The Diet of Higher Insulinemic Potential Is Not Associated with Worse Survival in Patients with Stage III Colon Cancer (Alliance)

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ABSTRACT

Background: Hyperinsulinemia is considered to be important in the development of colon cancer, but few studies have investigated the associations of hyperinsulinemia with colon cancer survival via dietary scores.

Methods: Empirical dietary index for hyperinsulinemia (EDIH) was derived to assess the insulinemic potential of daily diets reflecting the long-term insulin exposure, with higher (more positive) scores indicating higher insulinemic diets. We prospectively estimated the HRs and 95% confidence intervals (CI) to investigate the association of EDIH with disease-free, recurrence-free, and overall survival among patients with stage III colon cancer (1999–2009) enrolled in a randomized adjuvant chemotherapy trial (CALGB 89803).

Results: Of 1,024 patients (median follow-up: 7.3 years), 311 died, 350 had recurrences, and 394 had events for disease-free survival. Compared with patients in the lowest quintile of EDIH, the corresponding HRs of patients in the highest quintile for disease-free survival events, cancer recurrence, and overall mortality were 0.80 (95% CI, 0.56–1.15), 0.76 (95% CI, 0.51–1.11), and 0.77 (95% CI, 0.52–1.14).

Conclusions: Higher EDIH was not associated with the risk of colon cancer recurrence or mortality in this population of patients with stage III colon cancer.

Impact: EDIH, as a measure of dietary insulinemic potential, may be associated with colon cancer risk but not survival in patients with late-stage colon cancer.

Introduction

Hyperinsulinemia is considered an underlying mechanism linking diet and lifestyle to colon cancer risk and has been associated with inferior outcome among patients with colon cancer (1–3). Dietary factors can alter insulin levels, and there has been much interest in deriving dietary scores to predict hyperinsulinemia. The empirical dietary index for hyperinsulinemia (EDIH) was derived to assess the insulinemic potential of daily diets reflecting the long-term insulin exposure, and higher score was associated with a 26% greater risk of colorectal cancer (4). Few studies have investigated the relationship between EDIH and cancer outcome. In a prospective study of patients with stage III colon cancer, we investigated the hypothesis that higher dietary insulinemic potential, as measured by EDIH, would be associated with inferior patient outcomes.

Materials and Methods

As described previously (5, 6), 1,095 patients with stage III colon cancer were eligible in an adjuvant therapy trial (Cancer and Leukemia Group B, now the Alliance for Clinical Trials in Oncology, 89803) who completed the first survey of diet and lifestyle; 978 of these patients completed the second survey (1999–2001). Both surveys included the same validated food frequency questionnaire (FFQ; ref. 7). The study was approved by each site's institutional review board.

We excluded 38 patients who recurred before or within 90 days after the first questionnaire, or died within 90 days of the first questionnaire, and 33 patients who left ≥70 food items blank or had implausible calorie intake (men: <600 or >4,200 kcal/day; female: <500 or >3,200 kcal/day) on the first questionnaire, and finally included 1,024 patients.

EDIH has been described previously, with higher (more positive) scores indicating higher insulinemic diets (4). We calculated EDIH of each patient using the first FFQ, and updated EDIH on the basis of the results of the second FFQ using cumulative averaging as described previously (5). The primary outcomes include disease-free, recurrence-free, and overall survival since first questionnaire, as defined previously (5).

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Table 1. Characteristics of patients with stage III colon cancer ($N = 1{,}024$) by quintiles of EDIH.

	EDIH quintiles					
Characteristics[a]	**1** $N = 204$	**2** $N = 205$	**3** $N = 205$	**4** $N = 205$	**5** $N = 205$	P^b
Male	117 (57.4%)	102 (49.8%)	91 (44.4%)	82 (40.0%)	56 (27.3%)	<0.01
Age, years	63 (28–85)	60 (24–78)	60 (31–82)	61 (29–83)	57 (21–80)	<0.01
BMI, kg/m^2	25.9 (17.2–42.4)	27.3 (17.2–49.9)	27.3 (16.3–45.0)	27.5 (15.7–44.6)	28.2 (17.3–51.8)	<0.01
Race						0.05
White	180 (88.2%)	185 (90.2%)	187 (91.2%)	176 (85.9%)	181 (88.3%)	
Black	8 (3.9%)	10 (4.9%)	14 (6.8%)	18 (8.8%)	18 (8.8%)	
Other	16 (7.8%)	10 (4.9%)	4 (2.0%)	11 (5.4%)	6 (2.9%)	
Performance status						0.75
Fully active	152 (76.8%)	153 (75.7%)	154 (76.2%)	146 (73.4%)	145 (71.8%)	
Restricted in strenuous activity	46 (23.2%)	49 (24.3%)	48 (23.8%)	53 (26.6%)	57 (28.2%)	
Unknown	6	3	3	6	3	
Bowel wall invasion						0.65
Stage 1 and 2	28 (14.1%)	24 (11.9%)	34 (16.7%)	25 (12.7%)	26 (13.0%)	
Stage 3 and 4	170 (85.9%)	178 (88.1%)	169 (83.3%)	172 (87.3%)	174 (87.0%)	
Unknown	6	3	2	8	5	
Positive lymph nodes						0.05
1–3 or unknown	138 (69.3%)	134 (66.3%)	122 (60.1%)	135 (67.8%)	116 (57.4%)	
≥4	61 (30.7%)	68 (33.7%)	81 (39.9%)	64 (32.2%)	86 (42.6%)	
Unknown	5	3	2	6	3	
Tumor location						0.04
Left-sided	68 (34.2%)	97 (48.0%)	90 (44.6%)	85 (42.7%)	95 (47.5%)	
Transverse or right-sided	131 (65.8%)	105 (52.0%)	112 (55.4%)	114 (57.3%)	105 (52.5%)	
Unknown	5	3	3	6	5	
Treatment arm						0.69
Fluorouracil + leucovorin	112 (54.9%)	103 (50.2%)	100 (48.8%)	99 (48.3%)	102 (49.8%)	
Irinotecan, fluorouracil, leucovorin	92 (45.1%)	102 (49.8%)	105 (51.2%)	106 (51.7%)	103 (50.2%)	
Pack-years of smoking	0.3 (0.0–72.5)	0.6 (0.0–112.9)	0.6 (0.0–104.1)	1.3 (0.0–102.1)	0.6 (0.0–94.0)	0.10
Physical activity, MET-hour/week	4.5 (0.0–119.9)	4.4 (0.0–122.9)	5.4 (0.0–114.2)	6.1 (0.0–147.4)	4.4 (0.0–125.2)	0.81
Family history of colorectal cancer	49 (24.0%)	47 (22.9%)	50 (24.4%)	50 (24.4%)	60 (29.3%)	0.62
Regular aspirin user	13 (6.4%)	18 (8.8%)	16 (7.8%)	17 (8.3%)	19 (9.3%)	0.85
Calorie intake[c], kcal/day	1,530 (617–3,666)	1,684 (649–3,691)	1,794 (860–3,534)	2,144 (1,032–3,578)	2,412 (1,181–4,119)	<0.01
EDIH-positive associations[d]						
Red meat, servings/week	1.1 (0.0–6.4)	1.6 (0.0–9.0)	1.9 (0.0–6.9)	2.5 (0.0–8.9)	3.7 (0.0–12.7)	<0.01
Processed meat, servings/week	0.8 (0.0–3.8)	1.2 (0.0–7.5)	1.4 (0.0–6.2)	2.0 (0.0–14.0)	3.0 (0.0–27.0)	<0.01
Low-energy beverages, servings/week	0.5 (0.0–18.2)	1.0 (0.0–17.9)	0.7 (0.0–28.4)	0.4 (0.0–27.6)	0.5 (0.0–55.1)	0.01
Cream soups, servings/week	0.2 (0.0–1.0)	0.2 (0.0–1.7)	0.3 (0.0–3.0)	0.4 (0.0–3.0)	0.3 (0.0–5.5)	<0.01
Margarine, servings/week	0.7 (0.0–28.0)	1.9 (0.0–28.0)	3.0 (0.0–28.0)	3.0 (0.0–28.0)	3.0 (0.0–28.0)	<0.01
Poultry, servings/week	1.1 (0.0–5.5)	1.2 (0.0–6.0)	1.2 (0.0–7.0)	1.6 (0.0–6.0)	1.8 (0.0–8.5)	<0.01
Butter, servings/week	0.2 (0.0–17.5)	0.4 (0.0–17.5)	1.0 (0.0–18.4)	1.9 (0.0–28.0)	2.1 (0.0–28.0)	<0.01
French fries, servings/week	0.2 (0.0–1.7)	0.4 (0.0–3.0)	0.5 (0.0–3.0)	0.5 (0.0–3.2)	1.0 (0.0–5.5)	<0.01
Other fish, servings/week	0.9 (0.0–6.5)	1.0 (0.0–4.5)	1.0 (0.0–7.0)	1.1 (0.0–7.0)	1.0 (0.0–5.8)	<0.01
High-energy beverages, servings/week	0.8 (0.0–13.3)	1.4 (0.0–14.3)	2.4 (0.0–20.5)	3.1 (0.0–25.5)	6.8 (0.0–38.5)	<0.01
Tomatoes, servings/week	2.9 (0.0–10.7)	3.1 (0.0–13.0)	3.6 (0.2–13.9)	4.5 (0.2–18.0)	5.6 (0.2–18.0)	<0.01
Low-fat dairy products, servings/week	0.7 (0.0–13.0)	0.5 (0.0–17.5)	0.4 (0.0–17.4)	0.4 (0.0–19.6)	0.3 (0.0–15.9)	0.01
Eggs, servings/week	0.9 (0.0–4.8)	1.9 (0.0–7.0)	3.0 (0.0–14.0)	3.0 (0.0–14.0)	3.0 (0.0–14.0)	<0.01
EDIH-negative associations[d]						
Wine, servings/week	0.4 (0.0–23.9)	0.1 (0.0–14.5)	0.0 (0.0–20.5)	0.0 (0.0–12.5)	0.0 (0.0–12.7)	<0.01
Coffee, servings/week	7.0 (0.0–42.5)	7.0 (0.0–37.2)	7.5 (0.0–35.5)	6.3 (0.0–42.0)	6.1 (0.0–35.0)	0.02
Whole fruits, servings/week	11.1 (0.6–88.0)	10.4 (0.0–66.0)	9.2 (0.2–34.9)	9.6 (0.0–45.4)	8.1 (0.0–31.9)	<0.01
High-fat dairy products, servings/week	3.4 (0.0–39.7)	4.2 (0.0–50.2)	5.3 (0.0–31.9)	6.0 (0.0–38.7)	6.9 (0.1–40.0)	<0.01
Green leafy vegetables, servings/week	3.1 (0.0–17.5)	2.4 (0.0–14.7)	2.2 (0.0–15.3)	2.8 (0.1–15.4)	2.3 (0.0–10.6)	0.32

Abbreviations: BMI, body mass index; EDIH, empirical dietary index for hyperinsulinemia; MET, metabolic equivalent of task.
[a]Continuous variables presented as median (range), and categorical variables as number (percentage).
[b]*P* values calculated using the χ^2 test for categorical variables and Kruskal–Wallis test for continuous variables.
[c]Time-varying calorie intake.
[d]The food groups (servings/week) retained are defined in ref. 4.

We investigated the associations of EDIH with survivals via Cox proportional hazard regression. Model 1 was adjusted for age at diagnosis (years) and time-varying calorie intake. Model 2 was additionally adjusted for sex, treatment arm, T-stage (T1–T2 and T3–T4), positive lymph nodes (1–3 and ≥4), performance status (fully active and restricted in strenuous activity), aspirin (yes and no), tumor location

Table 2. Associations of EDIH with adverse outcomes[a] in patients with stage III colon cancer ($N = 1{,}024$).

	EDIH quintiles					
	1	2	3	4	5	P_{trend}
Cancer recurrence or death from any cause (disease-free survival)						
No. of events/at risk	#87/204	#76/205	#80/205	#71/205	#80/205	
Model 1 HR (95% CI)[b]	Reference	0.85 (0.62–1.16)	0.88 (0.64–1.20)	0.77 (0.55–1.07)	0.99 (0.70–1.40)	0.88
Model 2 HR (95% CI)[c]	Reference	0.78 (0.57–1.07)	0.80 (0.58–1.09)	0.65 (0.46–0.92)	0.80 (0.56–1.15)	0.21
Cancer recurrence (recurrence-free survival)						
No. of events/at risk	#78/204	#68/205	#72/205	#61/205	#71/205	
Model 1 HR (95% CI)[b]	Reference	0.84 (0.60–1.16)	0.86 (0.62–1.19)	0.71 (0.50–1.02)	0.91 (0.63–1.32)	0.53
Model 2 HR (95% CI)[c]	Reference	0.78 (0.56–1.09)	0.79 (0.56–1.10)	0.62 (0.43–0.90)	0.76 (0.51–1.11)	0.13
Overall mortality						
No. of events/at risk	#74/204	#56/205	#64/205	#52/205	#65/205	
Model 1 HR (95% CI)[b]	Reference	0.74 (0.52–1.05)	0.83 (0.59–1.17)	0.67 (0.46–0.98)	1.02 (0.70–1.50)	0.94
Model 2 HR (95% CI)[c]	Reference	0.65 (0.46–1.08)	0.72 (0.51–1.01)	0.53 (0.36–0.78)	0.77 (0.52–1.14)	0.21

Abbreviations: CI, confidence interval; EDIH, empirical dietary index for hyperinsulinemia; HR, hazard ratio.

[a]As defined previously (5), disease-free, recurrence-free, and overall survival since first questionnaire could be derived from adverse outcomes.

[b]Adjusted for age at diagnosis (years) and time-varying calorie intake.

[c]On the basis of model 1, additionally adjusted for sex, treatment arm, T-stage (T1–T2 and T3–T4), positive lymph nodes (1–3 and ≥4), performance status (fully active and restricted in strenuous activity), aspirin (yes and no), tumor location (left-sided, transverse, or right-sided), family history of colorectal cancer (yes and no), pack-years of smoking, and time-varying BMI (kg/m^2) and physical activity (MET-hour/week).

(left-sided, transverse, or right-sided), family history of colorectal cancer (yes and no), pack-years of smoking, and time-varying body mass index (BMI, kg/m^2) and physical activity [metabolic equivalent of task (MET)-hour/week]. In addition, we conducted separate analyses by sex.

Data were collected by the Alliance Statistics and Data Center and frozen on November 9, 2009. All analyses were conducted using SAS statistical software, version 9.4 (SAS Institute, Inc.) and two-sided $P < 0.05$ was considered statistically significant.

Results

Of the 1,024 patients with colon cancer (median follow-up: 7.3 years), 311 died, 350 had recurrences, and 394 had events for disease-free survival. Patients in the highest quintiles of EDIH were more likely to be female, younger, adipose, black, have more positive lymph nodes, and have left-sided tumors (**Table 1**). Also, they had higher intakes of all positive contributors to the EDIH except low-energy beverages and low-fat dairy products; for negative contributors to the EDIH, they had lower intakes of wine and whole fruits, but higher intakes of high-fat dairy products. Participants of different quintiles did not differ on performance status, stage, treatment arm, pack-years of smoking, physical activity, family history of colorectal cancer, or aspirin use. Patients in the highest quintile of EDIH appeared to experience a trend toward an improved disease-free, recurrence-free, and overall survival, although none statistically significant (**Table 2**). Moreover, the associations did not differ by sex ($P_{interaction} > 0.05$).

Discussion

Because hyperinsulinemia promotes colon carcinogenesis, a diet inducing an elevated insulin response may accelerate tumor growth, thereby contributing to worse survival (1). Previous studies reported higher EDIH was associated with higher risk of colorectal cancer and digestive system cancers (2, 8). In a prior analysis, an alternative measure of dietary insulinemic potential, dietary insulin index (DII) was associated with an inferior survival among patients with colon cancer (3). EDIH, an index intended to measure dietary insulinemic potential, would be associated with worse colon cancer survival. However, in our study, we observed a nonsignificant trend toward an improved outcome with higher EDIH. The unexpected results may be explained by different thoughts of constructing EDIH and DII to predict hyperinsulinemia that EDIH was to predict chronic insulin levels and DII was supposed to measure acute effects of food items on insulin secretion. Because we found insignificant interactions between EDIH and sex, we reasonably believe that sex may not drive these unexpected results.

Our study has many strengths, including ascertainment of cancer diagnosis and events, standardized treatment and follow-up, and detailed prognostic information. Dietary intake was self-reported and potentially subject to measurement errors. However, the FFQ in our cohort has been extensively validated both in healthy populations and cohorts of patients with cancer. In conclusion, the diet of higher insulinemic potential is not associated with worse survival in patients with stage III colon cancer.

Disclosure of Potential Conflicts of Interest

K. Ng is a consultant for Tarrex Biopharma; is an advisory board member for Bayer, Seattle Genetics, and Array Biopharma; and reports receiving commercial research grants from Revolution Medicines, Evergrande Group, Genentech, Gilead Sciences, Trovagene, Pharmavite, and Tarrex Biopharma. R.B. Mowat is an MD at Daiichi Sankyo. R. Whittom has an advisory board relationship with AstraZeneca Canada, Roche Canada, Bristol-Myers Squibb, and Purdue. A. Benson has a consulting/advisory relationship with National Comprehensive Cancer Network (NCCN), Bristol-Myers Squibb, ACCC, ECOG-ACRIN, Amgen, Imedex, Artemida Pharma, Intellisphere OncLiv, American College of Radiology, China National Medical Association 6th Affiliated Sun Yet-San Hospital, Springer, Health Advances, Patient Resource (educational document review), Lexicon, Research to Practice, AVBCC, Harborside, Guardant, Merck Sharpe and Dohme, Terumo, and Lexicon and reports receiving commercial research grants from Celgene, Infinity Pharmaceuticals, Amgen, ECOG-ACRIN, SynCore, Merck Sharp and Dohme, Taiho, Rafael Pharmaceuticals, MedImmune/AstraZeneca, Xencor, Bristol-Myers Squibb, PreECOG, and Astellas. H. Kindler is a consultant for AstraZeneca, Inventiva, Merck, Paradox, Deciphera, Aldeyra, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Erytech, Five Prime Therapeutics, Ipsen, and Kyowa. J.A. Meyerhardt reports receiving other remuneration from Taiho and COTA Healthcare. C.S. Fuchs reports receiving

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