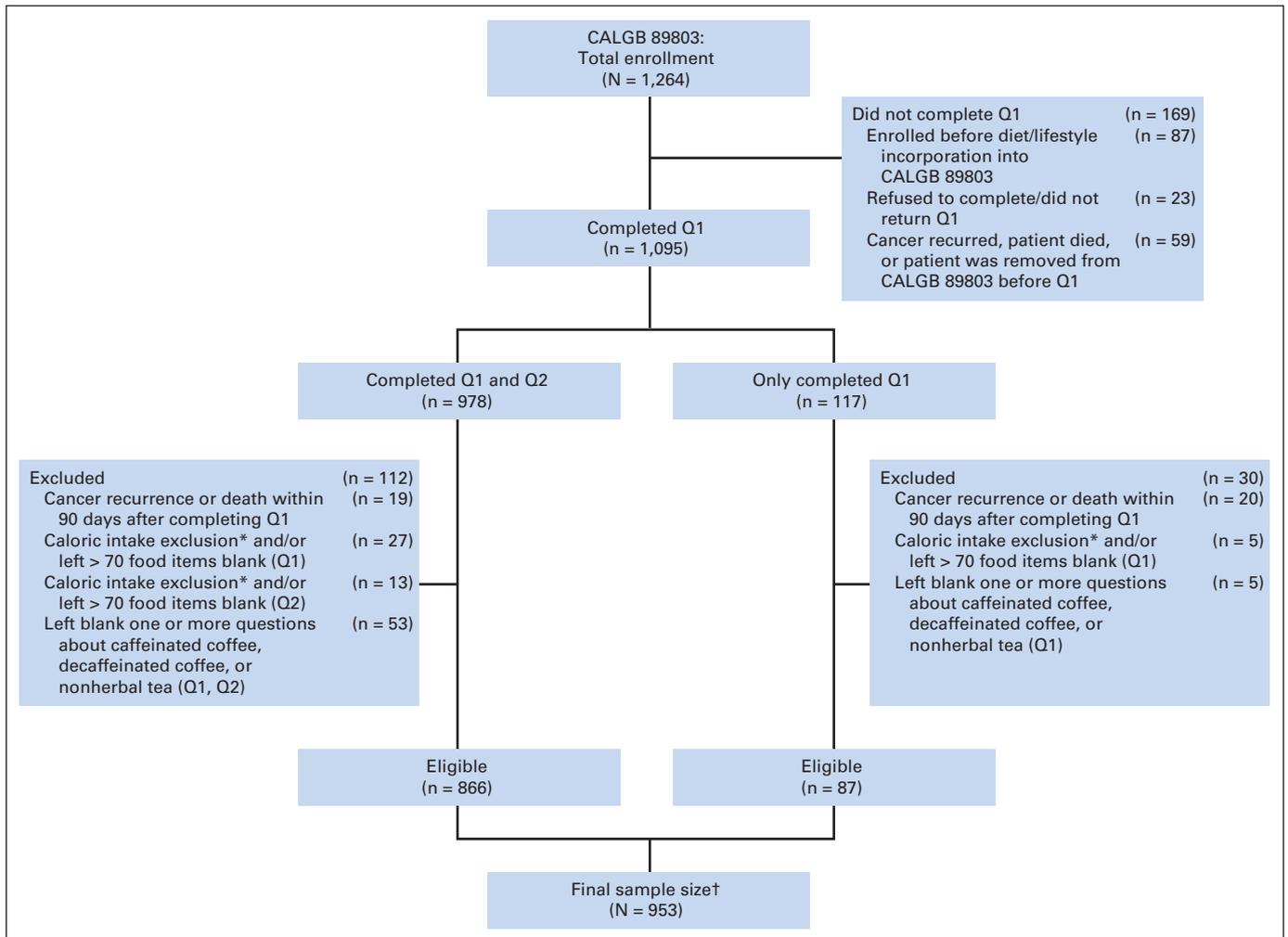
Fig 1. Derivation of the study cohort. (*) Caloric intake exclusion indicates fewer than 600 calories/d or more than 4,200 calories/d for men, and fewer than 500 calories/d or more than 3,500 calories/d for women. (†) Six patients in the final sample are missing physical activity in questionnaire 1 (Q1; midway through adjuvant therapy), and three are missing physical activity in questionnaire 2 (Q2; 6 months after completion of adjuvant therapy). One patient is missing body mass index in Q2. CALGB, Cancer and Leukemia Group B.

demonstrated that there were no appreciable differences in baseline characteristics between patients eligible for dietary analysis and the remaining patients enrolled onto CALGB 89803 not included in the dietary studies.[31] All patients provided study-specific informed consent.

Dietary Assessment

Patients in this analysis completed semiquantitative FFQs that included 131 food items, vitamin and mineral supplements, and open-ended sections for other supplements and foods not specifically listed.[32,33] Participants were asked how often, on average, during the previous 3 months, they consumed a specific food portion size, with up to nine possible responses, which ranged from never to six 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.[34,35] Nutrient values were energy adjusted using the residuals methods.[36]

On each questionnaire, we assessed intake of caffeinated or decaffeinated coffee, nonherbal tea, herbal tea, and different types of caffeinated soft drinks. We assessed total intake of caffeine by summing the caffeine content for a specific amount of each food during the study period (1 cup for coffee or tea, one 12-ounce bottle or can for carbonated beverages, and 1 ounce for chocolate) multiplied by a weight proportional to the frequency of its use.[22,35] In a separate validity study of our questionnaire, the correlation coefficients between two 1-week diet records and the FFQs for average intake of coffee and tea were 0.78 and 0.93, respectively.[37]

Patients who completed the first FFQ (Q1) without cancer recurrence before FFQ completion were included in these analyses. The median time from study entry to Q1 was 3.5 months (95% range, 2.5 to 5.0 months; full range, 0.2 to 9.9 months). We updated dietary exposures on the basis of results of the second FFQ (Q2) using cumulative averaging, as previously described,[14,31,38-40] but weighted proportional to times between Q1 and Q2, and then between Q2 and disease-free survival (DFS) time. For example, if a patient completed Q1 at 4 months, completed Q2 at 14 months, and had a cancer recurrence at 30 months, the total time between Q1 and cancer recurrence was 26 months, and 38% of that time was between Q1 and Q2 and 62% of that time was between Q2 and the recurrence.

Study End Points

The primary end point of our study was DFS, defined as time from completion of Q1 to tumor recurrence, occurrence of a new primary colon tumor, or death from any cause. We also assessed recurrence-free survival (RFS), defined as time from 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 physician evaluation. Finally, overall survival (OS) was defined as the time from completion of Q1 to death from any cause.

Statistical Analysis

In the clinical trial, there was no statistical difference in either DFS or OS between treatment arms.[29] Therefore, data for patients in both arms were combined and analyzed according to frequency categories of dietary intake. We assessed nonherbal tea alone because it is biologically distinct from herbal teas.[41] Intake of total coffee, caffeinated coffee, and tea was classified into five frequency categories (0, < 1, 1, 2 to 3, and ≥ 4 cups/d), consistent with previous studies.[42-45] Given the few participants reporting decaffeinated coffee intake of more than 2 cups/d, intake of decaffeinated coffee was classified by only four frequency categories to conserve statistical power (0, < 1, 1, and ≥ 2 cups/d).

Cox proportional hazards regression was used to determine the simultaneous impact of other variables potentially associated with each outcome.[46] As previously described,[36] we used time-varying covariates to adjust for total calories, physical activity as measured in metabolic equivalent task hours per week,[47] body mass index calculated as weight in kilograms divided by height squared in meters squared, alcohol consumption in grams per day, energy adjusted, and consumption of Western and prudent pattern diets, as defined previously.[14] Other covariates, including sex, age, depth of invasion through bowel wall, number of positive lymph nodes, baseline performance status,

treatment group, smoking history (yes, no, missing), and multivitamin use (consistent user, not consistent user, missing), were entered into the model as fixed covariates. In secondary multivariable analyses, we further adjusted for time-varying sugar-sweetened beverage intake and dietary glycemic load.[13,31] In analyses assessing caffeinated coffee consumption and decaffeinated coffee consumption as independent covariates, we included both caffeinated coffee and decaffeinated coffee intake in the multivariable model simultaneously; similarly, in analyses of tea intake, we included total coffee consumption in the model. Covariates with missing variables were coded with indicator variables.

Although results are displayed for visual effect in discrete categories, each primary statistical analysis was performed using consumption as a continuous measure to minimize bias created by selected categorization. We tested for linear trends across frequency categories of intake by assigning each participant the median value for each frequency category and modeling this value as a continuous variable, consistent with previous studies.[13,14,31] In subgroup exploratory analyses on the effect of total coffee consumption, we collapsed intake into four categories to conserve power, creating the following groupings: 0, less than 1, 1, and 2 or more cups/d. The proportionality of hazards assumption for the effect of each coffee type, caffeine, and tea was satisfied by examining each as a time-dependent covariate in the model. All analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC). A P value less than .05 was considered statistically significant. Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center at Duke University Medical Center. Data quality was ensured by review of data by the Alliance Statistics and Data Center and by the study chairperson following Alliance policies. All analyses were based on the study database frozen on November 9, 2009.

RESULTS

Baseline Characteristics

Baseline characteristics by frequency of total coffee consumption are displayed in Table 1. Frequent coffee drinkers were more physically active and more likely to be male, white, and current smokers; had higher intake of total energy, caffeine, and Western pattern diet; and had lower dietary glycemic load and lower prudent pattern diet. Baseline characteristics by frequency of caffeinated and decaffeinated coffee consumption are displayed in Appendix Table A1 (online only).

Impact of Coffee Intake on Cancer Recurrence and Death

The median follow-up time from completion of Q1 is 7.3 years. During follow-up, 329 of the 953 patients in this analysis experienced cancer recurrence or developed new primary tumors; 288 of these patients died. An additional 36 patients died without documented cancer recurrence.

The predefined primary end point in our analysis was DFS. Increasing total coffee intake was associated with a significant reduction in the risk of cancer recurrence or mortality after adjusting for other predictors of cancer recurrence (Table 2). Compared with abstainers, patients who consumed 4 cups/d or more of coffee experienced an adjusted hazard ratio (HR) for disease recurrence or mortality of 0.59 (95% CI, 0.35 to 1.00; P_{trend} = .003). Increasing total coffee intake was also associated with a significant improvement in OS (P_{trend} = .008) and a trend toward improved RFS that did not reach statistical significance (P_{trend} = .06). These results were largely unchanged when further adjusted for sugar-sweetened beverage intake and glycemic load (DFS, P_{trend} = .002; RFS, P_{trend} = .07; OS, P_{trend} = .01).

Improved outcomes were also associated with caffeinated coffee consumption. Compared with abstainers, patients who consumed 4

	Table 1. Baseline Characteristics (total coffee consumption) of 953 Participants				
	Total Coffee Intake (cups/d)				
Characteristic	0 (n = 154)	< 1 (n = 186)	1 (n = 238)	2-3 (n = 313)	≥ 4 (n = 62)
Coffee intake, cups/d					
Median	0	0.1	1.0	2.5	4.5
Range	0	0.003-0.498	0.5-1.475	1.502-3.430	3.658-6.559
Male sex, No. (%)	77 (50.0)	87 (46.8)	129 (54.2)	195 (62.3)	46 (74.2)
Age, years, median (range)	55 (34-81)	59 (21-85)	63 (28-83)	62 (26-79)	60 (29-78)
Race, No. (%)					
White	133 (86.4)	156 (83.9)	198 (83.2)	299 (95.5)	61 (98.4)
Black	13 (8.4)	19 (10.2)	25 (10.5)	3 (1.0)	1 (1.6)
Other	8 (5.2)	11 (5.9)	15 (6.3)	11 (3.5)	0 (0)
Baseline performance status, No. (%)*					
0	109 (70.8)	128 (68.8)	179 (75.2)	234 (74.8)	46 (74.2)
1-2	43 (27.9)	53 (28.5)	54 (22.7)	71 (22.7)	15 (24.2)
Status unknown	2 (1.3)	5 (2.7)	5 (2.1)	8 (2.6)	1. (1.6)
Invasion through bowel wall by T stage, No. (%)†					
T1-2	30 (19.5)	18 (9.7)	31 (13.0)	39 (12.5)	12 (19.4)
T3-4	117 (76.0)	152 (81.7)	190 (79.8)	255 (81.5)	43 (69.4)
T stage unknown	7 (4.5)	16 (8.5)	17 (7.1)	19 (6.1)	7 (11.3)
Positive lymph nodes, No. (%)					
1-3	97 (63.0)	122 (65.6)	160 (67.2)	177 (56.5)	42 (67.7)
≥ 4	54 (35.1)	59 (31.7)	73 (30.7)	129 (41.2)	20 (32.3)
Nodes unknown	3 (1.9)	5 (2.7)	5 (2.1)	7 (2.2)	0 (0)
Grade of differentiation, No. (%)					
Well	9 (5.8)	12 (6.5)	15 (6.3)	17 (5.4)	2 (3.2)
Moderate	108 (70.1)	129 (69.4)	178 (74.8)	199 (63.6)	43 (69.4)
Poor/undifferentiated	35 (22.7)	39 (21.0)	40 (16.8)	89 (28.4)	17 (27.4)
Grade unknown	2 (1.3)	6 (3.2)	5 (2.1)	8 (2.6)	0 (0)
Clinical bowel obstruction at presentation, No. (%)	36 (23.4)	46 (24.7)	49 (20.6)	57 (18.2)	18 (29.0)
Bowel perforation at presentation, No. (%)	9 (5.8)	8 (4.3)	10 (4.2)	8 (2.6)	4 (6.5)
Treatment arm, No. (%)					
FU/LV	86 (55.8)	94 (50.5)	128 (53.8)	149 (47.6)	29 (46.8)
IFL	68 (44.2)	92 (49.5)	110 (46.2)	164 (52.4)	33 (53.2)
BMI, kg/m², median (range)‡	27.6 (18-50)	27.4 (16-46)	27.3 (17-49)	27.3 (16-52)	27.5 (19-46)
Physical activity, MET-h/w, median (range)‡	4.7 (0-120)	4.9 (0-147)	3.5 (0-125)	6.0 (0-114)	8.9 (0-115)
Current smoker, No. (%)‡	10 (6.5)	13 (7.0)	18 (7.6)	39 (12.5)	14 (22.6)
Current use of multivitamin, No. (%)‡	78 (50.6)	104 (55.9)	122 (51.3)	136 (43.5)	29 (46.8)
Dietary intake, median (range)‡					
Total energy, kcal/d	1,937 (559-3,974)	1,915 (650-3,902)	1,805 (615-3,891)	2,012 (618-4,100)	2,224 (1,045-3,784)
Alcohol consumption, g/d	0 (0-66.9)	0.4 (0-54.7)	0.4 (0-83.2)	0.7 (0-93.0)	1.0 (0-46.9)
Glycemic load	151.9 (57.5-230.9)	152.1 (88.9-231.1)	148.5 (79.2-246.6)	145.9 (80.1-211.4)	138.2 (90.7-187.3)
Sugar-sweetened beverage, s/d	0.4 (0-4.8)	0.4 (0-5.4)	0.3 (0-5.9)	0.2 (0-5.1)	0.3 (0-3.4)
Total caffeine, mg/d	39 (0-543)	54 (1-441)	131 (2-886)	287 (2-1,376)	459 (0-975)
Western dietary pattern, No. ≥ median (%)‡	68 (44.2)	79 (42.5)	96 (40.3)	186 (59.4)	47 (75.8)
Prudent pattern diet, No. ≥ median (%)‡	70 (45.5)	100 (53.8)	130 (54.6)	154 (49.2)	23 (37.1)

Abbreviations: BMI, body mass index; FU/LV, fluorouracil and leucovorin; IFL, irinotecan, fluorouracil, and leucovorin; MET-h/w, metabolic equivalent task hours per week; s, servings.

*Baseline performance status (PS): PS 0 indicates fully active; PS 1, restricted in physically strenuous activity but ambulatory and able to perform light work; PS 2, ambulatory and capable of all self-care but unable to perform any work activities, up and approximately more than 50% of waking hours.

†T1-2 indicates level of invasion through the bowel wall not beyond the muscle layer; T3-4, level of invasion through the bowel wall beyond the muscle layer.

‡As reported on questionnaire 1.

cups/d or more of caffeinated coffee experienced a significant reduction in cancer recurrence or mortality (adjusted HR, 0.49; 95% CI, 0.26 to 0.92; P_{trend} = .003; Table 2). Similarly, increasing consumption of caffeinated coffee was associated with a statistically significant improvement in RFS (P_{trend} = .03) and OS (P_{trend} = .006). These results remained largely unchanged when adjusted for sugar-sweetened beverage intake and glycemic load (DFS, P_{trend} = .002; RFS, P_{trend} = .04; OS, P_{trend} = .01). In contrast, neither nonherbal tea nor decaffeinated coffee intake was associated with patient outcome. Secondary analyses showed no association of outcomes with herbal or total tea (data not shown).

We assessed the influence of total caffeine intake on patient outcome (Table 3). Compared with patients in the lowest quintile of caffeine intake, those in the highest quintile experienced a significant improvement in cancer recurrence or mortality (adjusted HR, 0.65; 95% CI, 0.46 to 0.91; P_{trend} = .005). In addition, increasing caffeine intake was associated with a statistically significant improvement in RFS (P_{trend} = .02) and OS (P_{trend} = .02). These results remained statistically

Table 2. Associations Between Colon Cancer Recurrence and Mortality and Total Coffee, Caffeinated Coffee, Decaffeinated Coffee, and Nonherbal Tea

| Variable | Categories of Intake (cups/d) | | | | | P_{trend}* |
	0	< 1	1	2-3	≥ 4	
Total coffee						
DFS						
Events and total	60 of 154	73 of 186	94 of 238	117 of 313	21 of 62	—
HR (95% CI)						
Adjusted 1†	1.0	0.99 (0.70 to 1.40)	0.94 (0.67 to 1.31)	0.71 (0.51 to 0.98)	0.59 (0.35 to 1.00)	.003
Adjusted 2‡	1.0	0.98 (0.69 to 1.39)	0.93 (0.66 to 1.30)	0.69 (0.49 to 0.96)	0.58 (0.34 to 0.99)	.002
RFS						
Events and total	52 of 154	65 of 186	81 of 238	111 of 313	20 of 62	—
HR (95% CI)						
Adjusted 1†	1.0	0.99 (0.68 to 1.44)	0.93 (0.65 to 1.33)	0.80 (0.56 to 1.13)	0.68 (0.40 to 1.18)	.06
Adjusted 2‡	1.0	0.98 (0.68 to 1.43)	0.97 (0.68 to 1.40)	0.80 (0.56 to 1.14)	0.71 (0.41 to 1.23)	.07
OS						
Events and total	48 of 154	59 of 186	74 of 238	89 of 313	18 of 62	—
HR (95% CI)						
Adjusted 1†	1.0	1.01 (0.68 to 1.49)	0.96 (0.66 to 1.40)	0.69 (0.47 to 1.01)	0.64 (0.36 to 1.13)	.008
Adjusted 2‡	1.0	0.97 (0.66 to 1.44)	0.97 (0.66 to 1.42)	0.69 (0.47 to 1.01)	0.66 (0.37 to 1.18)	.01
Caffeinated coffee						
DFS						
Events and total	94 of 238	101 of 247	67 of 183	91 of 247	12 of 38	—
HR (95% CI)						
Adjusted 1†	1.0	0.94 (0.70 to 1.27)	0.84 (0.61 to 1.16)	0.70 (0.51 to 0.94)	0.49 (0.26 to 0.92)	.003
Adjusted 2‡	1.0	0.94 (0.70 to 1.26)	0.84 (0.61 to 1.16)	0.69 (0.51 to 0.93)	0.48 (0.25 to 0.91)	.002
RFS						
Events and total	83 of 238	92 of 247	57 of 183	86 of 247	11 of 38	—
HR (95% CI)						
Adjusted 1†	1.0	0.93 (0.68 to 1.28)	0.81 (0.57 to 1.14)	0.76 (0.55 to 1.05)	0.53 (0.27 to 1.03)	.03
Adjusted 2‡	1.0	0.93 (0.68 to 1.27)	0.82 (0.58 to 1.16)	0.78 (0.56 to 1.07)	0.55 (0.28 to 1.06)	.04
OS						
Events and total	77 of 238	79 of 247	52 of 183	69 of 247	11 of 38	—
HR (95% CI)						
Adjusted 1†	1.0	0.88 (0.63 to 1.22)	0.83 (0.57 to 1.19)	0.64 (0.45 to 0.91)	0.52 (0.27 to 1.02)	.006
Adjusted 2‡	1.0	0.85 (0.61 to 1.19)	0.83 (0.58 to 1.20)	0.65 (0.45 to 0.92)	0.54 (0.28 to 1.06)	.01
Decaffeinated coffee						
DFS						
Events and total	190 of 477	107 of 301	31 of 94	37 of 81		—
HR (95% CI)						
Adjusted 1†	1.0	0.87 (0.69 to 1.11)	0.68 (0.46 to 1.01)	0.89 (0.62 to 1.29)		.46
Adjusted 2‡	1.0	0.87 (0.69 to 1.11)	0.68 (0.46 to 1.01)	0.86 (0.59 to 1.25)		.36
RFS						
Events and total	166 of 477	99 of 301	28 of 94	36 of 81		—
HR (95% CI)						
Adjusted 1†	1.0	0.91 (0.71 to 1.17)	0.73 (0.48 to 1.10)	1.09 (0.75 to 1.60)		.78
Adjusted 2‡	1.0	0.94 (0.73 to 1.21)	0.77 (0.51 to 1.16)	1.06 (0.72 to 1.55)		.90
OS						
Events and total	155 of 477	80 of 301	24 of 94	29 of 81		—
HR (95% CI)						
Adjusted 1†	1.0	0.84 (0.63 to 1.10)	0.64 (0.41 to 1.00)	0.91 (0.60 to 1.38)		.55
Adjusted 2‡	1.0	0.85 (0.64 to 1.12)	0.67 (0.43 to 1.05)	0.89 (0.59 to 1.36)		.53
Nonherbal tea						
DFS						
Events and total	88 of 226	179 of 474	52 of 140	35 of 85	11 of 28	—
HR (95% CI)						
Adjusted 1†	1.0	1.06 (0.81 to 1.37)	0.94 (0.66 to 1.34)	1.02 (0.68 to 1.53)	0.90 (0.48 to 1.71)	.66
Adjusted 2‡	1.0	1.07 (0.82 to 1.38)	0.94 (0.67 to 1.34)	1.01 (0.67 to 1.52)	0.87 (0.46 to 1.65)	.55
RFS						
Events and total	80 of 226	161 of 474	44 of 140	34 of 85	10 of 28	—
HR (95% CI)						
Adjusted 1†	1.0	1.04 (0.79 to 1.36)	0.87 (0.59 to 1.26)	1.08 (0.71 to 1.63)	0.93 (0.48 to 1.82)	.86
Adjusted 2‡	1.0	1.09 (0.83 to 1.43)	0.89 (0.61 to 1.30)	1.03 (0.67 to 1.57)	0.86 (0.44 to 1.68)	.51

(continued on following page)

Table 2. Associations Between Colon Cancer Recurrence and Mortality and Total Coffee, Caffeinated Coffee, Decaffeinated Coffee, and Nonherbal Tea (continued)

| | Categories of Intake (cups/d) | | | | | |
Variable	0	< 1	1	2-3	≥ 4	P_{trend}*
OS						
Events and total	74 of 226	139 of 474	38 of 140	28 of 85	9 of 28	—
HR (95% CI)						
Adjusted 1†	1.0	1.03 (0.77 to 1.38)	0.86 (0.58 to 1.28)	1.00 (0.64 to 1.56)	0.87 (0.43 to 1.77)	.6
Adjusted 2‡	1.0	1.08 (0.81 to 1.44)	0.87 (0.58 to 1.30)	0.95 (0.60 to 1.50)	0.82 (0.40 to 1.67)	.36

Abbreviations: DFS, disease-free survival; HR, hazard ratio; OS, overall survival; Q1, questionnaire 1 (midway through adjuvant therapy); Q2, questionnaire 2 (6 months after completion of adjuvant therapy); RFS, recurrence-free survival.
*Two-sided P value. Trend across consumption levels.
†Adjusting for sex, age, depth of invasion through bowel wall, number of positive lymph nodes, baseline performance status, chemotherapy treatment group, smoking history (Q1, Q2: yes, no, missing), multivitamin (Q1, Q2: consistent user, no, missing), and the following time-varying covariates: total energy intake, alcohol consumption, body mass index, physical activity level, Western dietary pattern, and prudent dietary pattern. Caffeinated coffee consumption and decaffeinated coffee consumption were simultaneously included in the model. The model for tea is adjusted for total coffee consumption.
‡Adjusting for all above covariates plus time-varying sugar-sweetened beverage intake and dietary glycemic load.

significant after adjusting for sugar-sweetened beverage intake and glycemic load (DFS, P_{trend} = .006; RFS, P_{trend} = .04; OS, P_{trend} = .04).

Stratified Analyses

We examined the influence of total coffee intake on DFS across strata of other potential predictors of patient outcome, comparing 2 cups/d or more with 0 to conserve statistical power (Fig 2). The association between total coffee intake and patient outcome seemed consistent across most strata of patient, disease, and treatment characteristics. The association of total coffee intake with improved DFS seemed slightly stronger among patients with Eastern Cooperative Oncology Group performance status of 1 to 2, and a test for interaction between total coffee intake and baseline performance status was statistically significant ($P_{interaction}$ = .04).

DISCUSSION

In this prospective study of patients with stage III colon cancer, increasing coffee intake was associated with a significant improvement in cancer recurrence or mortality (DFS) and all-cause mortality (OS). The significant association seemed confined to caffeinated coffee intake. Consistent with this finding, we observed a significant association between higher caffeine intake and improved DFS, RFS, and OS. These associations were independent of other predictors of patient outcome, diet, and lifestyle factors. Moreover, the effect of total coffee intake was largely maintained across other known or suspected predictors of cancer recurrence.

To our knowledge, this is the first study to examine the association between coffee intake and colon cancer recurrence and survival. We hypothesized that coffee might reduce colon cancer recurrence through improved insulin sensitization and decreased hyperinsulinemia, on the basis of previous studies supporting the role of high-energy balance states in promoting colon cancer recurrence and mortality[13,14,16,31] and studies demonstrating an inverse relationship between coffee consumption and risk of T2D.[19,20] The precise effect of caffeine on insulin sensitivity is controversial: Although one trial showed caffeine to cause an

Table 3. Associations Between Colon Cancer Recurrence and Mortality and Caffeine Consumption

| | Caffeine Intake by Quintiles | | | | | |
Survival Outcome	1	2	3	4	5	P_{trend}*
DFS						
Events and total	78 of 190	84 of 191	62 of 191	73 of 191	68 of 190	—
HR (95% CI), adjusted 1†	1.0	1.02 (0.75 to 1.40)	0.72 (0.51 to 1.00)	0.80 (0.57 to 1.11)	0.65 (0.46-0.91)	.005
HR (95% CI), adjusted 2‡	1.0	1.05 (0.77 to 1.44)	0.74 (0.53 to 1.05)	0.82 (0.59 to 1.14)	0.66 (0.47-0.93)	.006
RFS						
Events and total	70 of 190	75 of 191	58 of 191	60 of 191	66 of 190	—
HR (95% CI), adjusted 1†	1.0	0.98 (0.70 to 1.36)	0.73 (0.51 to 1.04)	0.70 (0.50 to 1.00)	0.71 (0.50 to 1.01)	.02
HR (95% CI), adjusted 2‡	1.0	1.05 (0.75 to 1.46)	0.76 (0.54 to 1.09)	0.75 (0.53 to 1.07)	0.76 (0.53 to 1.08)	.04
OS						
Events and total	60 of 190	69 of 191	45 of 191	58 of 191	56 of 190	—
HR (95% CI), adjusted 1†	1.0	1.05 (0.74 to 1.50)	0.67 (0.45 to 0.99)	0.83 (0.57 to 1.21)	0.68 (0.46 to 1.00)	.02
HR (95% CI), adjusted 2‡	1.0	1.11 (0.78 to 1.59)	0.68 (0.46 to 1.01)	0.88 (0.61 to 1.28)	0.72 (0.49 to 1.05)	.04

Abbreviations: DFS, disease-free survival; HR, hazard ratio; OS, overall survival; Q1, questionnaire 1 (midway through adjuvant therapy); Q2, questionnaire 2 (6 months after completion of adjuvant therapy); RFS, recurrence-free survival.
*Two-sided P value. Trend across consumption levels.
†Adjusting for sex, age, depth of invasion through bowel wall, number of positive lymph nodes, baseline performance status, chemotherapy treatment group, smoking history (Q1, Q2: yes, no, missing), multivitamin (Q1, Q2: consistent user, no, missing), and the following time-varying covariates: total energy intake, alcohol consumption, body mass index, physical activity level, Western dietary pattern, and prudent dietary pattern.
‡Adjusting for all above covariates plus time-varying sugar-sweetened beverage intake and dietary glycemic load.
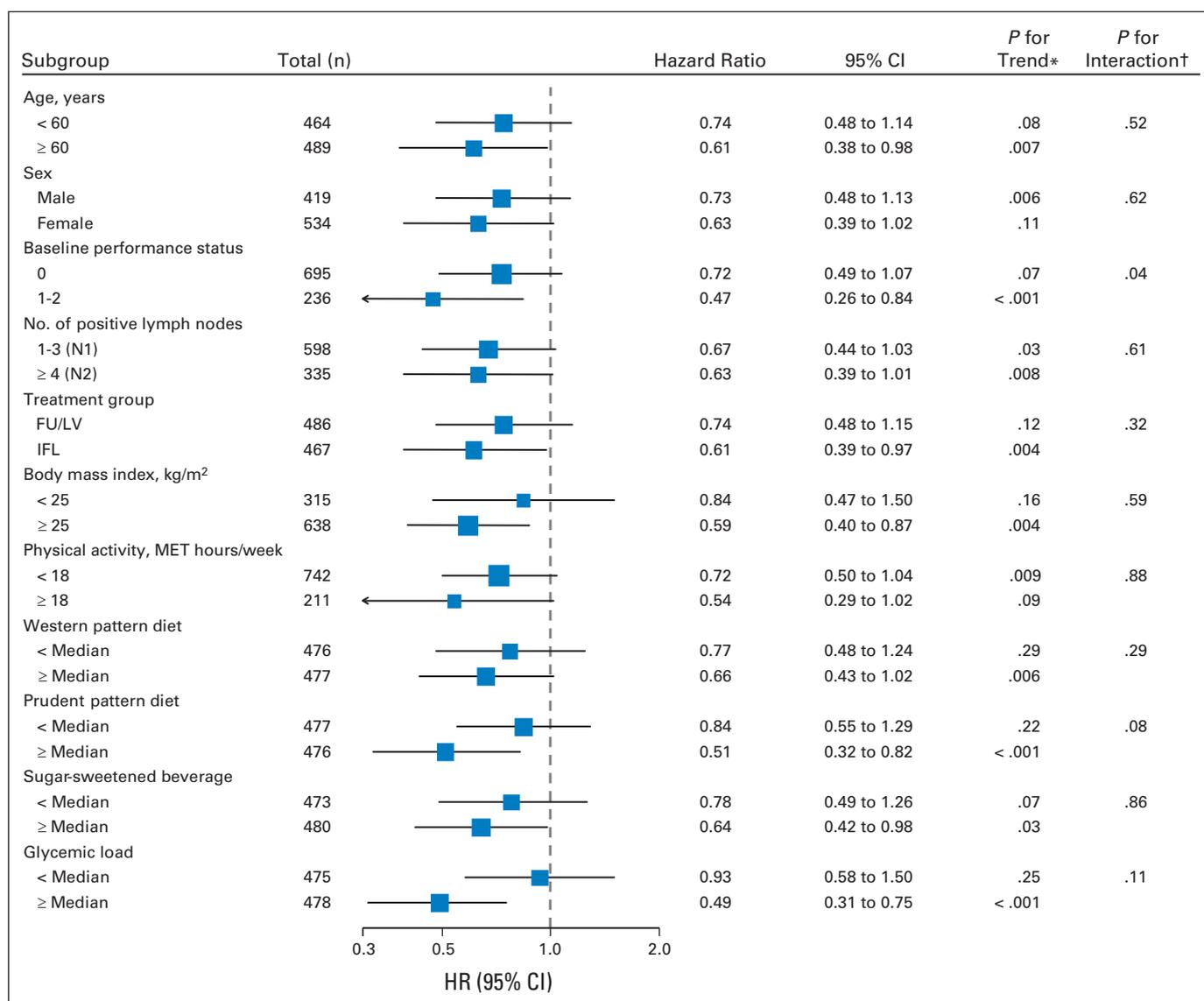
Fig 2. Multivariable hazard ratios (HRs) and 95% CIs for cancer recurrence or mortality across strata of various factors. Analyses used four categories (0, < 1, 1, and ≥ 2 cups/d). The forest plot represents the HRs of the comparison of 2 cups/d or more of total coffee intake with 0 cups/wk, adjusting for sex, age, depth of invasion through bowel wall, number of positive lymph nodes, baseline performance status, chemotherapy treatment group, smoking history (questionnaire 1 [Q1; midway through adjuvant therapy], questionnaire 2 [Q2; 6 months after completion of adjuvant therapy]: yes, no, missing), multivitamin (Q1, Q2: consistent user, no, missing), and the following time-varying covariates: total energy intake, alcohol consumption, body mass index, physical activity level, Western dietary pattern, prudent dietary pattern, sugar-sweetened beverage intake, and dietary glycemic load. FU/LV, fluorouracil plus leucovorin; IFL, irinotecan, fluorouracil, and leucovorin; MET, metabolic equivalent task. (*) Two-sided *P*, trend across consumption levels. (†) Two-sided *P*.

immediate decrease in insulin sensitivity,[48] another trial showed increased adiponectin, an endogenous insulin sensitizer, with caffeinated coffee.[24] Most prospective studies and meta-analyses studying the relationship between coffee consumption and risk of T2D have shown an inverse association for both caffeinated and decaffeinated coffee.[19-21,49] Furthermore, one prospective cohort identified an inverse association between decaffeinated coffee consumption and hemoglobin A1c level.[50]

Although our findings seemed limited to caffeinated coffee, statistical power to adequately examine decaffeinated coffee was limited. Coffee components beyond caffeine may play a role, such as chlorogenic acid, a hypoglycemic coffee phenol.[51,52] Alternatively, coffee and caffeine may affect colon cancer through other mechanisms, such as

anti-inflammatory,[53] antioxidant,[54,55] antiangiogenic, antimetastatic, and proapoptotic effects.[56-58]

We cannot completely exclude the possibility that the associations between total coffee, caffeinated coffee, and caffeine intake and improved DFS result from confounding variables. However, these associations persisted even after controlling for known or suspected predictors of patient outcome, including physical activity, dietary glycemic load, sugar-sweetened beverage intake, and Western and prudent dietary patterns. Furthermore, the association between coffee and improved DFS remained largely consistent across strata of these other predictors of patient outcome. Nonetheless, data on other potential confounders associated with coffee intake, such as poor sleeping habits, work shifts, and anxiety, were not examined in our trial.

Given that patients who consume coffee after cancer diagnosis may have similarly consumed coffee before diagnosis, we cannot exclude the possibility that coffee drinkers develop biologically less aggressive colon cancers. Nonetheless, we did not observe a meaningful association between coffee intake and tumor-related characteristics associated with cancer recurrence.

Testing for relationships between dietary factors and cancer recurrence and mortality in a large random assignment trial offers several advantages. Patient follow-up and treatment were carefully prescribed in the trial, with regular detailed medical examinations to prospectively record the date and nature of cancer recurrences. At study enrollment, all patients had lymph node–positive, nonmetastatic cancer, reducing impact of heterogeneity by disease stage. Prospective collection of detailed information on other potentially prognostic variables at the time of study enrollment reduced likelihood of reporting bias, facilitating more accurate adjustment for potential confounders. Finally, we updated dietary data 6 months after completion of adjuvant chemotherapy to reflect changes in diet that may have occurred after patients recovered from treatment effects and to reduce random error in reporting of dietary practices through repeated measurements. Any residual random error in reporting of dietary practices would likely bias findings toward the null hypothesis.

We considered the possibility that patients with occult cancer recurrences or other poor prognostic characteristics may have decreased their coffee intake. To minimize this bias, we excluded recurrences or deaths within 3 months of FFQ completion. Furthermore, because patients in this trial underwent comprehensive clinical and radiologic assessment before study enrollment, we would expect few patients to have occult cancer recurrences or other poor prognostic characteristics at baseline. To address potential change in dietary habits over time, we conducted a second FFQ 14 months after resection; nonetheless, we cannot exclude that additional dietary habit changes may have occurred after the second FFQ that were not captured in our analysis. However, any misclassification in dietary habits in our analysis would bias our results toward the null hypothesis. Moreover, previous studies have shown dietary patterns in men to be stable during a 1-year interval,[59] and stable in women during 5 years,[60] suggesting that dietary patterns may have remained largely stable beyond 24 months after resection. We further recognize that the caffeine content of coffee available across the United States may vary, potentially contributing to measurement error in our analysis; nonetheless, any misclassification in the measurement of caffeine intake would bias our results toward the null hypothesis. In addition, we note the number of patients in our study exceeding 3 cups/d of coffee was relatively small (n = 62); therefore, additional studies should be performed to replicate our findings.

Finally, patients in randomized trials may differ from the general population. However, the distribution of dietary and lifestyle practices reported by our cohort did not differ significantly from those reported in other US cohorts,[38] and this cohort, drawn from a large clinical trial, included patients from both community and academic centers throughout North America, improving external validity of our results.

In sum, this prospective study of patients with stage III colon cancer, embedded in a randomized clinical trial, demonstrates improved patient outcome with increased consumption of total coffee, caffeinated coffee, and caffeine. Although our observational study does not offer conclusive evidence for causality, our findings potentially inform colon cancer biology and offer further insight into the role of diet and lifestyle in outcome for patients with colon cancer. Further studies are needed to confirm our findings.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

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■ ■ ■

GLOSSARY TERMS

Cox proportional hazards: See *Cox proportional hazards regression model*.

C-peptide: A protein fragment produced during the enzymatic cleavage of proinsulin to create insulin. It is secreted by pancreatic β-cells at equimolar concentrations to insulin but has a half-life in the circulation of two to five times longer. Because its greater stability in the peripheral circulation, C-peptide has been measured in research studies as a marker of pancreatic β-cell secretory activity.

Western pattern diet: Western pattern diet is characterized by high intakes of red and processed meats, fat, refined grains, and dessert.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Coffee Intake, Recurrence, and Mortality in Stage III Colon Cancer: Results From CALGB 89803 (Alliance)

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Appendix

Table A1. Baseline Characteristics (caffeinated and decaffeinated coffee consumption) for 953 Participants

Characteristic	Caffeinated Coffee Intake (cups/d)					Decaffeinated Coffee Intake (cups/d)			
	0 (n = 238)	< 1 (n = 247)	1 (n = 183)	2-3 (n = 247)	≥ 4 (n = 38)	0 (n = 447)	< 1 (n = 301)	1 (n = 94)	≥ 2 (n = 81)
Intake, cups/d									
Median	0	0.1	1.0	2.5	4.5	0	0.1	1.0	2.5
Range (min)	0	0.0026	0.506	1.502	3.518	0	0.00007	0.513	1.576
Range (max)	0	0.4981	1.475	3.371	6.000	0	0.498	1.490	5.857
Male sex, No. (%)	114 (48)	142 (58)	98 (54)	151 (61)	29 (76)	272 (57)	151(50)	57 (61)	54 (67)
Age, years, median (range)	57 (34-85)	63 (21-82)	60 (28-83)	60 (26-79)	57 (29-78)	57 (21-82)	60 (24-85)	67 (36-80)	66 (46-78)
Race, No. (%)									
White	201 (84.5)	210 (85.0)	161 (88.0)	237 (96.0)	38 (100)	429 (89.9)	262 (87.0)	80 (85.1)	76 (93.8)
Black	27 (11.3)	22 (8.9)	10 (5.5)	2 (0.8)	0 (0)	25 (5.2)	24 (8.0)	10 (10.6)	2 (2.5)
Other	10 (4.2)	15 (6.1)	12 (6.6)	8 (3.2)	0 (0)	23 (4.8)	15 (5.0)	4 (4.3)	3 (3.7)
Baseline performance status, No. (%)*									
0	170 (71.4)	174 (70.4)	138 (75.4)	187 (75.7)	27 (71.1)	347 (72.7)	220 (73.1)	71 (75.5)	58 (71.6)
1-2	64 (26.9)	69 (27.9)	40 (21.9)	53 (21.5)	10 (26.3)	118 (24.7)	74 (24.6)	22 (23.4)	22 (27.2)
Status unknown	4 (1.7)	4 (1.6)	5 (2.7)	7 (2.8)	1 (2.6)	12 (2.5)	7 (2.3)	1 (1.1)	1 (1.2)
Invasion through bowel wall by T stage, No. (%)†									
T1-2	47 (19.7)	19 (7.7)	25 (13.7)	34 (13.8)	5 (13.2)	68 (14.3)	36 (12.0)	13 (13.8)	13 (16.0)
T3-4	179 (75.2)	212 (85.8)	144 (78.7)	193 (78.1)	29 (76.3)	370 (77.6)	247 (82.1)	77 (81.9)	63 (77.8)
T stage unknown	12 (5.0)	16 (6.5)	14 (7.7)	20 (8.1)	4 (10.5)	39 (8.2)	18 (6.0)	4 (4.3)	5 (6.2)
Positive lymph nodes, No. (%)									
1-3	149 (62.6)	158 (64.0)	122 (66.7)	146 (59.1)	23 (60.5)	302 (63.3)	190 (63.1)	58 (61.7)	48 (59.3)
≥ 4	84 (35.3)	85 (34.4)	56 (30.6)	95 (38.5)	15 (39.5)	163 (34.2)	105 (34.9)	35 (37.2)	32 (39.5)
Nodes unknown	5 (2.1)	4 (1.6)	5 (2.7)	6 (2.4)	0 (0)	12 (2.5)	6 (2.0)	1 (1.1)	1 (1.2)
Grade of differentiation, No. (%)									
Well	13 (5.5)	16 (6.5)	11 (6.0)	14 (5.7)	1 (2.6)	32 (6.7)	14 (4.7)	5 (5.3)	4 (4.9)
Moderate	160 (67.2)	181 (73.3)	136 (74.3)	155 (62.8)	25 (65.8)	321 (67.3)	213 (70.8)	69 (73.4)	54 (66.7)
Poor/undifferentiated	61 (25.6)	45 (18.2)	31 (16.9)	71 (28.7)	12 (31.6)	111 (23.3)	68 (22.6)	19 (20.2)	22 (27.2)
Grade unknown	4 (1.7)	5 (2.0)	5 (2.7)	7 (2.8)	0 (0)	13 (2.7)	6 (2.0)	1 (1.1)	1 (1.2)
Clinical bowel obstruction at presentation, No. (%)	52 (21.8)	57 (23.1)	34 (18.6)	53 (21.5)	10 (26.3)	106 (22.2)	66 (21.9)	23 (24.5)	11 (13.6)
Bowel perforation at presentation, No. (%)	13 (5.5)	10 (4.0)	5 (2.7)	8 (3.2)	3 (7.9)	22 (4.6)	10 (3.3)	6 (6.4)	1 (1.2)
Treatment arm, No. (%)									
FU/LV	120 (50.4)	124 (50.2)	100 (54.6)	122 (49.4)	20 (52.6)	255 (53.5)	156 (51.8)	44 (46.8)	31 (38.3)
IFL	118 (49.6)	123 (49.8)	83 (45.4)	125 (50.6)	18 (47.4)	222 (46.5)	145 (48.2)	50 (53.2)	50 (61.7)
BMI, kg/m² , median (range)‡	27.6 (17.2-49.9)	27.2 (16.3-46.2)	27.3 (17.3-46.3)	27.3 (15.7-51.8)	26.5 (19.0-46.2)	27.7 (15.7-49.9)	26.8 (17.2-51.8)	26.6 (17.2-49.4)	27.4 (18.5-40.3)
Physical activity, MET-h/w, median (range)‡	4.0 (0-119.9)	6.0 (0-147.4)	3.9 (0-125.2)	5.2 (0-114.2)	13.2 (0-114.6)	5.4 (0-147.4)	4.5 (0-112.7)	3.2 (0-87.5)	6.9 (0-112.7)
Current smoker, No. (%)‡	17 (7.1)	16 (6.5)	14 (7.7)	35 (14.2)	12 (31.6)	55 (11.5)	23 (7.6)	9 (9.6)	7 (8.6)
Currently uses multivitamin, No. (%)‡	126 (52.9)	131 (53.0)	91 (49.7)	105 (42.5)	16 (42.1)	209 (43.8)	172 (57.1)	50 (53.2)	38 (46.9)
Dietary intake‡									
Total energy, kcal/d	1,761 (559-3,974)	1,973 (650-3,902)	1,938 (615-3,844)	2,027 (618-4,100)	2,329 (1,050-3,784)	1,950 (559-4,100)	1,951 (727-3,902)	1,877 (685-3,891)	1,978 (1,045-3,240)
Alcohol consumption, g/d	0 (0-66.9)	0.4 (0-67.0)	0.6 (0-83.2)	0.8 (0-93.0)	1.2 (0-37.5)	0 (0-93.0)	0.6 (0-61.2)	0.4 (0-35.2)	0.4 (0-67.0)
Glycemic load	151.7 (57.5-247)	151.8 (88.9-231)	144.8 (79.2-232)	142.2 (80.1-204)	137.2 (97.2-187)	146.7 (57.5-231)	147.2 (82.4-232)	151.8 (99.8-247)	147.2 (90.7-208)
Sugar-sweetened beverage, s/d	0.4 (0-4.8)	0.4 (0-5.4)	0.3 (0-5.9)	0.3 (0-5.1)	0.4 (0-3.4)	0.4 (0-5.4)	0.3 (0-5.9)	0.4 (0-3.6)	0.2 (0-3.5)

Table A1. Baseline Characteristics (caffeinated and decaffeinated coffee consumption) for 953 Participants (continued)

Characteristic	Caffeinated Coffee Intake (cups/d)					Decaffeinated Coffee Intake (cups/d)			
	0 (n = 238)	< 1 (n = 247)	1 (n = 183)	2-3 (n = 247)	≥ 4 (n = 38)	0 (n = 447)	< 1 (n = 301)	1 (n = 94)	≥ 2 (n = 81)
Caffeine, mg/d	36 (0-543)	60 (2-593)	165 (3-886)	331 (2-1,376)	542 (10-975)	154 (0-1,376)	117 (1-1,098)	72 (2-637)	64 (0-793)
Western dietary pattern, No. ≥ median (%)‡	97 (40.8)	119 (48.2)	81 (44.3)	149 (60.3)	30 (78.9)	244 (51.2)	143 (47.5)	41 (43.6)	48 (59.3)
Prudent pattern diet, No. ≥ median (%)‡	111 (46.6)	135 (54.7)	100 (54.6)	120 (48.6)	11 (28.9)	231 (48.4)	160 (53.2)	46 (48.9)	40 (49.4)

Abbreviations: BMI, body mass index; FU/LV, fluorouracil and leucovorin; IFL, irinotecan, fluorouracil, and leucovorin; MET-h/w, metabolic equivalent task hours per week; min, minimum; max, maximum; s, servings.

*Baseline performance status (PS): PS 0 indicates fully active; PS 1, restricted in physically strenuous activity but ambulatory and able to perform light work; PS 2, ambulatory and capable of all self-care but unable to perform any work activities, up and approximately more than 50% of waking hours.

†T1-2 indicates level of invasion through the bowel wall not beyond the muscle layer; T3-4, level of invasion through the bowel wall beyond the muscle layer.

‡As reported on questionnaire 1.