JAMA Oncology | Original Investigation

Association of Survival With Adherence to the American Cancer Society Nutrition and Physical Activity Guidelines for Cancer Survivors After Colon Cancer Diagnosis
The CALGB 89803/Alliance Trial

Erin L. Van Blarigan, ScD; Charles S. Fuchs, MD, MPH; Donna Niedzwiecki, PhD; Sui Zhang, MS; Leonard B. Saltz, MD; Robert J. Mayer, MD; Rex B. Mowat, MD; Renaud Whittom, MD; Alexander Hantel, MD; Al Benson, MD; Daniel Atienza, MD; Michael Messino, MD; Hedy Kindler, MD; Alan Venook, MD; Shuji Ogino, MD, PhD; Edward L. Giovannucci, MD, ScD; Kimmie Ng, MD, MPH; Jeffrey A. Meyerhardt, MD, MPH

IMPORTANCE The American Cancer Society Nutrition and Physical Activity Guidelines for Cancer Survivors (ACS guidelines) include maintaining (1) a healthy body weight; (2) physical activity; and (3) a diet that includes vegetables, fruits, and whole grains. It is not known whether patients with colon cancer who follow these guidelines have improved survival.

OBJECTIVE To examine whether a lifestyle consistent with the ACS guidelines is associated with improved survival rates after colon cancer.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study included 992 patients with stage III colon cancer who were enrolled in the CALGB 89803 randomized adjuvant chemotherapy trial from 1999 through 2001. Data for the present study were analyzed between November 2016 and December 2017.

EXPOSURES We assigned an ACS guidelines score for each included patient based on body mass index; physical activity; and intake of vegetables, fruits, whole grains, and red/processed meats (score range, 0-6, with higher score indicating healthier behaviors). Secondarily, we examined a score that also included alcohol intake in addition to the other factors (range, 0-8). Lifestyle was assessed during and 6 months after chemotherapy.

MAIN OUTCOMES AND MEASURES Hazard ratios (HRs) and 95% confidence intervals (CIs) for disease-free, recurrence-free, and overall survival.

RESULTS Of the 992 patients enrolled in the study, 430 (43%) were women, and the mean (SD) age was 59.6 (11.2) years (range, 21-85 years). Over a 7-year median follow-up, we observed 335 recurrences and 299 deaths (43 deaths without recurrence). Compared with patients with a 0 to 1 ACS guidelines score (n = 262; 26%), patients with a 5 to 6 score (n = 91; 9%) had a 42% lower risk of death during the study period (HR, 0.58; 95% CI, 0.34-0.99; *P* = .01 for trend) and improved disease-free survival (HR, 0.69; 95% CI, 0.45-1.06; *P* = .03 for trend). When alcohol consumption was included in the score, the adjusted HRs comparing patients with scores of 6 to 8 (n = 162; 16%) vs those with scores of 0 to 2 (187; 91%) were 0.49 for overall survival (95% CI, 0.32-0.76; *P* = .002 for trend), 0.58 for disease-free survival (95% CI, 0.40, 0.84; *P* = .01 for trend), and 0.64 for recurrence-free survival (95% CI, 0.44-0.94; *P* = .05 for trend).

CONCLUSIONS AND RELEVANCE Having a healthy body weight, being physically active, and eating a diet rich in vegetables, fruits, and whole grains after diagnosis of stage III colon cancer was associated with a longer survival.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00003835

JAMA Oncol. doi:10.1001/jamaoncol.2018.0126
Published online April 12, 2018.

Editorial
Author Audio Interview
Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Erin L. Van Blarigan, ScD, University of California, San Francisco, 550 16th St, Second Floor, San Francisco, CA 94158 (erin.vanblarigan@ucsf.edu).

Colorectal cancer affects over 1.3 million individuals in the United States.[1] In response to the need for improved survivorship care, the American Cancer Society (ACS) published guidelines for nutrition during and after cancer treatment in 2001.[2-5] The current guidelines are to (1) achieve and maintain a healthy body weight; (2) engage in regular physical activity; and (3) achieve a dietary pattern high in vegetables, fruits, and whole grains.[3] A lifestyle consistent with the ACS guidelines in healthy people is associated with lower risk of cancer mortality and overall mortality.[6-8] Guideline adherence has also been correlated with higher quality of life among survivors of colorectal cancer.[9] It is not known, however, whether following the guidelines after colorectal cancer diagnosis is associated with reduced risk of recurrence or mortality.

Data suggest that lifestyle may have an impact on colorectal cancer outcomes.[10] Our group reported that a western dietary pattern was associated with a 3-fold increased risk of colon cancer recurrence and death,[11] and physical activity after diagnosis was associated with a 50% lower risk of recurrence and death.[12] Additionally, our group and others have reported that body size is associated with colorectal cancer recurrence and death, although the body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) associated with the lowest mortality rate may be higher in patients with cancer than in healthy individuals.[13] No study has looked at the combined effect of BMI, physical activity, and diet after colorectal cancer diagnosis.

We sought to determine whether patients with colon cancer who had a lifestyle consistent with the ACS Nutrition and Physical Activity Guidelines for Cancer Survivors (hereafter referred to as the ACS guidelines) had longer disease-free, recurrence-free, and overall survival.

Key Points

Question Do patients with colon cancer who follow the American Cancer Society's Nutrition and Physical Activity Guidelines for Cancer Survivors (ACS guidelines) have better survival rates than those who do not follow these guidelines?

Findings In this cohort study of 992 patients with colon cancer, a lifestyle consistent with the ACS guidelines was associated with a 42% lower risk of death during the study period. The 5-year survival probability was 85% for patients with high concordance with the guidelines and 76% for patients with low concordance with the guidelines, a 9% absolute reduction in risk of death at 5 years.

Meaning Patients with colon cancer who follow the ACS guidelines during and after treatment may have a higher 5-year survival rate.

Methods

Study Population

This prospective study was conducted among 1264 patients with stage III colon cancer enrolled in the Cancer and Leukemia Group B (CALGB) 89803 study, an adjuvant chemotherapy trial, between 1999 and 2001. CALGB is now part of the Alliance for Clinical Trials in Oncology. Patients were randomized within 8 weeks of cancer resection. A lifestyle survey was administered in the clinic midway through, and 6 months after, chemotherapy; 1095 (87%) patients completed survey 1, and 981 (78%) patients completed survey 2.[14] We excluded 8 patients whose cancer recurred before the survey and 57 patients for inadequate survey responses (dietary intake of >3500 or <500 kcal/d for women; >4200 or <600 kcal/d for men; or ≥70 items missing). We also excluded 19 individuals who experienced an event within 90 days of survey 1 and 12 individuals with a BMI lower than 18.5 to limit reverse causation due to underlying disease. Finally, we excluded 1 individual with missing BMI and 6 individuals with missing physical activity on both surveys. After exclusions, there were 992 patients eligible for analysis. The study was approved by the institutional review boards of all participating institutions, and each participant signed an informed consent statement in accordance with federal and institutional guidelines.

Dietary Assessment

Patients completed a validated food frequency questionnaire (FFQ) that queried intake of 131 items over the past 3 months in up to 9 frequency options ranging from never to 6 or more times per day, as previously described.[15-18] Items of interest included fruits, vegetables, whole grains, refined grains, red and processed meats, and alcohol (eTable 1 in the Supplement).

Physical Activity Assessment

Patients reported average time per week over the past 2 months performing 9 common leisure-time activities, as previously described.[12] Ten response options ranged from 0 to 11 or more hours per week for each activity. To calculate total metabolic equivalent task (MET) hours per week (MET-h/wk) of physical activity, we assigned each activity a MET value, multiplied the activity-specific MET value by the amount of time the participant engaged in that activity, and summed across all activities.[19]

ACS Guidelines Score

We quantified the degree of concordance between patients' lifestyles and the ACS guidelines using a score developed by McCullough et al.[8] The score included BMI, physical activity, and intake of vegetables and fruits, proportion of total grains consumed that were whole grains, and intake of red and processed meat (eTable 2 in the Supplement).[3,6] The overall score ranged from 0 to 6, with higher scores indicating behavior more consistent with the guidelines. In our primary analysis, we calculated the cumulative average ACS guidelines score using data from both surveys weighted to follow-up time, as previously described.[11,14,15]

We considered alternative scoring for BMI in an a priori secondary analysis. The ACS guidelines recommend a BMI of 18.5 to 24.9. However, a BMI of 23.0 to 29.9 has been associated with lower risk of recurrence or death among patients with colorectal cancer.[20] Therefore, we examined alternative cut points for BMI: 0 points for 35.0 or higher; 1 point for 18.5 to 22.9 or 30.0 to 34.9; and 2 points for 23.0 to 29.9.

In addition, alcohol consumption is included in the ACS guidelines for Cancer Prevention, but not among cancer survivors. Given patient interest and a possible benefit of low to moderate alcohol consumption for colon cancer survivors,[21]

we conducted a secondary analysis including alcohol intake in the score. For this analysis, we applied the cut points described by McCullough et al[8]: 0 points for more than 1 drink per day for women, or more than 2 drinks per day for men; 1 point for no drinks, both men and women; and 2 points for more than 0 but 1 or fewer drinks per day for women, or more than 0 but 2 or fewer drinks per day for men. A score using these cut points was more strongly associated with all-cause and cancer-specific mortality in healthy individuals compared with a score that assigned 2 points for no alcohol.[8] The ACS guidelines score including alcohol ranged from 0 to 8, with a score of 8 indicating complete concordance with the ACS guidelines plus low to moderate alcohol consumption.

Outcome Assessment

Our primary outcome for this analysis was overall survival, defined as time from survey 1 to death. We also examined disease-free and recurrence-free survival. Disease-free survival was defined as time to tumor recurrence, occurrence of a new primary colon tumor, or death from any cause. Recurrence-free survival was defined as time to tumor recurrence or new primary colon tumor; patients who died without recurrence were censored. Follow-up included nearly 100% of enrollees.

Statistical Analysis

There was no difference in survival between treatment arms in CALGB 89803, so we analyzed all patients as a prospective cohort.[22] We used Cox proportional hazards regression to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). We combined patients with ACS guidelines scores of 0 and 1 and patients with scores of 5 and 6 owing to low numbers in both categories (6% had 0 points [n = 61]; 20% had 1 point [n = 201]; 7% had 5 points [n = 72]; and 2% had 6 points [n = 19]). Our first model was adjusted for total caloric intake, age, and sex. Our multivariate model was additionally adjusted for T stage (T1-T2, T3-T4, missing), number of positive lymph nodes (1-3, ≥4, missing), Zubrod performance status (0, 1-2, missing), treatment arm, smoking status (never, past, current, missing), and aspirin use (yes, no, missing). Adjustment for race; median household income by zip code; glycemic load; and intake of long-chain ω3 fatty acids, nuts, coffee, or sugar-sweetened beverages did not change our results, and these variables were omitted from our final models. We confirmed that the proportional hazards assumption was valid by including a cross-product between the score and time in our multivariate model and using a Wald test.[23] We also examined whether age, sex, race, performance status, or treatment arm modified our results by including the cross-product between the score and potential effect modifier in our model and using a Wald test.

The Alliance Statistics and Data Center collected the data following strict policies for data quality. All analyses were based on the study database frozen on November 9, 2009.

Absolute Risk Difference, Number Needed to Treat, and PAR

We estimated the absolute risk difference of death at 5 years, the number needed to treat for 5 years to prevent 1 death, and the population-attributable risk (PAR) between patients with ACS guidelines scores of 4 or higher and 5 or higher vs lower scores. There were only 19 individuals with a score of 6, so we were unable to examine this group. The Cox proportional hazards model does not estimate the baseline hazard; therefore, we fit a Weibull survival model with proportional hazards to estimate the risk difference.[24] To calculate the number needed to treat, we divided 100 by the absolute risk difference. The number needed to treat represents the number of patients with stage III colon cancer and lower ACS guideline scores who would need to achieve the specified score for 5 years to prevent 1 death. For all analyses, we assumed that the patients' lifestyle measured at 2 time points approximately 1 year apart was a measure of their long-term lifestyle as a cancer survivor. The PAR is the percentage of deaths occurring among patients with stage III colon cancer that hypothetically could be prevented if all patients followed the ACS guidelines. We calculated the PAR based on the proportion of exposed individuals (P_e) and the HR using the following equation[25]: $PAR = [(HR^{-1}–1) \times P_e] \div ([(HR^{-1}–1) \times P_e] + 1)$. The HR in the original equation assumes that the desirable behavior is the reference, so we used the inverse of the HR when estimating the PAR.

Sensitivity Analyses

We performed several sensitivity analyses. First, we excluded 43 individuals who experienced an event 90 to 180 days after survey 1 to further evaluate reverse causation (individuals who experienced an event within 90 days were excluded in our primary analysis). Second, we were concerned that patients' lifestyle as reported on survey 1 might have been influenced by treatment, so we used survey 2 to classify patients' adherence to the guidelines and started follow-up at survey 2. Third, we explored change in the ACS guidelines score between survey 1 and survey 2 in relation to overall survival. We combined patients who increased their score by 2 (n = 81, 8%) or 3 (n = 18, 2%) points and patients who decreased their score by 2 (n = 69, 7%), 3 (n = 17, 2%), or 4 (n = 1, 0%) points. This model was adjusted for the factors in our multivariate model plus patients' score on survey 1. Finally, we examined whether results differed with 2 alternative diet subscores, one omitting variety of fruits and vegetables and the other omitting red and processed meats.

All statistical analyses were performed using SAS software, version 9.4, and 2-sided $P < .05$ was considered statistically significant.

Results

We observed 378 events of cancer recurrence or death among the 992 study patients with colon cancer (median follow-up, 7 years). There were 335 recurrences and 299 deaths; 256 deaths occurred (86%) after cancer recurrence. Patients whose lifestyle was consistent with the ACS guidelines were more likely to be white, women, and never smokers; there were no differences in age, aspirin use, performance status, or clinical factors (**Table 1**).

A lifestyle consistent with the ACS guidelines after colon cancer diagnosis was associated with longer survival (**Table 2**). Compared with patients with a score of 0 or 1, patients with a score of 5 or 6 had an adjusted HR for overall survival of 0.58 (95% CI, 0.34-0.99; $P = .01$ for trend). There was a statistically

Table 1. Characteristics of the 992 Patients With Stage III Colon Cancer by ACS Guidelines Score

Characteristic	ACS Guidelines Score					P Value[a]
	0-1 (n = 262)	2 (n = 248)	3 (n = 251)	4 (n = 140)	5-6 (n = 91)	
Age, median (IQR), y	59 (52-67)	61 (52-69)	61 (51-70)	61 (49-70)	59 (53-67)	.73
Male, No. (%)	135 (52)	151 (61)	142 (57)	91 (65)	43 (47)	.02
White race	218 (83)	227 (92)	224 (89)	129 (92)	85 (93)	.02
Performance status, No. (%)						.23
Fully active	173 (66)	184 (74)	189 (75)	109 (78)	71 (78)	
Restricted in strenuous activity	82 (31)	59 (24)	58 (23)	28 (20)	18 (20)	
Unknown	7 (3)	5 (2)	4 (2)	3 (2)	2 (2)	
Bowel wall invasion, No. (%)						.69
T1-T2	36 (14)	31 (13)	31 (12)	23 (16)	11 (12)	
T3-T4	212 (81)	201 (81)	202 (80)	103 (74)	75 (82)	
Unknown	14 (5)	16 (6)	18 (7)	14 (10)	5 (5)	
Positive lymph nodes, No. (%)						.95
1-3 (N1)	167 (64)	156 (63)	157 (63)	86 (61)	55 (60)	
≥4 (N2)	88 (34)	88 (35)	91 (36)	50 (36)	34 (37)	
Unknown	7 (3)	4 (2)	3 (1)	4 (3)	2 (2)	
Bowel abnormality, No. (%)						
Perforation	12 (5)	12 (5)	10 (4)	7 (5)	1 (1)	.57
Obstruction	48 (18)	49 (20)	56 (22)	34 (24)	30 (33)	.13
Grade of differentiation, No. (%)						.89
Well	15 (6)	11 (4)	14 (6)	9 (6)	4 (4)	
Moderate	188 (72)	172 (69)	177 (71)	91 (65)	65 (71)	
Poor	51 (19)	61 (25)	57 (23)	36 (26)	20 (22)	
Unknown	8 (3)	4 (2)	3 (1)	4 (3)	2 (2)	
Treatment arm, No. (%)						.17
Fluorouracil and leucovorin	134 (51)	112 (45)	125 (50)	79 (56)	52 (57)	
Irinotecan, fluorouracil, leucovorin	128 (49)	136 (55)	126 (50)	61 (44)	39 (43)	
Smoking status, No. (%)						.02
Current	16 (6)	36 (15)	32 (13)	13 (9)	5 (5)	
Past	126 (48)	116 (47)	95 (38)	61 (44)	40 (44)	
Never	118 (45)	96 (39)	121 (48)	66 (47)	46 (51)	
Unknown	2 (1)	0	3 (1)	0	0	
Regular aspirin use, No. (%)						.22
Yes	28 (11)	18 (7)	14 (6)	16 (11)	4 (4)	
No	217 (83)	216 (87)	225 (90)	119 (85)	83 (91)	
Unknown	17 (6)	14 (6)	12 (5)	5 (4)	4 (4)	
Total caloric intake, median (IQR), kcal/d	1874 (1461-2317)	1905 (1535-2321)	1912 (1498-2353)	1825 (1471-2362)	1905 (1549-2239)	.72
BMI, median (IQR)	33 (30-36)	29 (26-32)	26 (23-29)	25 (23-28)	23 (22-25)	<.001
Physical activity, median (IQR), MET-h/wk	2 (1-5)	6 (2-10)	9 (3-18)	22 (12-37)	31 (21-46)	<.001
Fruits and vegetables, median (IQR), servings/d	1.6 (0.9-2.9)	1.6 (1.0-2.9)	1.8 (1.1-3.3)	2.3 (1.2-3.5)	3.4 (1.8-5.0)	<.001
No. of unique fruits and vegetables consumed per month, median (IQR)	27 (22-30)	27 (24-31)	29 (24-33)	30 (26-32)	31 (27-34)	<.001
Total grains that are whole, median (IQR), %	30 (14-50)	46 (22-65)	50 (31-65)	56 (37-69)	62 (51-78)	<.001
Red meat and processed meat, median (IQR), servings/wk	7.2 (5.0-9.8)	6.1 (4.1-8.9)	5.3 (3.5-9.4)	4.9 (3.3-7.5)	3.9 (2.7-6.4)	<.001
Alcoholic drinks, median (IQR), drinks/wk	0.2 (0-1.6)	0.5 (0-3.6)	0.6 (0-3.5)	0.9 (0-3.8)	1.5 (0.2-6.0)	<.001

Abbreviations: ACS Guidelines, American Cancer Society Nutrition and Physical Activity Guidelines for Cancer Survivors[2-5]; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range; MET, metabolic equivalent task.

[a] *P* values calculated using a χ^2 test for categorical measures and a Kruskal-Wallis test for continuous measures.

Table 2. Cancer Recurrence and Mortality Among the 992 Patients With Stage III Colon Cancer by ACS Guidelines Score

Outcome	ACS Guidelines Score (0-6) 0-1	2	3	4	5-6	P Value for Trend[a]
No. at risk	262	248	251	140	91	NA
Overall Mortality						
Events	92	80	70	39	18	NA
Person-years	1485	1364	1397	853	552	NA
Model 1 HR (95% CI)[b]	1.00	0.94 (0.68-1.29)	0.78 (0.56-1.10)	0.73 (0.49-1.08)	0.56 (0.33-0.96)	.01
Model 2 HR (95% CI)[c]	1.00	0.96 (0.69-1.33)	0.78 (0.55-1.10)	0.73 (0.49-1.10)	0.58 (0.34-0.99)	.01
Cancer Recurrence or Death From Any Cause (Disease-Free Survival)						
Events	110	102	91	48	27	NA
Person-years	1292	1195	1234	770	496	NA
Model 1 HR (95% CI)[b]	1.00	0.99 (0.76-1.30)	0.88 (0.67-1.16)	0.75 (0.54-1.06)	0.69 (0.45-1.05)	.02
Model 2 HR (95% CI)[c]	1.00	1.01 (0.76-1.33)	0.88 (0.66-1.17)	0.78 (0.55-1.10)	0.69 (0.45-1.06)	.03
Cancer Recurrence (Recurrence-Free Survival)						
Events	97	88	80	43	27	NA
Person-years	1292	1195	1232	770	496	NA
Model 1 HR (95% CI)[b]	1.00	0.99 (0.74-1.32)	0.88 (0.66-1.19)	0.79 (0.55-1.13)	0.80 (0.52-1.22)	.11
Model 2 HR (95% CI)[c]	1.00	0.99 (0.74-1.33)	0.86 (0.64-1.17)	0.80 (0.56-1.16)	0.78 (0.51-1.20)	.11
ACS Guidelines Score Including Alcohol Consumption (0-8)						
Characteristic	**0-2**	**3**	**4**	**5**	**6-8**	NA
No. at risk	187	199	240	204	162	NA
Overall Mortality						
Events	72	63	73	55	36	NA
Person-years	1009	1139	1356	1151	995	NA
Model 1 HR (95% CI)[b]	1.00	0.70 (0.49-1.01)	0.72 (0.51-1.03)	0.70 (0.48-1.01)	0.49 (0.32-0.75)	.002
Model 2 HR (95% CI)[c]	1.00	0.70 (0.48-1.01)	0.71 (0.50-1.02)	0.67 (0.46-0.97)	0.49 (0.32-0.76)	.002
Cancer Recurrence or Death From Any Cause (Disease-Free Survival)						
Events	84	77	96	75	46	NA
Person-years	886	985	1177	1028	910	NA
Model 1 HR (95% CI)[b]	1.00	0.81 (0.60-1.11)	0.87 (0.65-1.17)	0.79 (0.58-1.07)	0.57 (0.40-0.82)	.01
Model 2 HR (95% CI)[c]	1.00	0.82 (0.60-1.12)	0.86 (0.64-1.16)	0.76 (0.56-1.05)	0.58 (0.40-0.84)	.009
Cancer Recurrence (Recurrence-Free Survival)						
Events	71	69	84	68	43	NA
Person-years	886	985	1177	1025	910	NA
Model 1 HR (95% CI)[b]	1.00	0.89 (0.63-1.23)	0.92 (0.67-1.26)	0.85 (0.61-1.18)	0.65 (0.44-0.95)	.07
Model 2 HR (95% CI)[c]	1.00	0.87 (0.63-1.22)	0.87 (0.63-1.20)	0.80 (0.57-1.13)	0.64 (0.44-0.94)	.05

Abbreviations: ACS Guidelines, American Cancer Society Nutrition and Physical Activity Guidelines for Cancer Survivors[2-5]; HR, hazard ratio; NA, not applicable.

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

[b] Cox proportional hazards regression model adjusted for age, sex, and total caloric intake.

[c] Cox proportional hazards regression model adjusted for variables in model 1 plus indicator variables for T-stage (T1-T2, T3-T4, missing), number of positive lymph nodes (1-3, ≥4, missing), baseline performance status (0, 1-2, missing), treatment arm, smoking status (never, past, current, missing), and aspirin use (yes, no, missing).

significant trend toward improved disease-free survival (ACS guidelines score of 5-6 vs 0-1, HR, 0.69; 95% CI, 0.45-1.06; *P* = .03 for trend) and a nonstatistically significant trend for improved recurrence-free survival (ACS guidelines score of 5-6 vs 0-1, HR, 0.78; 95% CI, 0.51-1.20; *P* = .11 for trend). There was no evidence of effect modification by age, sex, race, performance status, or treatment. As hypothesized, the association appeared stronger when we assigned 2 points in the ACS guidelines score to patients with a BMI of 23.0 to 29.9 (eTable 3 in the Supplement).

The results were strengthened and statistically significant for all outcomes when we included alcohol use in the ACS guidelines score (all supporting data reported in Table 2). The adjusted HRs comparing patients with a score of 6 to 8 vs those with a score of 0 to 2 were 0.49 (95% CI, 0.32-0.76; *P* = .002 for trend) for overall survival; 0.58 (95% CI, 0.40-0.84; *P* = .01 for trend) for disease-free survival; and 0.64 (95% CI, 0.44-0.94; *P* = .05 for trend) for recurrence-free survival.

Absolute Risk Difference, Number Needed to Treat, and PAR

Adherence to the ACS guidelines (score of 5-6) was associated with a 9.0% absolute reduction in the risk of death at 5 years (95% CI, 2.2%-15.9%) compared with a score of 0 to 4 (**Table 3**). Assuming a causal association, 12 patients with stage III colon cancer would need to adopt a lifestyle consistent with the ACS guidelines for 5 years to prevent 1 death. Applying the data from our study population, P_e = 0.09 (proportion of patients with 5-6 points), and HR = 0.6; hypothetically, 38%

Table 3. Hypothesized Absolute RD, NNT, and PAR of Death Among the 992 Patients With Stage III Colon Cancer by ACS Guidelines Score

ACS Guidelines Score	Patients, No. (%)	Deaths, No.	HR (95% CI)[a]	Hypothesized Values		
				RD (95% CI)[b]	NNT for 5 y[c]	PAR, %[d]
≥4	231 (23)	57	0.72 (0.54-0.96)	6.4 (1.4-11.5)	16	23.0
≥5	91 (9)	18	0.60 (0.37-0.97)	9.0 (2.2-15.9)	12	37.7

Abbreviations: ACS Guidelines, American Cancer Society Nutrition and Physical Activity Guidelines for Cancer Survivors[2-5]; HR, hazard ratio; NNT, needed to treat; PAR, population attributable risk; RD, risk difference.

[a] Cox proportional hazards model comparing patients with the score of interest vs patients with all lower scores. Adjustment for age, sex, total caloric intake, and clinical factors did not change the estimates, so these variables were omitted owing to the small number of events in the higher categories.

[b] Difference in probability of survival at 5 years in patients with the score of interest minus probability of survival at 5 years in patients with all lower scores calculated using a Weibull survival model with proportional hazards.

[c] The number of patients with lower scores who would need to achieve the specified score for 5 years to prevent 1 death. Estimated by 100 ÷ RD and rounded up to the nearest whole number.

[d] The percentage of deaths among patients with stage III colon cancer that would hypothetically not have occurred if all patients had the specified ACS guidelines score or higher. Estimated using the equation $PAR = [(HR^{-1}–1) \times P_e] \div ([(HR^{-1}–1) \times P_e] + 1)$.

of deaths among those with stage III colon cancer could be prevented if all patients followed the ACS guidelines.

Individual Score Components

The score components had independent, but not all statistically significant, associations with death after colon cancer (eTable 4 in the Supplement). Patients with a BMI of 25.0 to 29.9 had lower risk of death than patients with BMI 30 or higher (HR, 0.59; 95% CI, 0.44-0.80). A survival benefit was apparent starting at 8.75 MET-h/wk of physical activity (8.75-17.4 vs <8.75 MET-h/wk, HR, 0.64; 95% CI, 0.45-0.92). Consuming 5 or more servings per day of vegetables and fruits (HR, 0.60; 95% CI, 0.38-0.94) and choosing whole over refined grains (HR quartile [Q]4 vs Q1, 0.65; 95% CI, 0.45-0.94) were important dietary factors. Contrary to the guidelines, low intake of red and processed meat after colon cancer was associated with an increased risk of death (HR Q1 vs Q4, 1.72; 95% CI, 1.15-2.58). Finally, compared with abstainers, heavy drinkers had a nonstatistically significant increased risk of death (HR, 1.28; 95% CI, 0.81-2.01), while patients consuming low to moderate amounts of alcohol had a nonstatistically significant decreased risk of death (HR, 0.87; 95% CI, 0.66-1.14).

Sensitivity Analyses

Our results were unchanged when we started follow-up at survey 2 (HR for ACS guidelines score of 5-6 vs 0-1, 0.23; 95% CI, 0.08-0.63) or excluded 43 patients whose cancer recurred or who died 90 to 180 days after the survey (HR for score of 5-6 vs 0-1, 0.49; 95% CI, 0.27-0.88). Compared with the 356 patients who did not change their lifestyle from survey 1 to survey 2 (36%), patients who increased their ACS guidelines score by 2 or 3 points (n = 99; 10%) had an HR for overall survival of 0.67 (95% CI, 0.41-1.08; $P = .10$). The HR for overall survival remained essentially unchanged when omitting variety of fruits and vegetables (HR for score of 5-6 vs 0-1, 0.59; 95% CI, 0.35-1.00) or red and processed meats (HR for score of 5-6 vs 0-1, 0.63; 95% CI, 0.38-1.05) from the diet subscore.

Discussion

In this prospective study, patients with stage III colon cancer and a lifestyle consistent with the ACS guidelines (score, 5-6) had a 42% lower risk of death compared with patients who did not (score, 0-1). The absolute reduction in risk of death at 5 years was 9% comparing patients with a score of 5 or 6 vs those with a score of 0 to 4.

To our knowledge, no prior study has evaluated the ACS guidelines after colon cancer in relation to survival. Among 65 838 women without cancer, the ACS guidelines were associated with a 61% lower risk of colorectal cancer–specific mortality (HR, 0.39; 95% CI, 0.24-0.63; $P < .001$).[6] Among 2017 female cancer survivors, women with diets consistent with the American Institute for Cancer Research guidelines (similar to the ACS guidelines) had a 20% lower risk of death during the study period (HR, 0.80; 95% CI, 0.64-1.00; $P = .05$).[26] No association was observed among the 380 women with colorectal cancer in that study, but there were few events among those patients (n = 82), and diet was assessed approximately 9 years after diagnosis (after most events of colorectal cancer recurrence and death would have occurred). In 1 of the only other studies to examine a diet quality score after diagnosis, women with diets consistent with the Health Eating Index after breast cancer had a 26% lower risk of death during the study period (HR, 0.74; 95% CI, 0.55-0.99; $P = .04$).[27]

It is plausible that following the ACS guidelines after colon cancer diagnosis inhibits recurrence and death. Extensive data suggest that a healthy body size, physical activity, and diet rich in vegetables, fruits, and whole grains improves insulin sensitivity, decreases inflammation, and increases vitamin D levels.[28] These biomarkers have all been consistently associated with colorectal cancer survival.[28,29]

Each component of the score (BMI, physical activity, diet) was independently associated with survival after colon cancer. However, as previously reported, the BMI associated with the lowest risk of death for patients with colon cancer was higher than the ACS guidelines recommendation (23.0-29.9 vs 18.5-24.9).[20] This may reflect reverse causation, since weight loss commonly occurs as cancer progresses. Alternatively, it is possible that a BMI of 23.0 to 29.9 reflects an optimal muscle mass to fat ratio for patients with colon cancer.[30] For physical activity, we observed a benefit at 8.75 MET-h/week, approximately 150 minutes per week of moderate activity such as brisk walking. For diet, choosing whole over refined grains and eating 5 or more servings per day of vegetables and fruits were associated with improved colon cancer survival. Low intake

of red and processed meat did not appear to contribute to the benefit of the ACS guidelines, consistent with data from the Cancer Prevention Study II Nutrition Cohort.[31] Higher protein intake may be beneficial for cancer survivors.[32] Thus, it is possible that red meat is inversely associated with colon cancer mortality, despite being positively associated with colon cancer incidence. Further research is needed to inform guidelines regarding meat intake for patients with cancer.

Limitations

Our study has a number of strengths, including many events, standardized cancer treatment, repeated lifestyle assessments, and complete follow-up. However, there were several limitations. First, there was the potential for reverse causation. To limit reverse causation, we excluded patients whose cancer recurred or who died within 90 days of the survey and within up to 180 days of the survey in a sensitivity analysis. Additionally, all of the patients had comprehensive staging and good performance status when they completed survey 1. Second, we cannot conclude that the associations we observed are independent of patients' prediagnosis lifestyle or that changing behaviors after diagnosis will achieve the observed results. Third, there is measurement error in lifestyle assessments, but the error is likely nondifferential in our analysis owing to our prospective data. Fourth, our study population was predominantly white, and patients in trials may not be representative of all patients with colon cancer. We did not observe evidence of effect modification by race, but future studies in more diverse cohorts are needed. Finally, while adjustment for risk factors for cancer recurrence and death had little impact on our effect estimates, we cannot exclude the possibility of confounding or prove causation.

Conclusions

In conclusion, patients with colon cancer who had a healthy body weight, were physically active, and ate a diet rich in vegetables and fruits and chose whole over refined grains had a 42% lower risk of death during the study period than patients who did not engage in these behaviors. Clinical trials of lifestyle change in colon cancer are needed.

ARTICLE INFORMATION

Accepted for Publication: December 10, 2017.

Published Online: April 12, 2018. doi:10.1001/jamaoncol.2018.0126

Author Affiliations: Department of Epidemiology and Biostatistics, University of California, San Francisco (Van Blarigan); Department of Urology, University of California, San Francisco (Van Blarigan); Yale Cancer Center, Yale School of Medicine, New Haven, Connecticut (Fuchs); Alliance Statistics and Data Center, Duke University, Durham, North Carolina (Niedzwiecki); Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts (Zhang, Mayer, Ogino, Ng, Meyerhardt); Memorial Sloan Kettering Cancer Center, New York, New York (Saltz); Toledo Community Hospital Oncology Program, Toledo, Ohio (Mowat); Hôpital du Sacré-Coeur de Montréal, Montreal, Quebec, Canada (Whittom); Loyola University, Stritch School of Medicine, Naperville, Illinois (Hantel); Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, Illinois (Benson); Virginia Oncology Associates, Norfolk, Virginia (Atienza); Southeast Clinical Oncology Research Consortium, Mission Hospitals Inc, Asheville, North Carolina (Messino); University of Chicago Comprehensive Cancer Center, Chicago, Illinois (Kindler); Helen Diller Family Comprehensive Cancer Center, San Francisco, California (Venook); Division of Hematology/Oncology, Department of Medicine, University of California, San Francisco (Venook); Program in Molecular Pathology Epidemiology (MPE), Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (Ogino); Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts (Ogino, Giovannucci); Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (Giovannucci); Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, Massachusetts (Giovannucci).

Author Contributions: Drs Meyerhardt and Van Blarigan had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Van Blarigan, Fuchs, Saltz, Mayer, Venook, Giovannucci, Meyerhardt.
Acquisition, analysis, or interpretation of data: Van Blarigan, Fuchs, Niedzwiecki, Zhang, Saltz, Mowat, Whittom, Hantel, Benson, Atienza, Messino, Kindler, Venook, Ogino, Ng, Meyerhardt.
Drafting of the manuscript: Van Blarigan, Venook, Meyerhardt.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Van Blarigan, Niedzwiecki, Zhang, Venook, Ng.
Obtained funding: Fuchs, Ogino, Meyerhardt.
Administrative, technical, or material support: Fuchs, Zhang, Mayer, Hantel, Kindler, Venook.
Study supervision: Fuchs, Mowat, Venook, Meyerhardt.

Conflict of Interest Disclosures: The CALGB/Alliance trial was supported in part by funds from Pharmacia and Upjohn Company (now Pfizer Oncology) No other disclosures are reported.

Funding/Support: Research reported in this publication was supported by the National Institutes of Health (NIH) National Cancer Institute (NCI) under award Nos. U10CA180821 and U10CA180882 (to the Alliance for Clinical Trials in Oncology); U10CA032291, U10CA041287, U10CA045808, U10CA077651, U10CA138561, U10CA180791, and U10CA180820 (to ECOG-ACRIN); U10CA180836, U10CA180867, and U10CA180888 (to? SWOG); and UG1CA189858 (to the Southeast Clinical Oncology Research Consortium Inc). Dr Van Blarigan is supported by NCI K07 award K07CA197077. Drs Meyerhardt, Fuchs, and Ng are supported in part by NCI R01 awards R01CA118553, R01CA149222, and R01CA205406 and by GI SPORE grant P50CA127003. Dr Ogino is supported in part by NCI R35 award R35CA197735.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

REFERENCES

1. DeSantis CE, Lin CC, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2014. *CA Cancer J Clin*. 2014;64(4):252-271.

2. Brown J, Byers T, Thompson K, Eldridge B, Doyle C, Williams AM; American Cancer Society Workgroup on Nutrition and Physical Activity for Cancer Survivors. Nutrition during and after cancer treatment: a guide for informed choices by cancer survivors. *CA Cancer J Clin*. 2001;51(3):153-187.

3. Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. *CA Cancer J Clin*. 2012;62(4):243-274.

4. Doyle C, Kushi LH, Byers T, et al; 2006 Nutrition, Physical Activity and Cancer Survivorship Advisory Committee; American Cancer Society. Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. *CA Cancer J Clin*. 2006;56(6):323-353.

5. Brown JK, Byers T, Doyle C, et al; American Cancer Society. Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. *CA Cancer J Clin*. 2003;53(5):268-291.

6. Thomson CA, McCullough ML, Wertheim BC, et al. Nutrition and physical activity cancer prevention guidelines, cancer risk, and mortality in the women's health initiative. *Cancer Prev Res (Phila)*. 2014;7(1):42-53.

7. Romaguera D, Ward H, Wark PA, et al. Pre-diagnostic concordance with the WCRF/AICR

guidelines and survival in European colorectal cancer patients: a cohort study. *BMC Med*. 2015;13:107.

8. McCullough ML, Patel AV, Kushi LH, et al. Following cancer prevention guidelines reduces risk of cancer, cardiovascular disease, and all-cause mortality. *Cancer Epidemiol Biomarkers Prev*. 2011;20(6):1089-1097.

9. Blanchard CM, Courneya KS, Stein K; American Cancer Society's SCS-II. Cancer survivors' adherence to lifestyle behavior recommendations and associations with health-related quality of life: results from the American Cancer Society's SCS-II. *J Clin Oncol*. 2008;26(13):2198-2204.

10. Van Blarigan EL, Meyerhardt JA. Role of physical activity and diet after colorectal cancer diagnosis. *J Clin Oncol*. 2015;33(16):1825-1834.

11. Meyerhardt JA, Niedzwiecki D, Hollis D, et al. Association of dietary patterns with cancer recurrence and survival in patients with stage III colon cancer. *JAMA*. 2007;298(7):754-764.

12. Meyerhardt JA, Heseltine D, Niedzwiecki D, et al. Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. *J Clin Oncol*. 2006;24(22):3535-3541.

13. Meyerhardt JA, Niedzwiecki D, Hollis D, et al; Cancer and Leukemia Group B 89803. Impact of body mass index and weight change after treatment on cancer recurrence and survival in patients with stage III colon cancer: findings from Cancer and Leukemia Group B 89803. *J Clin Oncol*. 2008;26(25):4109-4115.

14. Meyerhardt JA, Sato K, Niedzwiecki D, 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):1702-1711.

15. Willett WC. *Nutritional Epidemiology*. 2nd ed. Oxford, England; Oxford University Press; 1998.

16. Meyerhardt JA, Heseltine D, Campos H, et al. Assessment of a dietary questionnaire in cancer patients receiving cytotoxic chemotherapy. *J Clin Oncol*. 2005;23(33):8453-8460.

17. 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):1114-1126.

18. Feskanich D, Rimm EB, Giovannucci EL, et al. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. *J Am Diet Assoc*. 1993;93(7):790-796.

19. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of physical activities: a second update of codes and MET values. *Med Sci Sports Exerc*. 2011;43(8):1575-1581.

20. Lee J, Meyerhardt JA, Giovannucci E, Jeon JY. Association between body mass index and prognosis of colorectal cancer: a meta-analysis of prospective cohort studies. *PLoS One*. 2015;10(3):e0120706.

21. Fung TT, Kashambwa R, Sato K, et al. Post diagnosis diet quality and colorectal cancer survival in women. *PLoS One*. 2014;9(12):e115377.

22. Saltz LB, Niedzwiecki D, Hollis D, 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. *J Clin Oncol*. 2007;25(23):3456-3461.

23. Rosner B. *Fundamentals of Biostatistics*. 6th ed. Pacific Grove, CA: Brooks/Cole; 2006.

24. Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. *Stat Med*. 2002;21(15):2175-2197.

25. Spiegelman D, Hertzmark E, Wand HC. Point and interval estimates of partial population attributable risks in cohort studies: examples and software. *Cancer Causes Control*. 2007;18(5):571-579.

26. Inoue-Choi M, Robien K, Lazovich D. Adherence to the WCRF/AICR guidelines for cancer prevention is associated with lower mortality among older female cancer survivors. *Cancer Epidemiol Biomarkers Prev*. 2013;22(5):792-802.

27. George SM, Ballard-Barbash R, Shikany JM, et al. Better postdiagnosis diet quality is associated with reduced risk of death among postmenopausal women with invasive breast cancer in the women's health initiative. *Cancer Epidemiol Biomarkers Prev*. 2014;23(4):575-583.

28. Zgaga L, Theodoratou E, Farrington SM, et al. Plasma vitamin D concentration influences survival outcome after a diagnosis of colorectal cancer. *J Clin Oncol*. 2014;32(23):2430-2439.

29. Kohler LN, Hibler EA, Harris RB, et al. Greater adherence to cancer prevention guidelines is associated with higher circulating concentrations of vitamin d metabolites in a cross-sectional analysis of pooled participants from 2 chemoprevention trials. *J Nutr*. 2017;147(3):421-429.

30. Caan BJ, Meyerhardt JA, Kroenke CH, et al. Explaining the obesity paradox: the association between body composition and colorectal cancer survival (C-SCANS Study). *Cancer Epidemiol Biomarkers Prev*. 2017;26(7):1008-1015.

31. McCullough ML, Gapstur SM, Shah R, Jacobs EJ, Campbell PT. Association between red and processed meat intake and mortality among colorectal cancer survivors. *J Clin Oncol*. 2013;31(22):2773-2782.

32. Holmes MD, Wang J, Hankinson SE, Tamimi RM, Chen WE. Protein intake and breast cancer survival in the Nurses' Health Study. *J Clin Oncol*. 2017;35(3):325-333.