Multivitamin Use Is Not Associated With Cancer Recurrence or Survival in Patients With Stage III Colon Cancer: Findings From CALGB 89803

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ABSTRACT

Purpose

Multivitamin use is widespread in the United States, especially among patients with cancer. However, the influence of multivitamin supplementation on cancer recurrence and death after a curative resection of colon cancer is unknown.

Patients and Methods

We conducted a prospective, observational study of 1,038 patients with stage III colon cancer enrolled in a randomized adjuvant chemotherapy trial. Patients reported on multivitamin use during and 6 months after adjuvant chemotherapy. Patients were observed until March 2009 for disease recurrence and death. To minimize bias by occult recurrence, we excluded patients who recurred or died within 90 days of their multivitamin assessment.

Results

Among 1,038 patients, 518 (49.9%) reported multivitamin use during adjuvant chemotherapy. Compared with nonusers, the multivariate hazard ratio (HR) for disease-free survival was 0.94 (95% CI, 0.77 to 1.15) for patients who used multivitamins. Similarly, multivitamin use during adjuvant chemotherapy was not significantly associated with recurrence-free survival (multivariate HR, 0.93; 95% CI, 0.75 to 1.15) or overall survival (multivariate HR 0.92; 95% CI, 0.74 to 1.16). Multivitamin use reported 6 months after completion of adjuvant chemotherapy was also not associated with improved patient outcome, and consistent use both during and following adjuvant therapy conferred no benefit. Neither an increasing number of tablets nor increasing duration of use before cancer diagnosis was associated with cancer recurrence or mortality. Multivitamin use also did not improve the rates of grade 3 and higher GI toxicity.

Conclusion

Multivitamin use during and after adjuvant chemotherapy was not significantly associated with improved outcomes in patients with stage III colon cancer.

J Clin Oncol 28:4354-4363. © 2010 by American Society of Clinical Oncology

INTRODUCTION

More than half of the American population currently uses dietary supplements.¹ Among these, multivitamins comprise the majority of supplements, used by approximately 30% of Americans in the belief that they will prevent and treat chronic diseases such as cancer. Although vitamin deficiency is uncommon in the United States, multivitamin use is growing, resulting in annual sales of more than \$20 billion. Despite health product claims touting the benefits of multivitamins, studies examining their efficacy in decreasing the risk of and mortality from cancer have been conflicting.

Epidemiologic and laboratory studies indicate that diet and other lifestyle factors have a significant influence on colon carcinogenesis. In particular, preclinical studies have demonstrated the antineoplastic properties of folate,^{2,3} vitamin C,⁴ vitamin D,⁵⁻⁷ vitamin E,⁴ calcium,⁸ and retinol.⁹ Administration of various nutrient mixtures have also resulted in growth inhibition of colon cancer xenografts¹⁰ and prevention of lung tumors in mice.¹¹ However, an observational study in the Women's Health Initiative found that multivitamin use did not reduce the risk of cancer, including colorectal cancer.¹² In contrast, other epidemiologic studies show a decreased risk of colorectal cancer with multivitamin

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Submitted January 11, 2010; accepted July 1, 2010; published online ahead of print at www.jco.org on August 30, 2010.

Written on behalf of Cancer and Leukemia Group B.

Supported by Grants No. P50CA127003 and T32CA009001-34 from the National Cancer Institute, National Institutes of Health (K.N.); by an American Society of Clinical Oncology Young Investigator Award (K.N.); by the Charles A. King Trust Postdoctoral Fellowship Award, Bank of America, Co-Trustee (K.N.); and by Pharmacia & Upjohn Company, now Pfizer Oncology. The research for CALGB (Cancer and Leukemia Group B) 89803 was also supported, in part, by grants from the National Cancer Institute (CA31946) to CALGB and to the CALGB Statistical Center (CA33601).

The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health, American Society of Clinical Oncology (ASCO), or The ASCO Foundation.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/10/2828-4354/\$20.00

DOI: 10.1200/JCO.2010.28.0362

supplementation,¹³ often only after past use¹⁴ or many years of supplementation.¹⁵

Beyond primary prevention, the effect of multivitamins on the outcome of patients with established colon cancer is unknown. In the United States, 26% to 77% of cancer survivors report multivitamin use.¹⁶ Consequently, it is critical to assess the impact of multivitamins on treatment and survival. We prospectively examined the influence of multivitamin use on survival in stage III colon cancer patients enrolled in a completed National Cancer Institute (NCI)–sponsored clinical trial of adjuvant chemotherapy.

PATIENTS AND METHODS

Study Population

Patients in this prospective cohort study were participants in the NCI-sponsored Cancer and Leukemia Group B (CALGB) trial for stage III colon cancer (89803) that compared adjuvant fluorouracil and leucovorin to irinotecan, fluorouracil, and leucovorin.¹⁷ From April 1999 to May 2001, 1,264 patients were enrolled. A self-administered questionnaire that captured diet and lifestyle habits was given to patients midway through their therapy (4 months after surgery; questionnaire 1 [Q1]) and again 6 months after completion of treatment (14 months after surgery; questionnaire 2 [Q2]). The protocol amendment to survey diet and lifestyle was activated after the first 87 patients were enrolled; therefore, only 1,177 patients were eligible for this companion study (Fig 1).

Patients were eligible for the treatment trial if they had undergone a complete surgical resection of the primary tumor within 56 days of study entry and had regional lymph node metastases but no distant metastases. Patients were required to have a baseline Eastern Cooperative Oncology Group performance status of 0 to 2 and adequate bone marrow, renal, and hepatic function. Median household income was estimated using concurrent census data determined by the patient's zip code. All patients signed informed consent, approved by each institution's review board.

Multivitamin Assessment

Multivitamin use was assessed both during (Q1) and after completion of adjuvant chemotherapy (Q2). On Q1, participants were asked, "Have you ever regularly taken multivitamins?" with an option for "Never have," "Have in the past only," or "Currently taking them." Those who reported past use were asked to provide the number of years of use (1 year or shorter, 2 to 4 years, 5 to 9 years, or 10 years or longer). Those who reported current use were asked about number of multivitamins taken per week (2 or fewer, 3 to 5, 6 to 9, or 10 or more) and years of use. In addition, current users were instructed to write in the brand of multivitamin consumed. On Q2, participants were asked, "Do you currently take a multivitamin?" with an option for yes or no. Current users were then asked to provide the number of multivitamins taken per week and brand used. We excluded patients who recurred or died within 90 days of their multivitamin assessment to avoid potential bias related to underlying illness.

Study End Points

The primary end point was disease-free survival (DFS), defined as time from completion of the questionnaire to tumor recurrence, occurrence of a new primary colon cancer, or death from any cause. Recurrence-free survival (RFS) was defined as the time from completion of the questionnaire to tumor recurrence, death with evidence of recurrence, or occurrence of a new primary colon tumor; patients who died without known recurrence were censored at the last documented evaluation. Finally, overall survival was defined as the time from completion of the questionnaire to death from any cause.

Statistical Analyses

Methods for detection of microsatellite instability (MSI) have been previously described,^{18,19} and results for the treatment trial have been reported.¹⁷ No significant differences were found between treatment arms, thus data for patients were combined and analyzed according to categories of multivitamin use during (Q1) and after adjuvant chemotherapy (Q2). All three end points were examined using Kaplan-Meier curves²⁰ and the log-rank test.²¹ Cox proportional hazards regression was used to determine the simultaneous impact of potential confounders.²² The proportionality of hazards assumption for the effect of multivitamin use was satisfied by examining it as a time-dependent covariate in the model. We tested for linear trend by entering the

Fig 1. Derivation of cohort size. CALGB, Cancer and Leukemia Group B; Q1, questionnaire 1; Q2, questionnaire 2.

Table 1. Baseline Characteristics by Multivitamin Use Reported During and After Adjuvant Chemotherapy

Characteristic	Multivitamin Use During Adjuvant Chemotherapy (Q1)			Multivitamin Use After Completion of Adjuvant Chemotherapy (Q2)		
	No (n = 520)	Yes (n = 518)	P ^a	No (n = 394)	Yes (n = 416)	P ^a
Median age, years	60.0	61.0	.43 ^b	60.0	60.0	.90 ^b
Range	26-83	21-85		29-81	21-85	
Sex, %			.004			.006
Male	60	52		61	52	
Female	40	48		39	48	
Race or ethnicity, %			.19			.13
White	87	90		88	92	
African American	8	6		7	5	
Other	5	4		5	3	
Median household income, ^c \$	40,647	41,347	.16 ^b	39,840	42,449	.001 ^b
Range	17,963-122,956	18,496-117,487		17,963-122,956	20,510-117,487	
Family history of colorectal cancer, %			.49			.28
Yes	19	17		21	18	
No	81	83		79	82	
Baseline ECOG performance status, ^d %			.16			.79
0	73	77		76	76	
1-2	27	23		24	24	
Invasion through bowel wall (T stage), ^e %			.05			.08
T1 and T2	12	16		13	17	
T3 and T4	88	84		87	83	
No. of positive lymph nodes (N stage), %			.19			.10
1-3 (N1)	62	66		64	70	
4+ (N2)	38	34		36	30	
Grade of differentiation, %			.90			.24
Well differentiated	6	6		7	5	
Moderately differentiated	71	71		73	71	
Poorly differentiated or undifferentiated	23	23		20	24	
Lymphovascular invasion, %			.36			.52
Yes	27	30		27	29	
No	73	70		73	71	
Perineural invasion, %			.47			.61
Yes	8	7		6	6	
No	92	93		94	94	
Clinical bowel perforation, %			.95			.35
Yes	5	5		3	4	
No	95	95		97	96	
Clinical bowel obstruction, %			.66			.35
Yes	23	22		23	20	
No	77	78		77	80	
Postoperative CEA, ^f ng/mL, %			.82			.74
< 5	92	93		95	95	
≥ 5	8	7		5	5	
Adjuvant chemotherapy arm, %			.58			.53
FU/LV	52	50		51	49	
IFL	48	50		49	51	
Median body mass index ^g , kg/m ²	27.5	27.2	.11 ^b	28.8	28.0	.02 ^b
Range	15.7-51.8	17.4-45.0		16.8-54.5	17.6-50.2	
Median physical activity, MET-hr/wk	4.1	5.4	.009 ^b	6.9	8.3	.13 ^b
Range	0-147.4	0-125.2		0-92.4	0-168.7	
Regular aspirin use, ^h %			.02			.37
Yes	12	17		9	11	
No	88	83		91	89	
Western dietary pattern, median score ⁱ	-0.063	-0.295	< .001 ^b	-0.082	-0.241	.01
Range	-2.441-6.412	-1.792-3.565		-1.727-3.884	-2.44-6.412	
Dietary and supplemental intake, median						
Vitamin A, U	7,946	14,121	< .001 ^b	7,034	13,348	< .001 ^b
Range	1,088-72,028	3363-64,526		869-117,858	2,371-79,030	

(continued on following page)

Table 1. Baseline Characteristics by Multivitamin Use Reported During and After Adjuvant Chemotherapy (continued)

Characteristic	Multivitamin Use During Adjuvant Chemotherapy (Q1)			Multivitamin Use After Completion of Adjuvant Chemotherapy (Q2)		
	No (n = 520)	Yes (n = 518)	P ^a	No (n = 394)	Yes (n = 416)	P ^a
Vitamin B6, mg	2.2	4.5	< .001 ^b	1.9	4.5	< .001 ^b
Range	0.8-154.0	0.9-340.1		0.5-171.2	0.8-325	
Vitamin B12, mcg	6.0	13.5	< .001 ^b	5.5	13.4	< .001 ^b
Range	0.9-65.2	3.5-2,294.0		1.5-51.5	1.2-2,033	
Folate, µg	388	817	< .001 ^b	349	765	< .001 ^b
Range	133-1,124	256-4,137		100-998	204-3,041	
Vitamin C, mg	136	249	< .001 ^b	109	225	< .001 ^b
Range	23-1,643	45-11,977		7-1,200	64-8,609	
Vitamin D, U	166	586	< .001 ^b	151	562	< .001 ^b
Range	26-929	84-1,979		25-834	45-1,692	
Vitamin E, mg	7.3	26.1	< .001 ^b	6.7	27.8	< .001 ^b
Range	2.8-500.4	4.6-1,359.3		2.4-577.7	4.4-1,084.6	
Calcium, mg	755	955	< .001 ^b	670	990	< .001 ^b
Range	239-2,599	297-3,418		290-3,003	325-3,339	
Retinol, U	1,759	5,618	< .001 ^b	1,598	4,874	< .001 ^b
Range	278-22,299	784-35,548		103-19,260	177-44,054	

Abbreviations: Q1, questionnaire 1; Q2, questionnaire 2; ECOG, Eastern Cooperative Oncology Group; CEA, carcinoembryonic antigen; FU/LV, fluorouracil/leucovorin; IFL, bolus fluorouracil, leucovorin, and irinotecan; MET, metabolic equivalent tasks; hr, hour.

^aP value calculated using χ^2 test unless otherwise noted.

^bP value calculated using Kruskal-Wallis test.

^cBased on 1999 census data as determined by patient zip code.

^dA performance status of 0 indicates a patient was fully active; 1, restricted in physically strenuous activity but ambulatory and able to carry out light work; 2, ambulatory and capable of all self-care but unable to carry out any work activities and up and about more than 50% of waking hours. Performance status was based on patient status at initiation of chemotherapy (entry into treatment trial).

^eT1 or T2 indicates level of invasion was through the bowel wall but not beyond the muscle layer; T3 or T4, level of invasion was through the bowel wall beyond the muscle layer.

^fPostoperative CEA was based on patient status at initiation of chemotherapy (entry into treatment trial).

^gBody mass index is calculated as weight in kilograms divided by height in meters squared. Body mass index was based on patient status at initiation of chemotherapy (entry into treatment trial).

^hRegular aspirin use is defined as three or more 325 mg tablets per week.

ⁱHigher scores are indicative of higher intake.

median value of each category of multivitamin use as a continuous variable in the model.²³ Tests of interaction between multivitamin use and potentially modifying covariates were assessed by entering the cross product of multivitamin use and the covariate of interest. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0, and logistic regression performed to examine the impact of multivitamins on grade 3 and higher toxicity.

Statistical significance was considered at the .05 level, and all *P* values were two sided. The sample size for the cohort was determined by the chemotherapy treatment trial, which had 82% power to detect hazard ratios (HR) of 0.77 (protective) or 1.3 (detrimental) for overall survival based on an estimated 356 deaths among 1,260 patients. In a posthoc calculation of power based on the known sample size and number of DFS events for this analysis, we had 80% power to detect HRs of 0.67 or 1.50.

Patient registration and clinical data collection were conducted by the CALGB Statistical Center, and analyses performed in conjunction with CALGB statisticians based on the database frozen on March 31, 2009. Using Clark's C,²⁴ the completeness of follow-up for this study was 84.2%; applying Wu's modification to adjust for unreported deaths,²⁵ a more realistic assessment was 85.9%.

RESULTS

Baseline Characteristics According to Multivitamin Use

Baseline characteristics for the patients for whom data on multivitamin use were captured are presented in Table 1. Among 1,038

patients who completed Q1 shortly after initiation of adjuvant chemotherapy, 518 (49.9%) reported multivitamin use. Among 810 patients who remained cancer free and completed Q2 administered 6 months after completion of therapy, 416 (51.4%) used multivitamins. Patients who reported multivitamin use were more likely to be female, had higher household income, had tumors with less extension through the bowel wall, had lower body mass index (BMI), were more physically active, were less likely to consume a Western pattern diet, and were more likely to report regular aspirin use and higher intake of individual vitamins. Other potentially prognostic patient and tumor characteristics did not differ significantly.

Impact of Multivitamin Use on Cancer Recurrence and Death

After a median follow-up of 7.3 years (10th and 90th percentiles: 4.4 and 8.1 years, respectively) among the 1,038 patients who completed Q1 shortly after initiation of adjuvant therapy, 351 patients recurred and 314 died. Among the 810 patients who completed Q2 6 months after completion of chemotherapy, after a median follow-up of 6.5 years (10th and 90th percentiles: 4.0 and 7.3 years), 190 recurred and 169 died. Compared to nonusers, multivitamin users during adjuvant chemotherapy did not experience a statistically significant difference in DFS, RFS, or overall survival (Fig 2). Multivitamin use after adjuvant therapy was also not associated with improved outcomes. The results remained largely unchanged after adjusting for

Fig 2. (A) Disease-free survival, (B) recurrence-free survival, and (C) overall survival by multivitamin use reported during adjuvant chemotherapy (questionnaire 1).

other predictors of cancer recurrence (Table 2). Compared to patients who did not use multivitamins during adjuvant chemotherapy, those who did had a multivariate HR for cancer recurrence or death of 0.94 (95% CI, 0.77 to 1.15). Similarly, multivitamin use after completion of adjuvant therapy did not significantly improve DFS (adjusted HR, 1.08; 95% CI, 0.83 to 1.41). We assessed the influence of socioeconomic status using concurrent census data on household income as determined by the patient's zip code, and found that it did not confound the relationship between multivitamin use and patient outcome. Household income also did not change the final adjusted HRs for DFS, RFS, and overall survival when added to our model.

We investigated whether there was a dose effect. Based on data reported during adjuvant therapy (Q1), we did not find a significant association between an increasing number of multivitamins consumed per week and patient outcome (P trend = .90 for DFS, .96 for RFS, and .93 for overall survival). There was also no improvement in DFS, RFS, or overall survival with increasing multivitamin tablets consumed after completion of chemotherapy (Q2). Similarly, we did not observe a significant relationship between increasing years of multivitamin use and patient outcome.

We further examined the influence of consistent multivitamin use on patient outcome, as defined by use both during and after adjuvant chemotherapy. Among 799 patients who completed both questionnaires, 26% never used multivitamins and 40% reported consistent use. Compared to never-users, patients who reported consistent multivitamin use did not experience a significant DFS, RFS, or overall survival benefit (Table 3).

Impact of Individual Vitamins on Multivitamin Use and Cancer Recurrence and Death

We examined selected vitamins that are present in multivitamin supplements. Addition of total dietary and supplemental intake of each vitamin individually to the multivariable model did not change the null relationship between multivitamin use during adjuvant chemotherapy and DFS (data not shown). Moreover, total intake of these individual vitamins during adjuvant treatment was not significantly associated with DFS after adjusting for multivitamin use and other prognostic factors (P trend = .84 for vitamin A; .34 for vitamin B6; .49 for vitamin B12; .49 for folate; .71 for vitamin C; .12 for vitamin D; .63 for vitamin E; .24 for calcium, and .45 for retinol). No significant interactions were seen between any of the vitamins and multivitamin use. The same results were seen when we added total individual vitamin intakes to the multivariate model assessing multivitamin use after completion of adjuvant chemotherapy (Q2).

Impact of Multivitamin Use Across Strata of Other Predictors of Patient Outcome

We examined the influence of multivitamin use during adjuvant chemotherapy on DFS across strata of other predictors of cancer outcome (Fig 3). Although most subgroups did not show a significant relationship between multivitamins and outcome, a significant interaction was observed with age (P = .007). In patients ≤ 60 years old, multivitamin use was associated with a significantly decreased risk of recurrence and death (adjusted HR, 0.68; 95% CI, 0.51 to 0.91), whereas no association was seen in patients older than 60. We considered the possibility that the benefit of multivitamin use among younger subjects may reflect the greater likelihood of a family history of colorectal cancer. However, further stratification of patients ≤ 60 years old by family history did not reveal significant differences in the beneficial effect of multivitamin use on DFS (adjusted HR, 0.63; 95% CI, 0.24 to 1.66 in patients with a family history; adjusted HR, 0.72; 95% CI, 0.53 to 0.99 in those without). In a related analysis, we explored the association between multivitamins, age, and tumoral microsatellite instability (MSI). Further adjustment of the multivariable model for MSI as determined by both genotyping of microsatellite markers and immunostaining for mismatch repair proteins did not alter the positive association between multivitamin use and DFS in patients ≤ 60 years of age (P interaction = .004 and .006, respectively). Of note, we did not see a significant interaction between age and

Table 2. Impact of Multivitamin Use on Colon Cancer Recurrence and Mortality

Parameter	Multivitamin Use During Adjuvant Chemotherapy (Q1)		Multivitamin Use After Completion of Adjuvant Chemotherapy (Q2)	
	No	Yes	No	Yes
Cancer recurrence or death from any cause (disease-free survival)				
No. at risk	520	518	394	416
No. of events	206	192	109	121
Unadjusted HR	Referent	0.89	Referent	1.02
95% CI		0.73-1.09		0.79-1.32
Adjusted HR*	Referent	0.94	Referent	1.10
95% CI		0.77-1.15		0.84-1.43
Cancer recurrence (recurrence-free survival)				
No. at risk	520	518	394	416
No. of events	183	168	92	98
Unadjusted HR	Referent	0.88	Referent	0.98
95% CI		0.72-1.09		0.74-1.30
Adjusted HR*	Referent	0.93	Referent	1.05
95% CI		0.75-1.15		0.78-1.40
Overall mortality (overall survival)				
No. at risk	520	518	394	416
No. of events	166	148	83	86
Unadjusted HR	Referent	0.86	Referent	0.97
95% CI		0.69-1.07		0.72-1.31
Adjusted HR*	Referent	0.92	Referent	1.11
95% CI		0.74-1.16		0.82-1.52

Abbreviations: Q1, questionnaire 1; Q2, questionnaire 2; HR, hazard ratio; CEA, carcinoembryonic antigen; FU/LV, fluorouracil/leucovorin; IFL, bolus fluorouracil, leucovorin, and irinotecan; MET, metabolic equivalent tasks; hr, hour.

*Adjusted for age (in years as a continuous variable), sex, family history of colorectal cancer (yes or no), baseline performance status (0 or 1 to 2), depth of invasion through bowel wall (T1 to T2 or T3 to T4), No. of positive lymph nodes (1 to 3 or 4 or more), grade of tumor differentiation (well differentiated, moderately differentiated, or poorly differentiated/undifferentiated), presence of bowel obstruction at time of surgery (yes or no), perineural invasion (yes or no), postoperative CEA (< 5 or $\geq$ 5), treatment arm (FU/LV or IFL), body mass index (in kg/m² as a continuous variable), physical activity (in MET-hr/week as a continuous variable), aspirin use (< 3 or $\geq$ 3 tablets per week), and Western pattern diet (as a continuous variable).

multivitamin use after completion of adjuvant chemotherapy (P interaction = 0.11).

BMI may also modify the relationship between multivitamin use and DFS (P interaction = .05). Obese patients (BMI $\geq$ 30 kg/m²) who used multivitamins during adjuvant chemotherapy had significantly improved DFS (adjusted HR, 0.57; 95% CI, 0.39 to 0.82) compared to those who did not report multivitamin use (Fig 3). In contrast, overweight patients (BMI 25 to 29.9 kg/m²) who used multivitamins experienced an inferior outcome (adjusted HR, 1.52; 95% CI, 1.06 to 2.17), whereas multivitamin use in those with BMI lower than 25 kg/m² was not significantly associated with DFS (adjusted HR, 0.87; 95% CI, 0.61 to 1.24). Of note, the test for statistical interaction between BMI and multivitamin use after completion of adjuvant chemotherapy was not significant (P interaction = .38).

Impact of Multivitamin Use on Toxicity

We explored the influence of multivitamins on the incidence of the most common grade 3 and higher toxicities.¹⁷ There were no significant differences in the rates of grade 3 and higher leukopenia, neutropenia, nausea, vomiting, and diarrhea between multivitamin users and nonusers after adjusting for potential confounding factors (Table 4). However, multivitamin use was inversely associated with grade 3 and higher fatigue (adjusted odds ratio [OR], 0.61; 95% CI, 0.39 to 0.94).

DISCUSSION

In this large cohort of patients with stage III colon cancer treated with surgery and adjuvant chemotherapy, neither multivitamin use during or after adjuvant therapy was significantly associated with improved DFS, RFS, or overall survival. Moreover, multivitamin use did not improve chemotherapy-related gastrointestinal toxicity, although there was a potential benefit on fatigue. Importantly, multivitamin use was not found to be detrimental to patient outcome. To our knowledge, this is the first study to examine the impact of multivitamin use on survival among patients with established colon cancer.

Several observational studies have investigated the association between multivitamin use and colorectal cancer incidence, with conflicting results. A case-control analysis using the Surveillance, Epidemiology, and End Results registry found a 51% reduction in the risk of colorectal cancer in those who used multivitamins for 10 years (P trend < .001).¹³ Similarly, in a prospective cohort study using the Nurses' Health Study, there was no benefit of multivitamin use on colorectal cancer until 15 years of use, at which time a 75% reduction in risk was observed (P trend < .001).¹⁵ In contrast, a prospective cohort study using the Women's Health Study showed no association between multivitamin use and colorectal cancer during 10 years of follow-up,²⁶ and participants in the

Table 3. Impact of Consistent Multivitamin Use on Colon Cancer Recurrence and Mortality

Parameter	Pattern of Multivitamin Use		
	Never Used	Inconsistent Use*	Consistent Use†
Cancer recurrence or death from any cause (disease-free survival)			
No. at risk	210	267	322
No. of events	63	73	92
Unadjusted HR	Referent	0.89	0.90
95% CI		0.64-1.25	0.65-1.24
Adjusted HR‡	Referent	0.99	1.02
95% CI		0.70-1.40	0.73-1.41
Cancer recurrence (recurrence-free survival)			
No. at risk	210	267	322
No. of events	53	59	76
Unadjusted HR	Referent	0.86	0.88
95% CI		0.59-1.25	0.62-1.26
Adjusted HR‡	Referent	0.89	0.96
95% CI		0.61-1.31	0.67-1.38
Overall mortality (overall survival)			
No. at risk	210	267	322
No. of events	47	58	63
Unadjusted HR	Referent	0.97	0.85
95% CI		0.66-1.43	0.58-1.24
Adjusted HR‡	Referent	1.19	1.07
95% CI		0.80-1.77	0.72-1.57

Abbreviations: HR, hazard ratio; Q1, questionnaire 1; Q2, questionnaire 2; CEA, carcinoembryonic antigen; FU/LV, fluorouracil/leucovorin; IFL, bolus fluorouracil, leucovorin, and irinotecan; MET, metabolic equivalent tasks; hr, hour.

*Inconsistent use includes patients who reported multivitamin use prior to Q1 only, on Q1 only, prior to Q1 and on Q2, and on Q2 only.

†Consistent use includes patients who reported multivitamin use on both Q1 and Q2.

‡Adjusted for age (in years as a continuous variable), sex, family history of colorectal cancer (yes or no), baseline performance status (0 or 1 to 2), depth of invasion through bowel wall (T1 to T2 or T3 to T4), No. of positive lymph nodes (1 to 3 or 4 or more), grade of tumor differentiation (well differentiated, moderately differentiated, or poorly differentiated/undifferentiated), presence of bowel obstruction at time of surgery (yes or no), perineural invasion (yes or no), postoperative CEA (< 5 or ≥ 5), treatment arm (FU/LV or IFL), body mass index at time of Q2 (in kg/m² as a continuous variable), physical activity at time of Q2 (in MET-hr/week as a continuous variable), aspirin use at time of Q2 (< 3 or ≥ 3 tablets per week), and Western pattern diet at time of Q2 (as a continuous variable).

Women's Health Initiative who used multivitamins did not have a lower risk of several cancers, including colorectal cancer (HR, 0.99; 95% CI, 0.88 to 1.11).¹²

Multivitamins consist of several vitamins and micronutrients that have been purported to influence colorectal carcinogenesis. Among these, folate is thought to be the micronutrient most likely responsible for any potential benefit of multivitamins. Folate acts as a cofactor in single-carbon transfer in nucleic and amino acid metabolism, therefore a deficiency could lead to disturbances in DNA replication, methylation, and repair.^{2,3} The amount of folic acid in multivitamins was increased in 1973 from 100 to 400 µg,²⁷ a level considerably higher than median dietary intake. Numerous epidemiologic studies have demonstrated that higher folate intake is associated with a lower risk of colorectal adenoma and cancer.^{28,29} However, a placebo-controlled trial demonstrated a 67% increase in the risk of advanced colorectal lesions and a more than two-fold increase in the risk of developing at least three adenomas with supplemental folic acid among subjects with prior adenomas.³⁰ Animal studies have suggested that the timing of folic acid supplementation may be critical; administration before the existence of neoplastic lesions may prevent tumor development, whereas administration afterwards may promote tumor progression.³¹ Of note, in another analysis of stage I to III colorectal cancer patients, higher plasma folate levels were not associated with inferior survival.³²

Higher circulating plasma 25-hydroxyvitamin D₃ [25(OH)D] has been associated with a reduced risk of colorectal cancer,³³ and

in a cohort of 304 patients with stage I to IV disease, we observed a significant reduction in overall mortality with increasing plasma 25(OH)D.³⁴ However, given the limited quantity of vitamin D in standard multivitamin tablets (200 to 400 U), regular multivitamin use is unlikely to materially increase 25(OH)D levels.³⁵

In our secondary subset analyses, multivitamin use was associated with improved DFS in patients ≤ 60 years of age, but not in those older than 60. Of note, this exploratory finding may simply reflect chance. Nonetheless, the Nutrition Intervention Trials conducted in Linxian County, China, found that the benefit of beta-carotene, vitamin E, and selenium in reducing cancer mortality was greater in participants younger than 55 years of age.³⁶ In addition, we observed a significant benefit from multivitamin use among obese patients, who often have greater levels of oxidative stress.³⁷ It is possible that one or several of the micronutrients with antioxidant properties in multivitamins is contributing to improved outcomes in this subgroup of patients. These interactions with younger age and higher BMI require confirmation in other studies.

There are several advantages to using a cohort within a NCI-sponsored clinical trial. First, all patients had stage III cancer, reducing the impact of heterogeneity by disease stage. Second, treatment and follow-up were standardized, and the date and nature of recurrence were recorded prospectively. Finally, detailed information on prognostic factors was collected routinely.

Fig 3. Multivariate hazard ratios (HRs) and 95% CI for cancer recurrence and death (disease-free survival) across strata of various factors, comparing multivitamin use during adjuvant chemotherapy with no use. ECOG, Eastern Cooperative Oncology Group; PS, performance status; T, depth of invasion through bowel wall; N1, one to three lymph nodes; N2, four or more lymph nodes; mod diff, moderately differentiated; undiff, undifferentiated; FU/LV, fluorouracil/leucovorin; IFL, bolus fluorouracil, leucovorin, and irinotecan; BMI, body mass index (kg/m^2); Met, metabolic equivalent tasks; hr, hour; wk, week.

Several potential limitations deserve comment. Patients who enroll in randomized trials may differ from the population at large. However, the prevalence of multivitamin use in our cohort falls within the range reported for patients with cancer overall.¹⁶ Moreover, since the study included patients from both community and academic centers throughout North America, our findings should reflect the general population.

Because we relied on self-reported multivitamin use, misclassification of the exposure is possible. However, prior studies

have demonstrated such data to be reliable.³⁸ Moreover, multivitamin use was recorded before any knowledge of cancer-related outcomes, thus reducing the likelihood of reporting biases. Finally, patients who consume supplements often engage in other healthful behaviors. In this study, we controlled for physical activity, BMI, and performance status, among other factors. However, residual confounding from unknown variables is possible.

Table 4. Impact of Multivitamin Use During Adjuvant Chemotherapy on the Incidence of Selected Grade 3 and Higher Toxicities (n = 1,034)

Adverse Event	Multivitamin Use During Adjuvant Chemotherapy (Q1)	
	No	Yes
Leukopenia		
No. at risk	518	516
No. of events	50	45
%	9.7	8.7
Unadjusted OR	Referent	0.89
Range		0.59-1.37
Adjusted OR*	Referent	0.79
Range		0.51-1.23
Neutropenia		
No. at risk	518	516
No. of events	117	130
%	22.6	25.2
Unadjusted OR	Referent	1.15
Range		0.87-1.54
Adjusted OR*	Referent	1.19
Range		0.71-1.59
Nausea		
No. at risk	518	516
No. of events	69	72
%	13.3	14.0
Unadjusted OR	Referent	1.06
Range		0.74-1.51
Adjusted OR*	Referent	1.00
Range		0.69-1.43
Vomiting		
No. at risk	518	516
No. of events	47	59
%	9.1	11.4
Unadjusted OR	Referent	1.29
Range		0.86-1.94
Adjusted OR*	Referent	1.19
Range		0.79-1.80
Diarrhea		
No. at risk	518	516
No. of events	162	185
%	31.3	35.9
Unadjusted OR	Referent	1.23
Range		0.95-1.59
Adjusted OR*	Referent	1.19
Range		0.91-1.55
Fatigue		
No. at risk	518	516
No. of events	56	38
%	10.8	7.4
Unadjusted OR	Referent	0.66
Range		0.43-1.01
Adjusted OR*	Referent	0.61
Range		0.39-0.94
Any of the above		
No. at risk	518	516
No. of events	283	289
%	54.6	56.0
Unadjusted OR	Referent	1.06
Range		0.83-1.35
Adjusted OR*	Referent	0.99
Range		0.76-1.27

(continued in next column)

Table 4. Impact of Multivitamin Use During Adjuvant Chemotherapy on the Incidence of Selected Grade 3 and Higher Toxicities (n = 1,034) (continued)

NOTE. Adverse events were rated according to the National Cancer Institute Common Toxicity Criteria version 2.0.

Abbreviations: Q1, questionnaire 1; OR, odds ratio; FU/LV, fluorouracil/leucovorin; IFL, bolus fluorouracil, leucovorin, and irinotecan; MET, metabolic equivalent tasks; hr, hour.

*Adjusted for age (in years as a continuous variable), sex, baseline Eastern Cooperative Oncology Group performance status (0 or 1 to 2), treatment arm (FU/LV or IFL), and physical activity at time of Q1 (in MET-hr/week as a continuous variable).

In conclusion, our large prospective study of patients with stage III colon cancer found no significant benefit for multivitamin supplementation on patient outcome. These results are consistent with a conference statement from the National Institutes of Health that concluded there was insufficient evidence to recommend either for or against the use of multivitamins for chronic disease prevention.¹ Nonetheless, further research is needed to assess the utility of individual vitamins in patients with established colorectal cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory**

Role: None **Stock Ownership:** None **Honoraria:** Charles S. Fuchs, Amgen, AstraZeneca, Imclone, Genentech, Bristol-Myers Squibb, Roche, Mersana, Pozen, Myriad Genetics, Alnylam, Merck, Genomic Health

Research Funding: None **Expert Testimony:** None **Other**

Remuneration: None

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