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Dietary Glycemic Load and Cancer Recurrence and Survival in Patients with Stage III Colon Cancer: Findings From CALGB 89803

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Background The influence of glycemic load and related measures on survival among colon cancer patients remains largely unknown.

Methods We conducted a prospective, observational study of 1011 stage III colon cancer patients reporting dietary intake during and 6 months after participation in an adjuvant chemotherapy trial. We examined the influence of glycemic load, glycemic index, fructose, and carbohydrate intakes on cancer recurrence and mortality using Cox proportional hazards regression; all tests of statistical significance were two-sided.

Results Stage III colon cancer patients in the highest quintile of dietary glycemic load experienced an adjusted hazard ratio (HR) for disease-free survival of 1.79 (95% confidence interval [CI] = 1.29 to 2.48), compared with those in the lowest quintile (P_{trend} across quintiles <.001). Increased glycemic load was associated with similar detriments in recurrence-free (P_{trend} across quintiles <.001) and overall survival (P_{trend} across quintiles <.001). These associations differed statistically significant by body mass index (BMI) ($P_{interaction}$ =.01). Whereas glycemic load was not associated with disease-free survival in patients with BMI < 25 kg/m^2, higher glycemic load was statistically significant associated with worse disease-free survival among overweight or obese participants (BMI ≥ 25 kg/m^2; HR = 2.26; 95% CI = 1.53 to 3.32; P_{trend} across quintiles <.001). Increasing total carbohydrate intake was similarly associated with inferior disease-free, recurrence-free, and overall survival (P_{trend} across quintiles <.001).

Conclusion Higher dietary glycemic load and total carbohydrate intake were statistically significant associated with an increased risk of recurrence and mortality in stage III colon cancer patients. These findings support the role of energy balance factors in colon cancer progression and may offer potential opportunities to improve patient survival.

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Preclinical and clinical evidence indicates that hyperinsulinemia may play an important role in the development of colorectal cancer (1,2). Many of the established risk factors of colorectal cancer, including obesity (3,4) and physical inactivity (5), directly influence insulin levels. Other studies have observed elevated risks of colon cancer among those with a history of type 2 diabetes mellitus (6) or elevated blood insulin or plasma C-peptide levels (7–10).

Diet influences systemic insulin levels. Foods with low glucose indexes have reduced serum insulin and glucose responses, compared with foods with high indexes. The physiological response to carbohydrates can be quantified by the glycemic index, a qualitative assessment of foods calculated as a percentage of the body's plasma glucose response to specific foods compared with the response induced by the same amount of carbohydrate from a standard carbohydrate source, usually white bread or pure glucose (11,12). The glycemic load is calculated by multiplying the carbohydrate index of each food by its glycemic index and the frequency of consumption, providing a qualitative and quantitative measurement (13). Glycemic load and other carbohydrate measures have been associated with the risk of developing colorectal cancer in some (14–17), but not all (18–21), studies.

Recent studies have found a direct association between host factors leading to hyperinsulemia and cancer recurrences and mortality in colorectal cancer survivors (22–28). In a study of stage III colon cancer patients, the highest quintile of consumption of a Western pattern diet (characterized by high intakes of meat, fat, refined grains, and sugar desserts) was associated with a threefold increase in cancer recurrence and deaths compared with the lowest quintile (27). To further understand which component of a Western pattern diet is associated with poorer outcomes and define the impact of dietary glycemic measures on colon cancer survival, we prospectively examined the association between dietary glycemic load and index, total fructose intake, and total carbohydrates intake on cancer recurrences and survival in a cohort of stage III colon cancer patients enrolled in an adjuvant chemotherapy trial in which extensive data on dietary intake, height, weight, and physical

activity were collected at the study onset prior to any subsequent events of cancer recurrence.

Methods

Study Population

This prospective cohort was derived from participants in the National Cancer Institute–sponsored Cancer and Leukemia Group B (CALGB) 89803 adjuvant therapy trial for stage III colon cancer (29) (ClinicalTrials.gov identifier NCT00003835; http://clinicaltrials.gov/ct2/show/NCT00003835; accessed August 2, 2012) comparing therapy with weekly 5-fluorouracil and leucovorin to weekly irinotecan, 5-fluorouracil, and leucovorin (30). Between May 1999 and May 2001, 1264 patients were enrolled in the trial. After 87 patients were enrolled, an amendment required participants to complete a questionnaire capturing diet and lifestyle habits midway through adjuvant therapy (Q1) and 6 months after completion of adjuvant therapy (Q2). Figure 1 illustrates the derivation of the final sample size of 1011 patients for this study. Supplementary Table 1 (available online) shows that there were no appreciable differences in baseline characteristics between the 1011 patients who were eligible for these analyses and the other 253 patients treated on CALGB 89803 but not included in this study.

Patients were eligible if they underwent a complete surgical resection of the primary tumor within 56 days of trial entry, had regional lymph node metastases but no evidence of distant metastases, had baseline Eastern Cooperative Oncology Group performance status of 0–2 (31), and had adequate bone marrow, renal, and hepatic function. All patients signed informed consent, which was approved by each site's institutional review board.

Dietary Assessment

Patients completed semiquantitative food frequency questionnaires (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 over 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 using composition values from Department of Agriculture sources supplemented with other data (34). All nutrient values were energy-adjusted using the residuals methods (35).

The glycemic index value was calculated as follows: Σ incremental blood glucose area under the curve of test food × 100% Σ incremental blood glucose area under the curve of reference food. Using these glycemic index values, the mean dietary glycemic load was calculated by multiplying the carbohydrate content for each food by its glycemic index value, multiplying that product by the servings of that food per day, and summing values for all food items reported. Each glycemic load unit represents the equivalent of 1 gram of carbohydrate from white bread (13). The overall dietary glycemic index was calculated by dividing glycemic load by the total amount of carbohydrate. Total fructose intake was calculated as free fructose plus fructose from sucrose intake.

In a validity study of 173 women, correlation coefficients between the average intake assessed by two 1-week diet records and the FFQs were as follows: 0.71 for white bread, 0.77 for dark bread, 0.66 for potatoes, 0.84 for orange or grapefruit juice, and 0.56 for noncarbonated fruit drinks (36). In a study specific to cancer patients on chemotherapy, dietary glycemic load as measured by the questionnaire was inversely associated with plasma high-density lipoprotein (P =.007) (37).

Patients who completed the first FFQ (Q1) and whose cancer had not recurred prior to its completion were included in these analyses. The median time from study entry to Q1 was 3.5 months (95% range = 2.5–5.0 months; full range = 0.2–9.9 months). To avoid potential biases due to declining health immediately before recurrence or death, we excluded from analyses patients who experienced either event within 90 days following completion of Q1 (Figure 1). We updated dietary exposures based on the results of the second FFQ (Q2) using cumulative averaging as previously described (17,27,38,39) but weighted proportional to times between Q1 and Q2 and then between Q2 and disease-free survival 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. We therefore calculated the glycemic load as follows: cumulative averaging glycemic load = (glycemic load at Q1 × 0.38) + {[(glycemic load at Q1 + glycemic load at Q2) / 2] × 0.62}.

Endpoints

The primary endpoint was disease-free survival, defined as time from the completion of Q1 to tumor recurrence, occurrence of a new colon primary tumor, or death from any cause. Recurrence-free survival was defined as time from the completion of Q1 to tumor recurrence or occurrence of a new colon primary tumor, censoring patients who died without known recurrence at last recorded evaluation. Overall survival was defined as time from the completion of Q1 to death from any cause.

Statistical Analysis

In the clinical trial, there was no statistical difference in either disease-free or overall survival between the treatment arms (30). Therefore, data for patients in both arms were combined and analyzed according to quintiles of each exposure. Cox proportional hazards regression (40) was used to adjust for potential confounders. We used time-varying covariates to adjust for physical activity and body mass index (BMI) with updating from Q2. Other covariates were entered into the model as fixed covariates. Covariates with missing variables were coded with indicator variables. We tested for linear trend across quintiles by assigning each participant the median value for the quintile and modeling this value as a continuous variable, consistent with prior studies (41–43). The Cox regression models met the assumption of proportionality by both time-dependent covariate and Schoenfeld residuals methods. All P values are two-sided, with P less than.05 considered statistically significant; P values were not adjusted for multiple comparisons. Tests for effect modification by sex and other potential interactions were performed and reported.

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 frozen on March 31, 2009.

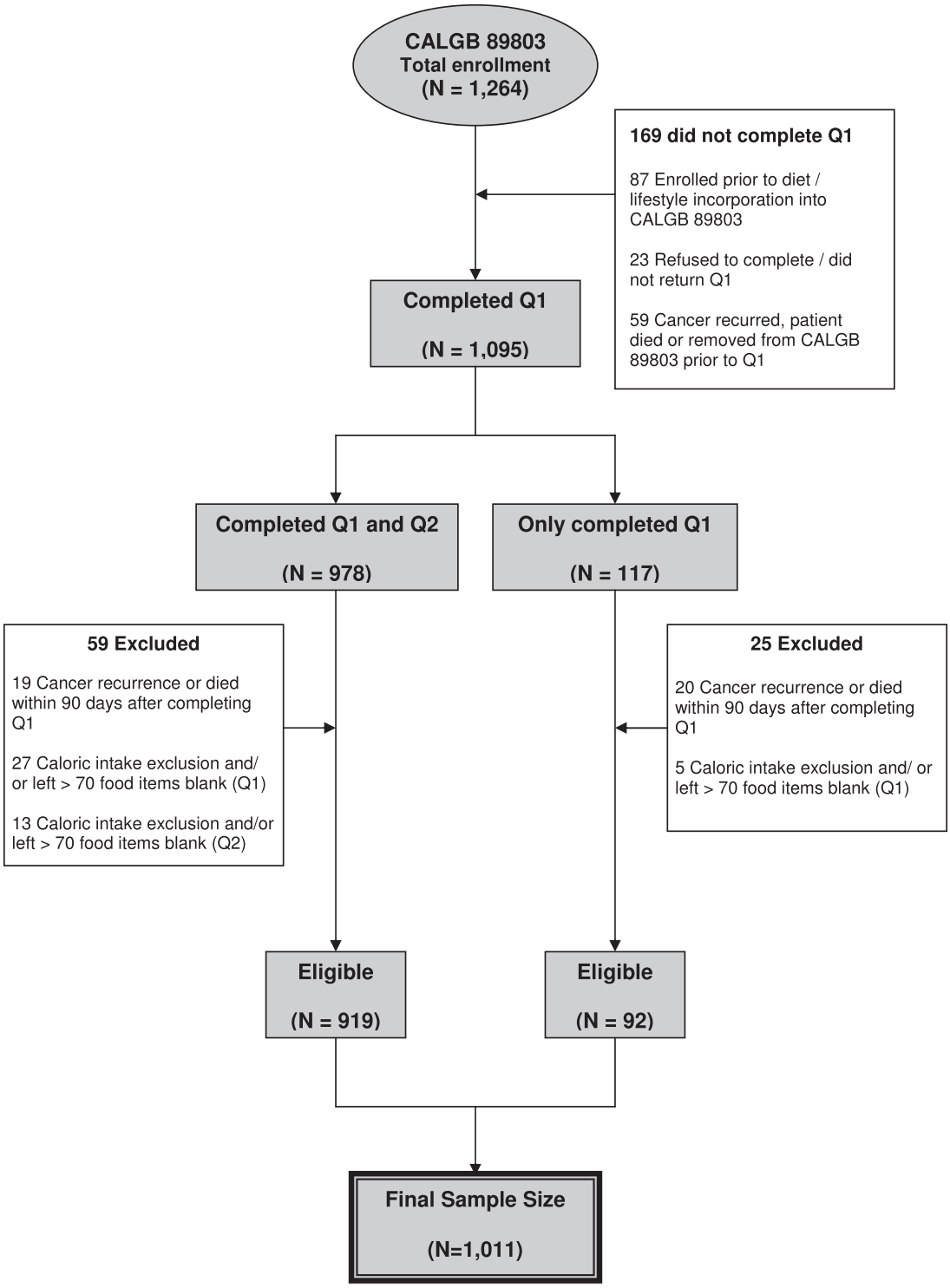

Figure 1. Derivation of cohort. Q1 = questionnaire 1 (midway through adjuvant therapy); Q2 = questionnaire 2 (6 months after completion of adjuvant therapy). Caloric intake exclusion = Less than 600 calories or greater than 4200 calories per day for men and less than 500 calories or greater than 3500 calories per day for women.

Results

Baseline Characteristics

Study participants were drawn from a multicenter study of adjuvant chemotherapy after surgery in patients with stage III colon cancer. We calculated participant's dietary glycemic load, glycemic index, total fructose intake, and total carbohydrate intake using cumulative updating to reflect average intake reported during and after adjuvant chemotherapy. Baseline characteristics by quintiles of dietary glycemic load and index are shown in Table 1. Similar baseline characteristic distributions

Table 1. Baseline characteristics of 1011 patients by quintile for dietary glycemic load and glycemic index*

	Dietary glycemic load					Dietary glycemic index				
	1	2	3	4	5	1	2	3	4	5
	(n = 202)	(n = 202)	(n = 203)	(n = 202)	(n = 202)	(n = 202)	(n = 202)	(n = 203)	(n = 202)	(n = 202)
Median (range)	112.1 (65–123)	130.1 (123–135)	141.5 (135–147)	153.8 (147–162)	172.0 (162–221)	51.1 (39–52)	53.2 (52–54)	54.7 (54–55)	56.1 (55–57)	58.2 (57–63)
Male, No. (%)	140 (69.3)	104 (51.5)	108 (53.2)	106 (52.5)	111 (55.0)	95 (47.0)	114 (56.4)	115 (56.7)	128 (63.4)	117 (57.9)
Age, median (range), y	61 (28–79)	58 (35–81)	60 (34–83)	60 (21–82)	60 (24–85)	61 (35–82)	61 (24–81)	63 (26–83)	58 (28–85)	57 (21–80)
Race, No. (%)										
White	187 (92.6)	184 (91.0)	184 (90.6)	175 (86.6)	169 (83.6)	182 (90.2)	183 (90.6)	181 (89.1)	181 (89.6)	172 (85.2)
Black	7 (3.4)	12 (6.0)	12 (6.0)	17 (8.4)	17 (8.4)	7 (3.4)	10 (5.0)	18 (8.9)	15 (7.4)	15 (7.4)
Other	8 (4.0)	6 (3.0)	7 (3.4)	10 (5.0)	16 (8.0)	13 (6.4)	9 (4.4)	4 (2.0)	6 (3.0)	15 (7.4)
Baseline performance status, No. (%)†										
0	153 (75.7)	144 (71.3)	147 (72.4)	158 (78.2)	140 (60.3)	149 (73.8)	147 (72.8)	145 (71.4)	154 (76.2)	147 (72.8)
1–2	45 (22.3)	55 (27.2)	54 (26.6)	41 (20.3)	53 (26.2)	49 (24.3)	50 (24.8)	56 (27.6)	46 (22.8)	47 (23.3)
Status unknown	4 (2.0)	3 (1.5)	2 (1.0)	3 (1.5)	9 (4.5)	4 (2.0)	5 (2.5)	2 (1.0)	2 (1.0)	8 (4.0)
Invasion through bowel wall by T stage, No. (%)‡										
T1–2	27 (13.4)	27 (13.4)	33 (16.2)	28 (13.8)	21 (10.4)	31 (15.4)	30 (14.9)	26 (12.8)	30 (14.9)	19 (9.4)
T3–4	172 (85.1)	172 (85.1)	166 (81.8)	170 (84.2)	171 (84.6)	168 (83.1)	165 (81.6)	173 (85.2)	170 (84.1)	175 (86.6)
T stage unknown	3 (1.5)	3 (1.5)	4 (2.0)	4 (2.0)	10 (5.0)	3 (1.5)	7 (3.5)	4 (2.0)	2 (1.0)	8 (4.0)
Positive lymph nodes, No. (%)										
1–3	132 (65.3)	137 (67.8)	132 (65.0)	128 (63.4)	106 (52.5)	134 (66.3)	136 (67.3)	129 (63.5)	112 (55.4)	124 (61.3)
≥4	67 (33.2)	63 (31.2)	69 (34.0)	71 (35.1)	86 (42.6)	65 (32.2)	61 (30.2)	72 (35.5)	89 (44.1)	69 (34.2)
Nodes unknown	3 (1.5)	2 (1.0)	2 (1.0)	3 (1.5)	10 (4.9)	3 (1.5)	5 (2.5)	2 (1.0)	1 (0.5)	9 (4.5)
Grade of differentiation, No. (%)										
Well	9 (4.5)	15 (7.4)	10 (4.9)	13 (6.4)	10 (5.0)	7 (3.5)	14 (6.9)	14 (6.9)	7 (3.5)	15 (7.4)
Moderate	139 (68.8)	134 (66.3)	158 (77.8)	141 (69.8)	129 (63.9)	145 (71.8)	137 (67.8)	140 (69.0)	152 (75.2)	127 (62.9)
Poor/Undifferentiated	50 (24.8)	51 (25.2)	33 (16.3)	44 (21.8)	54 (26.7)	47 (23.3)	46 (22.8)	46 (22.7)	42 (20.8)	51 (25.2)
Grade unknown	4 (2.0)	2 (1.0)	2 (1.0)	4 (2.0)	9 (4.5)	3 (1.5)	5 (2.5)	3 (1.5)	1 (0.5)	9 (4.5)
Clinical bowel obstruction at presentation, No. (%)	43 (21.3)	45 (22.3)	49 (24.1)	49 (24.3)	36 (17.8)	38 (18.8)	44 (21.8)	50 (24.6)	43 (21.3)	47 (23.3)
Bowel perforation at presentation, No. (%)	11 (5.4)	11 (5.4)	12 (5.9)	2 (1.0)	7 (3.5)	16 (7.9)	7 (3.5)	8 (3.9)	5 (2.5)	7 (3.5)
Treatment arm, No. (%)										
5-FU/LV	97 (48.0)	103 (51.0)	101 (49.8)	110 (54.5)	102 (50.5)	105 (52.0)	95 (47.0)	115 (56.7)	100 (49.5)	98 (48.5)
IFL	105 (52.0)	99 (49.0)	102 (50.2)	92 (45.5)	100 (49.5)	97 (48.0)	107 (53.0)	88 (43.3)	102 (50.5)	104 (51.5)
Body mass index, median (range), kg/m²§	28.0 (18–52)	27.6 (16–47)	26.7 (16–50)	26.6 (17–49)	27.5 (17–43)	26.8 (17–52)	27.4 (17–47)	27.2 (16–46)	27.7 (17–50)	27.5 (16–49)
Physical activity, median (range), MET h/wk§	6.5 (0–125)	3.7 (0–119)	4.3 (0–120)	5.9 (0–147)	4.2 (0–125)	5.9 (0–120)	6.3 (0–125)	4.6 (0–119)	5.4 (0–114)	3.7 (0–147)
Cereal fiber, median (range), g§	4.6 (1–17)	5.4 (1–21)	5.5 (0–23)	6.4 (1–16)	6.7 (2–29)	5.2 (0–21)	5.6 (2–23)	5.7 (1–29)	6.0 (2–23)	5.8 (2–23)
Western dietary pattern, No. < median (%)§	84 (41.6)	94 (46.5)	96 (47.3)	112 (55.45)	120 (59.4)	134 (66.3)	87 (43.1)	87 (42.9)	97 (48.0))	101 (50)
Prudent pattern diet, No. < median, (%)§	103 (51.0)	96 (47.5)	91 (44.8)	102 (50.5)	114 (56.4)	58 (28.7)	78 (38.6)	95 (46.8)	127 (62.9)	148 (73.3)

* 5-FU = 5-fluorouracil; IFL = irinotecan, 5-fluorouracil, leucovorin; LV = leucovorin; MET = metabolic equivalent tasks.

† Baseline performance status: PS 0 = fully active; PS 1 = restricted in physically strenuous activity but ambulatory and able to carry out light work; PS 2 = ambulatory and capable of all self care but unable to carry out any work activities, up and about more than 50% of waking hours.

‡ T1-2 = 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.

§ Based on questionnaire 1.

were seen for total fructose and total carbohydrate intakes (data not shown).

Colon Cancer Recurrences and Survival

The median follow-up from the time of completion of Q1 was 7.3 years. In total, 343 of the 1011 patients included in this analysis had cancer recurrence; 262 of these 343 patients died. An additional 43 patients died without documented cancer recurrence.

The primary endpoint of this analysis was disease-free survival. Higher dietary glycemic load was associated with statistically significant worse disease-free, recurrence-free, and overall survival (Table 2). Compared with patients with the lowest glycemic load quintile, those in the highest quintile experienced an adjusted hazard ratio (HR) for disease-free survival of 1.79 (95 % confidence interval [CI] = 1.29 to 2.48; P_{trend} across quintiles <.001). Although the association does not appear linear when reviewing the point estimates by quintile, the P_{trend} across quintiles does reflect data across all quintiles, thereby demonstrating an association with increasing level of glycemic load. To isolate the influence of glycemic load on cancer recurrence, we used the endpoint recurrence-free survival and confirmed that higher glycemic load was associated with a stastistically significantly increased risk in cancer recurrence (P_{trend} across quintiles <.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 Q1 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 Q1 (n = 967), and our results remained largely unchanged. Patients in the highest quintile of dietary glycemic load had an adjusted hazard ratio for cancer recurrence or death of 1.67 (95% CI = 1.18 to 2.35; P_{trend} across quintiles <.001). Conversely, because Q1 was not uniformly completed at 3 months from study entry as recommended in the protocol, we modeled our analyses using survival times from study entry [the same time variable used in the treatment trial analysis (30)]. Patients in the highest quintile of dietary glycemic load had an adjusted hazard ratio for cancer recurrence or death of 1.67 (95% CI = 1.21 to 2.32; P_{trend} across quintiles <.001).

We similarly examined the association of other dietary markers associated with insulin resistance on cancer recurrence and mortality (Table 2). Dietary glycemic index was not associated with disease-free, recurrence-free, or overall survival. Total fructose intake was statistically significant associated with recurrence-free survival (HR = 1.42; 95% CI = 1.02 to 1.97, comparing extreme quintiles). In contrast, the relation between total fructose intake and disease-free or overall survival did not reach statistical significance.

Increasing total carbohydrate intake was statistically significant associated with disease-free, recurrence-free, and overall survival. Compared with patients in the lowest quintile of total carbohydrate intake, those in the highest quintile of total carbohydrate intake experienced a hazard ratio for cancer recurrence or death from any cause of 1.80 (95% CI = 1.61 to 2.48; P_{trend} across quintiles <.001). Increasing total carbohydrate intake appeared to confer similar deleterious associations for both recurrence-free and overall survival.

Stratified Analyses

We examined the influence of dietary glycemic load on disease-free survival across strata of other potential predictors of patient outcome (Table 3). We found that the influence of dietary glycemic load on disease-free survival was statistically significant modified by BMI ($P_{interaction}$ =.01). Whereas glycemic load was not associated with disease-free survival in those with BMI < 25 kg/m^2, higher glycemic load was statistically significant associated with worse disease-free survival among overweight or obese participants (BMI ≥ 25 kg/m^2; adjusted HR = 2.26; 95% CI = 1.53 to 3.32, comparing extreme quintiles; P_{trend} across quintiles <.001). Of note, we observed a similar interaction between increasing quintiles of carbohydrate and BMI ($P_{interaction}$ =.006). No statistically significant interactions were demonstrated by age, sex, performance status, number of positive lymph nodes, treatment group, or level of physical activity (data not shown).

Given our prior data associating Western pattern diet with disease-free survival in this cohort (27), we examined whether the glycemic load findings persisted across strata of Western pattern diet (Figure 2). Regardless of the level of Western pattern diet, increasing glycemic load was associated with worse disease-free survival.

Discussion

In this cohort of stage III colon cancer patients enrolled in a clinical trial of postoperative adjuvant chemotherapy, increasing dietary glycemic load and total carbohydrate intake were each associated with an increased risk of cancer recurrence or death. Moreover, the deleterious association of dietary glycemic load and total carbohydrate intake on survival was principally observed in patients who were overweight or obese.

Dietary glycemic load and glycemic index have been extensively studied as potential risk factors for the development of colorectal cancer, with mixed results (14–21,44–47). In a meta-analysis of case–control and cohort studies, both glycemic load (relative risk [RR] = 1.26; 95% CI = 1.11 to 1.44) and glycemic index (RR = 1.18; 95% CI = 1.05 to 1.34) were statistically significant, albeit modestly, associated with a greater risk of colorectal cancer. In studies reporting positive associations, dietary glycemic load and total carbohydrate or fructose intake were often stronger predictors of the risk than dietary glycemic index (14,17).

Weight, physical activity, and diet are well-established risk factors for colorectal cancer (48). In contrast, fewer studies have examined the influence of these behaviors on survival among patients with colorectal cancer. In recent observations, obesity, sedentary lifestyle, and Western dietary pattern have each been associated with an increased risk for cancer recurrence and death among patients who have undergone curative surgical resection for colorectal cancer (49,50). Although the mediators for this increased risk of recurrence and death are poorly defined, hyperinsulinemia and perturbations in the insulinlike growth factor axis have been proposed as underlying biologic mechanisms for these observations. Regular consumption of high-glycemic meals results in increased insulin levels, decreased leptin, and increased BMI (51–54). In preclinical studies of intestinal epithelial cells and colon cancer cell lines, insulin binds to the insulin receptor on the cell surface and stimulates cell proliferation while inhibiting apoptosis

Table 2. Associations between colon cancer recurrence and mortality and dietary glycemic load, glycemic index, total fructose intake, and total carbohydrate intake

Outcome	Quintile					
Glycemic Exposure	**1 (n = 202)**	**2 (n = 202)**	**3 (n = 203)**	**4 (n = 202)**	**5 (n = 202)**	**P_{trend}***
Disease-free survival						
Dietary glycemic load						
No. of events for energy-adjusted model	72	63	72	83	96	
Energy adjusted only, HR (95% CI)	1 (Referent)	0.86 (0.61 to 1.20)	0.99 (0.72 to 1.37)	1.27 (0.92 to 1.74)	1.60 (1.18 to 2.18)	<.001
Multivariable adjusted, HR (95% CI)†	1 (Referent)	0.92 (0.65 to 1.31)	1.07 (0.77 to 1.50)	1.50 (1.08 to 2.08)	1.79 (1.29 to 2.48)	<.001
Multivariable adjusted, HR (95% CI)‡	1 (Referent)	0.92 (0.65 to 1.30)	1.07 (0.76 to 1.50)	1.49 (1.07 to 2.07)	1.77 (1.28 to 2.46)	<.001
Dietary glycemic index						
No. of events for energy-adjusted model	73	72	78	85	78	
Energy adjusted only	1 (Referent)	0.97 (0.70 to 1.34)	1.11 (0.81 to 1.53)	1.22 (0.89 to 1.66)	1.12 (0.81 to 1.54)	.21
Multivariable adjusted, HR (95% CI)†	1 (Referent)	0.96 (0.69 to 1.34)	1.11 (0.80 to 1.53)	1.10 (0.79 to 1.52)	1.12 (0.81 to 1.56)	.34
Multivariable adjusted, HR (95% CI)‡	1 (Referent)	0.99 (0.71 to 1.39)	1.14 (0.81 to 1.58)	1.13 (0.80 to 1.59)	1.12 (0.81 to 1.65)	.30
Total fructose intake						
# of events for energy adjusted model	83	66	73	72	92	
Energy adjusted only	1 (Referent)	0.77 (0.56 to 1.06)	0.86 (0.63 to 1.18)	0.88 (0.64 to 1.21)	1.25 (0.93 to 1.68)	.10
Multivariable adjusted, HR (95% CI)†	1 (Referent)	0.81 (0.58 to 1.12)	0.88 (0.64 to 1.21)	0.97 (0.70 to 1.33)	1.28 (0.94 to 1.73)	.06
Multivariable adjusted, HR (95% CI)‡	1 (Referent)	0.81 (0.58 to 1.12)	0.87 (0.63 to 1.20)	0.96 (0.69 to 1.32)	1.26 (0.92 to 1.71)	.08
Total carbohydrate intake						
No. of events for energy-adjusted model	69	63	76	83	95	
Energy adjusted only	1 (Referent)	0.93 (0.66 to 1.31)	1.11 (0.80 to 1.54)	1.36 (0.99 to 1.88)	1.69 (0.24 to 2.31)	<.001
Multivariable adjusted, HR (95% CI)†	1 (Referent)	1.00 (0.70 to 1.41)	1.16 (0.83 to 1.62)	1.52 (1.10 to 2.11)	1.80 (1.61 to 2.48)	<.001
Multivariable adjusted, HR (95% CI)‡	1 (Referent)	1.00 (0.71 to 1.42)	1.16 (0.83 to 1.62)	1.53 (1.10 to 2.12)	1.81 (1.31 to 2.50)	<.001
Recurrence-free survival						
Dietary glycemic load						
No. of events for energy-adjusted model	58	57	60	78	90	
Energy adjusted only	1 (Referent)	0.97 (0.67 to 1.40)	1.03 (0.72 to 1.48)	1.47 (1.05 to 2.07)	1.86 (1.34 to 2.59)	<.001
Multivariable adjusted, HR (95% CI)†	1 (Referent)	1.01 (0.70 to 1.47)	1.07 (0.74 to 1.56)	1.69 (1.19 to 2.41)	1.98 (1.39 to 2.80)	<.001
Multivariable adjusted, HR (95% CI)‡	1 (Referent)	1.01 (0.70 to 1.47)	1.07 (0.74 to 1.56)	1.70 (1.18 to 2.40)	1.97 (1.39 to 2.79)	<.001
Dietary glycemic index						
No. of events for energy-adjusted model	62	60	70	78	73	
Energy adjusted only	1 (Referent)	0.95 (0.66 to 1.35)	1.17 (0.83 to 1.65)	1.31 (0.94 to 1.83)	1.23 (0.88 to 1.73)	.06
Multivariable adjusted, HR (95% CI)†	1 (Referent)	0.96 (0.67 to 1.38)	1.18 (0.83 to 1.66)	1.17 (0.83 to 1.65)	1.20 (0.84 to 1.70)	.17
Multivariable adjusted, HR (95% CI)‡	1 (Referent)	0.99 (0.69 to 1.43)	1.21 (0.85 to 1.73)	1.21 (0.84 to 1.73)	1.24 (0.85 to 1.81)	.14
Total fructose intake						
No. of events for energy-adjusted model	69	56	66	65	87	
Energy adjusted only	1 (Referent)	0.79 (0.56 to 1.12)	0.94 (0.67 to 1.32)	0.96 (0.68 to 1.34)	1.42 (1.03 to 1.94)	.01
Multivariable adjusted, HR (95% CI)†	1 (Referent)	0.82 (0.58 to 1.18)	0.94 (0.66 to 1.33)	1.03 (0.73 to 1.46)	1.42 (1.02 to 1.97)	.01
Multivariable adjusted, HR (95% CI)‡	1 (Referent)	0.82 (0.58 to 1.17)	0.95 (0.67 to 1.33)	1.04 (0.74 to 1.47)	1.43 (1.04 to 1.98)	.01
Total carbohydrate intake						
No. of events for energy-adjusted model	56	55	65	78	89	
Energy adjusted only	1 (Referent)	1.01 (0.69 to 1.46)	1.17 (0.82 to 1.67)	1.57 (1.11 to 2.21)	1.95 (1.39 to 2.72)	<.001
Multivariable adjusted, HR (95% CI)†	1 (Referent)	1.06 (0.73 to 1.55)	1.19 (0.83 to 1.72)	1.75 (1.24 to 2.48)	2.05 (1.45 to 2.88)	<.001
Multivariable adjusted, HR (95% CI)‡	1 (Referent)	1.07 (0.73 to 1.56)	1.20 (0.83 to 1.73)	1.76 (1.24 to 2.50)	2.06 (1.45 to 2.91)	<.001
Overall survival						
Dietary glycemic load						
No. of events for energy-adjusted model	57	46	57	68	77	
Energy adjusted only	1 (Referent)	0.75 (0.51 to 1.11)	0.95 (0.66 to 1.38)	1.25 (0.88 to 1.78)	1.52 (1.08 to 2.14)	<.001
Multivariable adjusted, HR (95% CI)†	1 (Referent)	0.84 (0.56 to 1.25)	1.06 (0.73 to 1.55)	1.53 (1.06 to 2.22)	1.76 (1.22 to 2.54)	<.001
Multivariable adjusted, HR (95% CI)‡	1 (Referent)	0.83 (0.55 to 1.23)	1.05 (0.72 to 1.54)	1.50 (1.04 to 2.17)	1.74 (1.20 to 2.51)	<.001
Glycemic index						
No. of events for energy-adjusted model	58	55	64	65	63	
Energy adjusted only	1 (Referent)	0.91 (0.63 to 1.31)	1.14 (0.80 to 1.63)	1.13 (0.79 to 1.61)	1.11 (0.78 to 1.59)	.30
Multivariable adjusted, HR (95% CI)†	1 (Referent)	0.88 (0.61 to 1.28)	1.15 (0.80 to 1.64)	1.02 (0.70 to 1.64)	1.13 (0.78 to 1.63)	.36
Multivariable adjusted, HR (95% CI)‡	1 (Referent)	0.94 (0.64 to 1.37)	1.22 (0.84 to 1.77)	1.09 (0.74 to 1.61)	1.23 (0.83 to 1.82)	.22

(Table continues)

Table 2 (Continued).

Outcome	Quintile					
Glycemic Exposure	**1 (n = 202)**	**2 (n = 202)**	**3 (n = 203)**	**4 (n = 202)**	**5 (n = 202)**	**P_{trend}***
Total fructose intake						
No. of events for energy-adjusted model	69	55	53	58	70	
Energy adjusted only	1 (Referent)	0.79 (0.55 to 1.12)	0.76 (0.53 to 1.09)	0.87 (0.61 to 1.23)	1.12 (0.80 to 1.56)	.43
Multivariable adjusted, HR (95% CI)†	1 (Referent)	0.84 (0.59 to 1.20)	0.78 (0.54 to 1.12)	0.96 (0.68 to 1.37)	1.17 (0.83 to 1.65)	.27
Multivariable adjusted, HR (95% CI)‡	1 (Referent)	0.82 (0.57 to 1.18)	0.74 (0.51 to 1.08)	0.92 (0.64 to 1.32)	1.11 (0.79 to 1.58)	.40
Total carbohydrate intake						
No. of events for energy-adjusted model	52	50	58	67	78	
Energy adjusted only	1 (Referent)	0.94 (0.64 to 1.38)	1.08 (0.75 to 1.58)	1.43 (0.99 to 2.05)	1.73 (1.22 to 2.46)	<.001
Multivariable adjusted, HR (95% CI)†	1 (Referent)	1.01 (0.68 to 1.50)	1.13 (0.77 to 1.65)	1.62 (1.12 to 2.34)	1.84 (1.28 to 2.64)	<.001
Multivariable adjusted, HR (95% CI)‡	1 (Referent)	1.00 (0.68 to 1.49)	1.11 (0.76 to 1.63)	1.60 (1.11 to 2.32)	1.80 (1.25 to 2.60)	<.001

* Two-sided *P* value. Trend across quintiles. HR=hazard ratio; CI = confidence interval.

† Adjusting with Cox proportional hazards regression for sex, age, depth of invasion through bowel wall, number of positive lymph nodes, baseline performance status, treatment group, time-varying body mass index, time-varying physical activity level, and time-varying cereal fiber.

‡ Adjusting for above and time-varying dietary pattern.

Table 3. Subgroup analyses of multivariable-adjusted disease-free survival by quintile of dietary glycemic load*

		Dietary glycemic load by quintile						
Subgroup	**No. of patients**	**1 (n = 202) HR (95% CI)**	**2 (n = 202) HR (95% CI)**	**3 (n = 203) HR (95% CI)**	**4 (n = 202) HR (95% CI)**	**5 (n = 202) HR (95% CI)**	**P_{trend}†**	**$P_{interaction}$**
Age, y								
<60	485	1 (Reference)	0.95 (0.57 to 1.59)	0.97 (0.58 to 1.62)	1.22 (0.73 to 2.04)	1.61 (0.99 to 2.61)	.03	.49
≥60	526	1 (Reference)	0.90 (0.56 to 1.46)	1.26 (0.80 to 1.99)	1.82 (1.18 to 2.81)	1.86 (1.19 to 2.91)	<.001	
Sex								
Male	569	1 (Reference)	0.95 (0.62 to 1.45)	0.89 (0.58 to 1.37)	1.63 (1.09 to 2.42)	1.63 (1.09 to 2.42)	<.001	.46
Female	442	1 (Reference)	0.90 (0.47 to 1.72)	1.32 (0.71 to 2.46)	1.28 (0.68 to 2.40)	2.10 (1.13 to 3.92)	<.001	
Baseline performance status‡								
0	742	1 (Reference)	0.92 (0.60 to 1.41)	1.01 (0.66 to 1.53)	1.71 (1.16 to 2.51)	1.65 (1.11 to 2.44)	<.001	.81
1–2	248	1 (Reference)	1.03 (0.54 to 1.97)	1.36 (0.73 to 2.51)	1.02 (0.50 to 2.08)	2.10 (1.08 to 4.05)	.06	
No. of positive lymph nodes								
1–3 (N1)	635	1 (Reference)	0.96 (0.61 to 1.53)	1.26 (0.81 to 1.98)	1.44 (0.91 to 2.26)	2.19 (1.39 to 3.47)	<.001	.71
≥ 4 (N2)	356	1 (Reference)	0.87 (0.51 to 1.52)	0.84 (0.49 to 1.44)	1.58 (0.95 to 2.63)	1.40 (0.85 to 2.29)	.01	
Treatment group								
5-FU/LV	513	1 (Reference)	0.78 (0.47 to 1.30)	1.20 (0.74 to 1.94)	1.35 (0.85 to 2.16)	1.84 (1.16 to 2.93)	.001	.49
IFL	498	1 (Reference)	1.09 (0.68 to 1.77)	1.00 (0.62 to 1.62)	1.66 (1.04 to 2.66)	1.76 (1.10 to 2.81)	.002	
Body mass index								
<25 kg/m^2	332	1 (Reference)	0.65 (0.35 to 1.23)	0.81 (0.46 to 1.43)	1.00 (0.56 to 1.80)	0.91 (0.48 to 1.73)	.41	.01
>25 kg/m^2	679	1 (Reference)	0.99 (0.65 to 1.51)	1.07 (0.70 to 1.64)	1.70 (1.13 to 2.56)	2.26 (1.53 to 3.32)	<.001	
Physical activity, MET-hours/wk								
<18	785	1 (Reference)	0.75 (0.51 to 1.10)	0.96 (0.67 to 1.40)	1.21 (0.83 to 1.76)	1.51 (1.04 to 2.18)	.001	.28
≥18	220	1 (Reference)	2.37 (1.06 to 5.31)	1.34 (0.55 to 3.27)	3.67 (1.72 to 7.83)	3.29 (1.54 to 7.04)	<.001	

* Adjusting with Cox proportional hazards regression for sex, age, depth of invasion through bowel wall, number of positive lymph nodes, baseline performance status, treatment group, time-varying body mass index, time-varying physical activity level, and time-varying cereal fiber. HR = hazard ratio; CI = confidence interval; 5-FU = 5-fluorouracil; IFL = irinotecan, 5-fluorouracil, leuocovorin; MET= metabolic equivalence tasks.

† Two-sided *P* value. Trend across quintiles.

‡ Baseline performance status: PS 0 = fully active; PS 1 = restricted in physically strenuous activity but ambulatory and able to carry out light work; PS 2 = ambulatory and capable of all self care but unable to carry out any work activities, up and about more than 50% of waking hours.

(55–58). Studies have demonstrated a correlation between plasma C-peptide, a marker of longer-term insulin production, and dietary glycemic load, fructose, and carbohydrates (59,60). In a cohort of nonmetastatic colorectal cancer patients, subjects with higher levels of baseline circulating C-peptide experienced statistically significantly increased colorectal cancer-specific mortality when compared with patients with the lowest levels (61). In light of the current findings in stage III patients, we hypothesize that excess

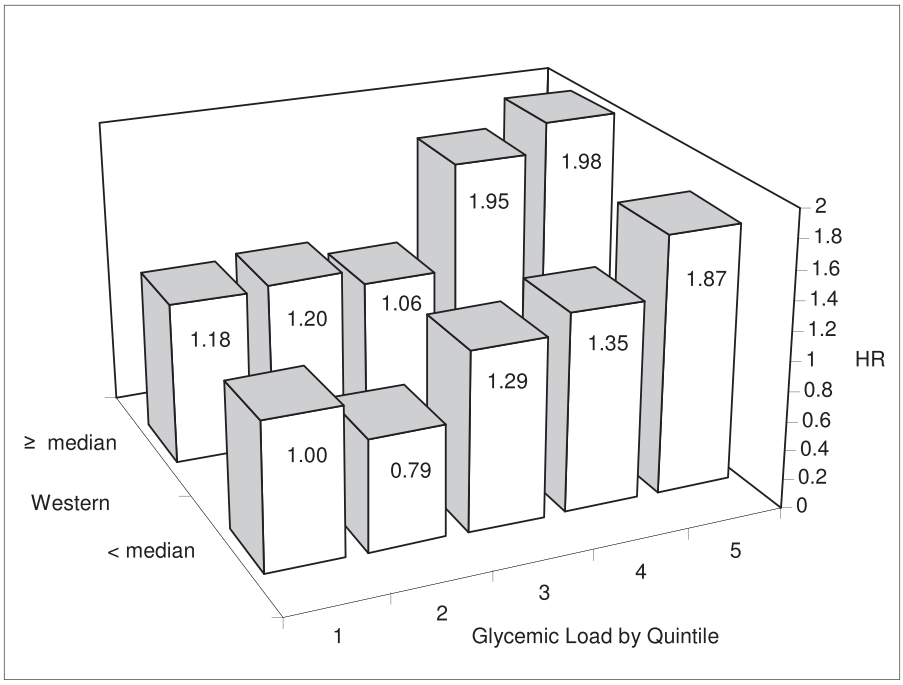

Figure 2. Hazard ratio (HR) for disease-free survival according to combinations of the dietary glycemic load by quintile and median levels of Western pattern diet.

energy balance, including higher dietary glycemic load, may stimulate systemic insulin production, which may, in turn, promote cell proliferation and inhibit apoptosis of micrometastases. In CALGB 89803, blood samples were not collected from participants to further study potential correlations between glycemic load and carbohydrate intake and hormonal markers, although an ongoing adjuvant colon cancer study (CALGB 80702) is collecting both FFQs and blood samples to allow such studies in the future.

There are several advantages to a cohort of patients treated within a National Cancer Institute–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 was prospectively collected at study entry. Finally, we updated dietary data to reflect changes in diet that may occur after patients have completed adjuvant therapy and recovered from treatment effects.

Our study is not without limitations. Patients who enroll in randomized 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 patients enrolled from community and academic centers across North America.

Also, we cannot completely exclude the possibility that diets associated with increased dietary glycemic load and total carbohydrates may be reflective of other cancer-specific predictors of poor prognosis. However, we did not observe any statistically significant association between these exposures and other patient or tumor-associated predictors of disease-free survival. Moreover, the detrimental association of these dietary exposures remained largely unchanged across the number of positive lymph nodes and performance status. We adjusted for other energy balance factors, including BMI and physical activity, and the associations remained statistically significant.

We considered the possibility that patients with either occult cancer recurrences or other statistically significant poor prognostic characteristics may have increased their dietary glycemic load or carbohydrate intake as an alternative source of needed calories. To minimize this bias, we excluded recurrences or deaths within 90 days of FFQ completion. When we extended this restriction to 6 months, we continued to observe a deleterious influence of dietary glycemic load on patient outcome. In addition, the association between dietary glycemic load and total carbohydrate intake and cancer recurrence or death appeared greatest among patients who were either overweight or obese. Finally, because patients on this clinical trial underwent comprehensive staging at study entry and were followed with prescribed follow-up visits and testing, we would expect few patients to have undetected recurrences over extended periods.

Given that patients who consume high glycemic loads or carbohydrates after cancer diagnosis may have consumed a similar diet before diagnosis, we cannot exclude the possibility that individuals with these dietary exposures acquire tumors that are biologically more aggressive. Nonetheless, as stated above, we did not observe any statistically significant association between these dietary habits and tumor-related characteristics associated with cancer recurrence.

Diet was self-reported in this study. The FFQ from this study has been extensively validated in healthy populations (32,33) as well as in a population of patients receiving cytotoxic chemotherapy (37). Diet was recorded prior to any knowledge of colon cancer-related outcomes, thus reducing the likelihood of reporting biases.

Following a curative surgical resection of stage III colon cancer, clinical trials have demonstrated adjuvant chemotherapy improves disease-free and overall survival. The current prospective analysis,

imbedded in such a clinical trial, suggests that a specific dietary behavior, in the form of higher dietary glycemic load and total carbohydrate intake, is statistically significant associated with impaired disease-free survival among patients treated with adjuvant therapy. Although our observational study does not provide conclusive evidence for causality, these findings support the potential role of energy balance factors in colon cancer progression and may offer opportunities to further improve patient survival. Further analyses are underway to confirm these associations in other cohorts of colon cancer survivors.

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