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Dietary fat intake after colon cancer diagnosis in relation to cancer recurrence and survival: CALGB 89803 (Alliance)

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Abstract

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Conflicts of Interest Statement: The authors have no relevant conflicts of interest.

Background: Higher intake of long-chain ω-3 polyunsaturated fatty acids and nuts, rich plant sources of unsaturated fats, after colon cancer diagnosis are associated with improved survival. It is not known whether the amount or distribution of other types of fat are associated with survival after colon cancer.

Methods: We prospectively examined post-diagnostic total, animal, and vegetable fats as well as saturated, monounsaturated, polyunsaturated, and *trans* fat in relation to disease-free survival among 1,011 patients with stage III colon cancer. Patients were enrolled between 1999 and 2001 at the onset of adjuvant chemotherapy and followed for recurrence or death through 2009.

Results: During median follow-up of 7 years, we observed 305 deaths and 81 recurrences (total events: 386). Neither total nor any specific type of dietary fat examined was statistically significantly associated with risk of cancer recurrence or death from any cause (disease-free survival) after stage III colon cancer.

Conclusion: The amount and type (animal, vegetable, saturated, monounsaturated, polyunsaturated, *trans*) of dietary fat consumed after colon cancer does not appear to be substantially associated with risk of recurrence or survival.

Impact: Neither total, nor major types (animal, vegetable, saturated, monounsaturated, polyunsaturated, *trans*), of dietary fat consumed after colon cancer was associated with cancer recurrence or survival.

INTRODUCTION

Over 1.3 million Americans live with colorectal cancer. Data from our group suggest marine ω-3 polyunsaturated fatty acids and nuts, plant sources of unsaturated fat, may reduce risk of colon cancer death (1,2). However, it is unknown if the total amount, or major types (animal, vegetable, saturated, monounsaturated, polyunsaturated, *trans*), of dietary fat are associated with colon cancer survival. Thus, we prospectively examined dietary fat and disease-free survival among colon cancer patients. We hypothesized that high vegetable fat and low animal fat intake would be associated with longer disease-free survival.

MATERIALS AND METHODS

This study was conducted among 1,095 stage III colon cancer patients enrolled in a chemotherapy trial [Cancer and Leukemia Group B (CALGB) 89803] between 1999 and 2001 who completed a lifestyle survey, as previously described (3,4). CALGB is now part of the Alliance for Clinical Trials in Oncology. Written informed consent was obtained from all patients; the study was IRB-approved and conducted in accordance with recognized ethical guidelines.

We excluded 8 patients who recurred prior to the survey, 30 who recurred or died within 90 days of the survey, and 46 who reported implausible energy (<600 or >4200 kcal/day for men, <500 or >3200 kcal/day for women) or left ≥70 survey items blank, leaving 1,011 eligible patients.

Diet was assessed via food frequency questionnaire (FFQ) during and 6 months after therapy (~3 and 15 months after diagnosis)(5). Exposures of interest included total, animal, and

vegetable fat as well as saturated, monounsaturated, polyunsaturated (total, ω-3, ω-6), and *trans* fat. Our primary outcome, disease-free survival, was time from the first FFQ to recurrence, new primary colon tumor, or death from any cause.

We examined dietary fats in relation to disease-free survival using Cox proportional hazards regression. We used the nutrient residual method to adjust dietary fat for energy, and calculated post-diagnostic intakes using a weighted average from available surveys (3,6). Our Model 1 was adjusted for sex, energy (kcal/d), and age at diagnosis (years). Model 2 was additionally adjusted for T-stage (T1-T2, T3-T4, unknown), positive lymph nodes (1–3, ≥4, unknown), performance status (fully active, restricted in strenuous activity, unknown), treatment arm, body mass index (BMI; kg/m^2), physical activity (MET-h/wk), smoking (current, past, never, unknown), aspirin use (yes, no, unknown), and intake (g/d) of protein, alcohol, and fats other than the fat of interest. We considered adjustment for other dietary factors, including western dietary pattern, prudent dietary pattern, folate, vitamin D, and calcium; point estimates did not materially change.

The Alliance Statistics and Data Center collected the data; the database was frozen Nov. 9, 2009. All statistical analyses were conducted using SAS v. 9.4 and 2-sided *p*-values <.05 were considered statistically significant.

RESULTS

We observed 305 deaths and 81 recurrences (386 total events) among 1,011 colon cancer patients (median follow-up: 6.6 years). Patients who consumed more vegetable fat were older and consumed less animal fat, carbohydrates, and protein than those who consumed less vegetable fat (Table 1). Quartiles 2 and 3 of vegetable fat were more likely to receive irinotecan than quartiles 1 or 4. Patients who consumed more animal fat were younger, had higher BMI, and consumed less vegetable fat and carbohydrates and more protein compared to patients who consumed less animal fat. Neither total fat, nor any type of fat examined (animal, vegetable, saturated, monounsaturated, polyunsaturated, *trans*), was statistically significantly associated with disease-free survival after colon cancer (Table 2). Post-hoc, we estimated that the minimum detectable beneficial hazard ratio across extreme quartiles was 0.58 with 80% power, assuming a linear relationship and 2-tailed alpha= 0.05 (7).

DISCUSSION

We observed no statistically significant associations between dietary fat and disease-free survival in this prospective study among 1,011 stage III colon cancer patients. Our team previously reported that a Western dietary pattern and high glycemic load diets are associated with higher risk of recurrence and death after colon cancer (3,6), while long-chain ω-3 polyunsaturated fatty acids and nuts (rich plant sources of unsaturated fats) are associated with lower risk (1,2). Based on these data, we hypothesized that higher vegetable fat intake would be associated with improved survival, but observed no association. Song et al. recently reported that higher fiber intake was associated with lower risk of colorectal cancer mortality in an independent cohort (8). Thus, the beneficial effect of nuts may be related to their low glycemic index and fiber rather than fat content.

Our analysis has many strengths, including large number of events, standardized treatment, and complete follow-up. This was an observational study however, and therefore confounding is possible. Additionally, there is error in diet assessment, but it is expected to be non-differential due to our prospective assessment. In conclusion, neither the total amount nor amount of major types of dietary fat (i.e., saturated, monounsaturated, polyunsaturated) consumed after colon cancer was associated with disease-free survival.

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REFERENCES

1. Van Blarigan EL, Fuchs CS, Niedzwiecki D, Ye X, Zhang S, Song M, et al. Marine omega-3 Polyunsaturated Fatty Acid and Fish Intake after Colon Cancer Diagnosis and Survival: CALGB 89803 (Alliance). Cancer Epidemiol Biomarkers Prev 2018;27(4):438–45 doi 10.1158/1055-9965.EPI-17-0689. [PubMed: 29358223]
2. Fadelu T, Zhang S, Niedzwiecki D, Ye X, Saltz LB, Mayer RJ, et al. Nut Consumption and Survival in Patients With Stage III Colon Cancer: Results From CALGB 89803 (Alliance). J Clin Oncol 2018;36(11):1112–20 doi 10.1200/JCO.2017.75.5413. [PubMed: 29489429]
3. Meyerhardt JA, Niedzwiecki D, Hollis D, Saltz LB, Hu FB, Mayer RJ, et al. Association of dietary patterns with cancer recurrence and survival in patients with stage III colon cancer. JAMA 2007;298(7):754–64 doi 10.1001/jama.298.7.754. [PubMed: 17699009]
4. Saltz LB, Niedzwiecki D, Hollis D, Goldberg RM, Hantel A, Thomas JP, et al. Irinotecan fluorouracil plus leucovorin is not superior to fluorouracil plus leucovorin alone as adjuvant treatment for stage III colon cancer: results of CALGB 89803. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2007;25(23):3456–61 doi 10.1200/JCO.2007.11.2144. [PubMed: 17687149]
5. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol 1992;135(10):1114–26; discussion 27–36. [PubMed: 1632423]
6. Meyerhardt JA, Sato K, Niedzwiecki D, Ye C, Saltz LB, Mayer RJ, et al. Dietary glycemic load and cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. J Natl Cancer Inst 2012;104(22):1702–11 doi 10.1093/jnci/djs399. [PubMed: 23136358]
7. Chapman DG, Nam JM. Asymptotic power of chi square tests for linear trends in proportions. Biometrics 1968;24(2):315–27. [PubMed: 5683872]

8. Song M, Wu K, Meyerhardt JA, Ogino S, Wang M, Fuchs CS, et al. Fiber Intake and Survival After Colorectal Cancer Diagnosis. JAMA Oncol 2018;4(1):71–9 doi 10.1001/jamaoncol.2017.3684. [PubMed: 29098294]

Table 1.

Characteristics of 1,011 stage III colon cancer patients, by post-diagnostic intake of animal and vegetable fat.

	Quartile of Animal Fat			Quartile of Vegetable Fat		
	1	**4**		**1**	**4**	
N	252	253		252	253	
Characteristic, median (IQR) or %			***p-value***			***p-value***
Male	56	60	0.26	54	54	0.20
Age, years	62 (54, 70)	57 (51, 67)	0.01	60 (51, 69)	62 (54, 69)	0.03
Race			0.14			0.41
White	89	86		86	90	
Black	5	10		8	6	
Other	6	4		6	4	
Performance status			0.29			0.40
Fully active	76	68		72	73	
Restricted in strenuous activity	21	30		27	26	
Unknown	3	2		1	1	
Bowel wall invasion			0.89			0.87
T1-T2	15	14		12	13	
T3-T4	77	80		83	79	
Unknown	8	6		5	8	
Positive lymph nodes			0.65			0.26
1–3 (N1)	62	64		67	64	
≥4 (N2)	35	34		32	35	
Unknown	3	2		1	1	
Clinical bowel abnormality						
Perforation	3	6	0.34	3	7	0.10
Obstruction	23	25	0.31	22	23	0.32
Grade of differentiation			0.88			0.26
Well	4	6		7	6	
Moderate	71	68		68	72	
Poor	22	24		25	21	
Unknown	3	2		1	1	
Treatment arm			0.88			0.006
Fluorouracil + leucovorin	51	51		56	57	
Irinotecan, fluorouracil, leucovorin	49	49		44	43	
Smoking status			0.33			0.94
Current	6	13		12	10	

	Quartile of Animal Fat			Quartile of Vegetable Fat		
	1	4		1	4	
Past	48	44		44	43	
Never	45	42		44	45	
Unknown	1	1		1	1	
Aspirin user	9	8	0.72	7	7	0.73
BMI, kg/m^2	26.7 (23.8, 29.9)	29.3 (25.0, 33.9)	<0.001	27.5 (24.1, 32.1)	28.3 (24.7, 31.8)	0.26
Physical activity, MET h/wk	7.7 (2.2, 23.2)	5.9 (1.7, 16.7)	0.09	7.4 (2.7, 18.1)	5.7 (1.6, 16.5)	0.11
Energy, kcal/d	1848 (1532, 2327)	1915 (1502, 2334)	0.59	1866 (1553, 2336)	1794 (1457, 2309)	0.29
Animal fat, g/d	27 (23, 29)	50 (47, 55)	<0.001	39 (31, 48)	35 (29, 42)	<0.001
Vegetable fat, g/d	34 (28, 42)	30 (24, 36)	<0.001	23 (20, 25)	46 (42, 52)	<0.001
Carbohydrate, g/d	284 (266, 307)	225 (205, 241)	<0.001	267 (240, 293)	237 (213, 260)	<0.001
Protein, g/d	76 (66, 87)	89 (81, 100)	<0.001	89 (76, 101)	76 (68, 86)	<0.001

Abbreviations: BMI, body mass index; MET, metabolic equivalent task.

[1] *P*-value calculated using chi-square tests for categorical measures and Kruskal Wallis tests for continuous measures.

Table 2.

Relative risk of cancer recurrence or death from any cause (disease-free survival) among 1,011 colon cancer patients, by post-diagnostic fat intake.

	Quartile of intake				
	1	**2**	**3**	**4**	***P-trend*[1]**
Total fat					
Median, g/d	57	68	76	87	
Events	96	94	94	102	
Model 1 HR (95% CI) [2]	1.00	0.98 (0.74, 1.31)	0.99 (0.74, 1.31)	1.07 (0.81, 1.42)	0.62
Model 2 HR (95% CI) [3]	1.00	1.08 (0.80, 1.46)	1.03 (0.76, 1.39)	1.10 (0.82, 1.49)	0.58
Animal fat					
Median, g/d	27	34	41	50	
Events	108	94	89	95	
Model 1 HR (95% CI) [2]	1.00	0.89 (0.67, 1.17)	0.78 (0.59, 1.03)	0.87 (0.66, 1.15)	0.25
Model 2 HR (95% CI) [3]	1.00	0.84 (0.62, 1.14)	0.74 (0.54, 1.02)	0.78 (0.54, 1.14)	0.16
Vegetable fat					
Median, g/d	23	30	35	46	
Events	90	90	101	105	
Model 1 HR (95% CI) [2]	1.00	0.99 (0.73, 1.32)	1.15 (0.86, 1.53)	1.22 (0.92, 1.62)	0.11
Model 2 HR (95% CI) [3]	1.00	0.98 (0.72, 1.34)	1.09 (0.79, 1.49)	1.17 (0.84, 1.62)	0.27
Saturated fat					
Median, g/d	18	22	25	30	
Events	96	88	94	108	
Model 1 HR (95% CI) [2]	1.00	0.90 (0.67, 1.20)	0.95 (0.71, 1.26)	1.14 (0.87, 1.51)	0.27
Model 2 HR (95% CI) [3]	1.00	0.97 (0.70, 1.34)	0.96 (0.68, 1.37)	1.15 (0.77, 1.72)	0.44
Monounsaturated fat					
Median, g/d	21	26	29	34	
Events	102	102	80	102	
Model 1 HR (95% CI) [2]	1.00	0.96 (0.73, 1.26)	0.75 (0.56, 1.00)	0.99 (0.75, 1.30)	0.64
Model 2 HR (95% CI) [3]	1.00	0.92 (0.67, 1.26)	0.63 (0.43, 0.91)	0.71 (0.46, 1.09)	0.08
Polyunsaturated fat					
Median, g/d	10	12	14	18	
Events	101	84	94	107	
Model 1 HR (95% CI) [2]	1.00	0.81 (0.60, 1.08)	0.90 (0.68, 1.19)	1.09 (0.83, 1.43)	0.28
Model 2 HR (95% CI) [3]	1.00	0.87 (0.63, 1.18)	0.98 (0.71, 1.35)	1.25 (0.89, 1.75)	0.08
ω-6 Polyunsaturated fatty acids					

	Quartile of intake				
	1	**2**	**3**	**4**	***P-trend*[1]**
Median, g/d	9	11	13	16	
Events	106	79	95	106	
Model 1 HR (95% CI) [2]	1.00	0.70 (0.52, 0.94)	0.89 (0.67, 1.17)	1.01 (0.78, 1.33)	0.46
Model 2 HR (95% CI) [3]	1.00	0.78 (0.57, 1.08)	0.97 (0.70, 1.35)	1.16 (0.76, 1.77)	0.34
ω-3 Polyunsaturated fatty acids[4]					
Median, g/d	0.9	1.2	1.5	2.0	
Events	97	92	94	103	
Model 1 HR (95% CI) [2]	1.00	0.93 (0.70, 1.24)	0.96 (0.72, 1.28)	1.11 (0.84, 1.46)	0.38
Model 2 HR (95% CI) [3]	1.00	0.80 (0.59, 1.08)	0.89 (0.65, 1.22)	0.88 (0.59, 1.30)	0.65
***Trans* fatty acids**					
Median, g/d	1.8	2.4	2.9	3.6	
Events	99	83	93	111	
Model 1 HR (95% CI) [2]	1.00	0.77 (0.57, 1.03)	0.85 (0.64, 1.13)	1.09 (0.83, 1.43)	0.36
Model 2 HR (95% CI) [3]	1.00	0.71 (0.52, 0.98)	0.77 (0.55, 1.09)	0.93 (0.64, 1.36)	0.99

Abbreviations: HR, hazard ratio; CI, confidence interval.

[1] *P*-trend calculated by modeling the median of each category as a continuous term.

[2] Cox proportional hazards regression model adjusted for age, sex, and energy (kcal/d).

[3] Cox proportional hazards regression model adjusted for variables in Model 1 plus T-stage, number of positive lymph nodes, baseline performance status, treatment arm, body mass index (kg/m^2), physical activity (MET-h/wk), smoking, aspirin use, and intake of protein (g/d), alcohol (g/d), and fats other than the fat of interest (g/d).

[4] Total ω-3 polyunsaturated fats is predominantly alpha-linolenic acid (ALA), but also includes marine ω-3 polyunsaturated fats, eicosapentaaenoic acid (EPA) and docosahexaenoic acid (DHA), which we previously reported to be beneficial.(1)