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ORIGINAL ARTICLE

Post-diagnostic multivitamin supplement use and colorectal cancer survival: A prospective cohort study

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Abstract

Background: Use of multivitamin supplements has been associated with lower incidence of colorectal cancer (CRC). However, its influence on CRC survival remains unknown.

Methods: Among 2424 patients with stage I–III CRC who provided detailed information about multivitamin supplements in the Nurses' Health Study and Health Professionals Follow-up Study, the authors calculated multivariable hazard ratios (HRs) of multivitamin supplements for all-cause and CRC-specific mortality according to post-diagnostic use and dose of multivitamin supplements.

Results: During a median follow-up of 11 years, the authors documented 1512 deaths, among which 343 were of CRC. Compared to non-uses, post-diagnostic users of multivitamin supplements at a dose of 3–5 tablets/week had lower

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CRC-specific mortality (HR, 0.55; 95% confidence interval [CI], 0.36–0.83, $p = .005$), and post-diagnostic users at doses of 3–5 and 6–9 tablets/week had lower all-cause mortality (HR, 0.81; 95% CI, 0.67–0.99, $p = .04$; HR, 0.79; 95% CI, 0.70–0.88), $p < .001$). The dose–response analysis showed a curvilinear relationship for both CRC-specific ($p_{nonlinearity} < .001$) and all-cause mortality ($p_{nonlinearity} = .004$), with the maximum risk reduction observed at 3–5 tablets/week and no further reduction at higher doses. Compared to non-users in both pre- and post-diagnosis periods, new post-diagnostic users at dose of <10 tablets/week had a lower all-cause mortality (HR, 0.81; 95% CI, 0.71–0.94, $p = .005$), whereas new users at a dose of ≥10 tablets/week (HR, 1.58; 95% CI, 1.07–2.33) and discontinued users (HR, 1.35; 95% CI, 1.14–1.59) had a higher risk of mortality.

Conclusions: Use of multivitamin supplements at a moderate dose after a diagnosis of nonmetastatic CRC is associated with lower CRC-specific and overall mortality, whereas a high dose (≥10 tablets/week) use is associated with higher CRC-specific mortality.

KEYWORDS
colorectal cancer, mortality, multivitamin, nonmetastasis, post-diagnosis, survival

INTRODUCTION

Globally, colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer-related death.[1] There were more than 776,000 CRC survivors in the United States in 2019 and the number continues to increase because of the aging of the population and the advances in early detection and treatment.[2] Many cancer survivors are highly motivated to seek self-care strategies. A total of 38%–50% of CRC survivors reported use of multivitamin supplements, the most commonly used supplement,[3,4] highlighting the need to examine the influence of multivitamin use on CRC survivorship.

Preclinical studies have demonstrated the anti-CRC properties of multivitamin components, such as vitamin C, vitamin D, folate, retinol, and selenium, through their antiproliferative, pro-apoptotic, and antimigratory effects,[5–7] and anti-inflammatory properties,[8–10] as well as targeting the redox axis,[11,12] modulating immune infiltration,[13–15] and reducing drug resistance via epigenetic regulation.[16–18] Multivitamins have also been shown to reduce promoter methylation of cancer susceptibility genes and affect reprogramming of the epigenome.[19] The component calcium has been linked to better survival in CRC patients.[20] Moreover, recent randomized controlled trials showed that vitamin C and vitamin D improved the prognosis of advanced CRC patients.[21,22] In addition, many micronutrients in multivitamins may increase gut microbial diversity and fecal production of short-chain fatty acids,[23] protect the integrity of gastrointestinal epithelia, and enhance local and systemic immunity.[24–26]

There are data indicating that use of multivitamin supplements may reduce the incidence of CRC in cancer-free individuals.[27] Thus far, however, only one study has examined the prognostic influence of multivitamin supplementation after diagnosis in patients with stage III colon cancer. The study reported no association between post-diagnostic multivitamin use and recurrence-free, disease-free, or overall survival.[28] Thus, to extend our knowledge, we examined post-diagnostic multivitamin supplementation in relation to mortality in CRC patients from two large prospective cohorts, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS). We focused on patients with nonmetastatic CRC in the primary analysis, because a large proportion of stage IV patients did not provide post-diagnosis exposure data (78%). We conducted detailed dose–response analysis and investigated the joint association of pre- and post-diagnostic multivitamin use with mortality.

MATERIALS AND METHODS

Study population

The NHS enrolled 121,701 United States (US) registered female nurses who were 30–55 years old in 1976. The HPFS enrolled 51,529 US male health professionals who were 40–75 years old in 1986. Details about the two cohorts have been described.[29,30] Briefly, participants were mailed a questionnaire inquiring about their medical history and lifestyle information at baseline and every 2 years thereafter. Dietary data were collected and updated every 4 years using the food frequency questionnaires (FFQs). In the present analysis, we used 1980 for the NHS and 1986 for the HPFS as baseline, when we first collected detailed data on multivitamin supplement use and intake dose. The follow-up rates have been over 90% for each of the questionnaire cycles in both cohorts. Ethical approval was provided in the Supporting Information.

Ascertainment of CRC cases

On each biennial follow-up questionnaire, participants were asked whether they had a diagnosis of CRC during the previous 2 years. For participants who reported CRC diagnosis, we asked for their permission to acquire medical records and pathologic reports. Study physicians, blinded to exposure data, reviewed all medical records to confirm CRC diagnosis and to record the disease stage, histologic findings, and tumor location.[31] In this analysis, we included a total of 2424 participants who were diagnosed with stage I–III CRC throughout follow-up and completed the questionnaire after diagnosis (see the flowchart in Figure S1).

Ascertainment of deaths

Deaths were identified through review of the National Death Index, and family members or the postal system in response to the follow-up questionnaires. The cause of death was assigned by study physicians based on all available data including medical records. More than 98% of deaths have been identified using these methods.[32]

Assessment of multivitamin supplement and diet

On biennial questionnaires, participants were asked to report whether they currently used multivitamin supplements. Status (non-use and user) and intake dose (0, 1–2, 3–5, 6–9, and ≥10 tablets/week) of multivitamin supplements were updated at each follow-up cycle. Multivitamin use did not include taking multiple single agent pills. For post-diagnostic supplement use, the first questionnaire collected at least 6 months after diagnosis was used to avoid assessment during the period of active treatment. Pre-diagnostic supplement use was based on the last questionnaire reported before CRC diagnosis.

Dietary intake was assessed repeatedly by FFQs in which participants were asked how often, on average, they consumed each food of a standard portion size during the previous year. We calculated the daily intake for each nutrient by multiplying the reported frequency of consumption of each item by its nutrient content, summing across from all foods, and adjusting for total caloric intake using the nutrient residual method.[33] FFQs have shown good reproducibility and validity for assessing food and nutrient intake.[34] We calculated the dietary quality score, Alternate Healthy Eating Index (AHEI), to measure adherence to a healthy eating pattern that has been linked to lower risk of chronic diseases[35] (see the Supporting Information).

Statistical analysis

We calculated person-time of follow-up from the return date of the questionnaire that was used for post-diagnostic assessment to death, or the end of the study period (June 1, 2018), whichever came first. In the current study, CRC mortality and all-cause mortality were considered as the primary end points. Deaths from other causes were considered as the secondary end points.

We used cause-specific Cox proportional hazards regression models with time since diagnosis as the time scale, accounting for left truncation due to differences between participants in the timing of post-diagnostic assessment.[36] We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) of death, adjusted for pre-diagnostic use of multivitamin supplements and other potential predictors for cancer survival, including age at diagnosis, sex, year of diagnosis, tumor stage, anatomic subsite, and differentiation, body mass index, physical activity, pack-years of smoking, alcohol consumption, regular use of aspirin and other nonsteroidal anti-inflammatory drugs, dietary consumption of red and processed meats, total fiber, marine omega-3 fatty acid, and calcium, and AHEI. We tested proportional hazards assumption by including the interaction term between multivitamin supplement use and time into the Cox model and did not find statistical evidence for violation of this assumption.

To minimize any bias resulting from the availability of post-diagnostic questionnaire data, we applied the inverse probability weighting method to all survival analyses.[37] We examined the dose–response relationship between the dose of multivitamin supplements and mortality using the restricted cubic spline analysis, by treating the median value in each category of multivitamin supplements as a continuous variable in the model.[38] To assess whether the results are independent of dietary intake of individual micronutrients, we conducted a sensitivity analysis by further adjusting in the multivariable model for consumption of individual vitamins and minerals from food sources. We also adjusted for and stratified by the use of chemotherapy in a subset of 516 patients who provided the treatment data. In addition, we conducted a sensitivity analysis by including stage IV CRC patients (detailed methods in the Supporting Information).

We also assessed the joint association of pre- and post-diagnostic multivitamin use by classifying patients according to their status of multivitamin use before and after CRC diagnosis and treating non-uses in both periods as the reference group. Finally, we conducted the stratified analysis according to clinicopathological and lifestyle factors. p value for interaction was calculated using the likelihood ratio test. We used SAS 9.4 for all analyses (SAS Institute, Cary, North Carolina). All statistical tests were two-sided, and $p < .05$ was considered statistically significant.

RESULTS

Basic characteristics of participants

As shown in Table 1, during a median of 11 years of follow-up of 2424 eligible patients diagnosed with stage I–III CRC, we documented 1512 deaths, of which 343 were classified as CRC-specific deaths. Other major causes of death included cardiovascular diseases (n = 330), other cancers than CRC (n = 209), dementia

TABLE 1 Post-diagnostic characteristics of CRC patients according to use of multivitamin supplements (n = 2424).[a]

	Non-user (n = 992)	1–2 tablets/week (n = 53)	3–5 tablets/week (n = 177)	6–9 tablets/week (n = 1092)	≥10 tablets/week (n = 110)
Age, years	68.1 (9.8)	67.7 (8.8)	67.9 (10)	70 (8.9)	69.1 (9.6)
Women, %	67	68	69	64	63
BMI, kg/m^2	26.3 (4.8)	27.3 (6.4)	26 (4.5)	26 (4.6)	25.4 (4.1)
Physical activity, MET-hours/week	16.3 (21.7)	23.8 (26.9)	17.9 (22.9)	20.6 (26.6)	23.1 (29.8)
Pack-years of smoking	17.6 (23.5)	13.6 (20.9)	14.2 (20.2)	16.6 (22)	16.2 (19.8)
Current smokers, %	8	9	7	5	1
Regular use of aspirin, %[b]	36	23	40	45	45
Dietary consumption					
Alcohol, g/day	7.3 (11.6)	8.6 (14.8)	6.4 (12.1)	8 (13.3)	8.7 (13.3)
Red and processed meats, serving/week	5.6 (4.2)	5.6 (4.2)	6.3 (4.2)	5.6 (4.2)	4.9 (4.2)
Vitamin A, IU/day	10,982.5 (5682.8)	11,530.6 (7737.9)	11,558.7 (5582.2)	11,545.2 (6320.3)	12,408.6 (6751.9)
Vitamin C, mg/day	141.7 (68)	152.4 (62.9)	144.1 (60.1)	147.8 (69.5)	146.2 (61.3)
Vitamin D, IU/day	216.6 (132.3)	221.3 (122.6)	213.7 (116.4)	225.8 (126.2)	217.2 (107.2)
Vitamin E, mg/day	7.9 (3.5)	9.2 (4.5)	8.3 (4.8)	8.3 (4)	9.2 (4.2)
Vitamin K, μg/day	153.6 (93.1)	169.6 (103.1)	162.9 (98.4)	159.2 (92.4)	175.7 (116.3)
Thiamine (vitamin B1), mg/day	1.5 (0.4)	1.5 (0.3)	1.5 (0.3)	1.5 (0.4)	1.5 (0.3)
Riboflavin (vitamin B2), mg/day	1.9 (0.6)	1.9 (0.5)	1.9 (0.5)	2 (0.6)	1.9 (0.5)
Pyridoxine (vitamin B6), mg/day	2.1 (0.7)	2.1 (0.4)	2.1 (0.5)	2.2 (0.6)	2.1 (0.6)
Vitamin B12, μg/day	6.9 (4.7)	8.1 (4.9)	6.3 (3.3)	7 (4.2)	6.8 (4.2)
Folate, μg/day	395.8 (159.5)	398.7 (100.9)	392.6 (113.9)	424.6 (151.6)	405.2 (129.7)
Niacin, mg/day	21.8 (5.6)	21.6 (4.5)	21.1 (5.2)	22.4 (5.9)	21.4 (5.7)
Total carotene, IU/day	9153.9 (5573.6)	9253.2 (7411)	9843.1 (5352.6)	9732.1 (6290.8)	10,631.3 (6652.3)
Total fiber, g/day	20.4 (6.9)	22.7 (6.5)	21.1 (6.5)	21.6 (6.5)	21.5 (6.3)
Calcium, mg/day	785.8 (307.9)	804.7 (320.2)	781.5 (303.4)	846.9 (307.5)	786.7 (284)
Potassium, mg/day	3060.7 (647)	3128.8 (521.6)	3081.2 (630.5)	3198.1 (643.1)	3136.6 (670.7)
Marine omega-3 fatty acid, g/week	1.4 (1.4)	1.4 (1.4)	1.4 (1.4)	1.4 (1.4)	1.4 (1.4)
AHEI dietary quality score	54.0 (11.5)	58.0 (11.9)	55.2 (11)	55.7 (11.2)	58.8 (12.2)
Prevalence of comorbidity, %					
Cardiovascular disease	75	74	77	75	79
Hypertension	72	68	77	76	73
Hypercholesterolemia	59	57	63	57	54
Diabetes	58	52	60	59	63
Cancer subsite, %					
Proximal colon	44	43	40	45	37
Distal colon	29	28	33	30	33
Rectum	22	25	22	20	26
Unspecified	6	4	5	5	5
Differentiation, %					
Well differentiated	15	21	12	15	13
Grade 2 moderately differentiated	59	45	58	57	59

TABLE 1 (Continued)

	Non-user (n = 992)	1–2 tablets/ week (n = 53)	3–5 tablets/week (n = 177)	6–9 tablets/week (n = 1092)	≥10 tablets/week (n = 110)
Grade 3 poorly differentiated	11	23	15	14	10
Unspecified	16	11	16	15	19
Stage, %					
Stage I	32	25	27	34	33
Stage II	30	32	33	30	33
Stage III	22	34	28	25	19
Unspecified	16	9	12	12	15

Abbreviations: AHEI, Alternate Healthy Eating Index; BMI, body mass index; CRC, colorectal cancer; IU, international unit; MET, metabolic equivalent.
[a]Means are calculated for continuous variables; percentages for categorical variables, and all variables are age-standardized except age.
[b]Regular users are defined as ≥2 standard (325 mg) tablets of aspirin per week.

(n = 116), and respiratory disease (n = 104). The mean time interval between CRC diagnosis and the return of the post-diagnostic questionnaire was 2.5 years (SD = 1.2 years). Users at different doses and non-uses of post-diagnostic multivitamin supplements did not show substantial difference in their lifestyle or clinicopathological characteristics. We did not observe substantial difference in the prevalence of major comorbidities according to multivitamin intake, including cardiovascular disease, hypertension, hypercholesterolemia, and diabetes.

Multivitamin supplements after diagnosis and survival

Compared to non-uses, users of multivitamin supplements at a dose of 3–5 tablets/week after CRC diagnosis had a significant lower CRC-specific mortality (multivariable HR, 0.55; 95% CI, 0.36–0.83, p = .005), and users at a dose of 3–5 and 6–9 tablets/week after CRC diagnosis had lower all-cause mortality (HR, 0.81; 95% CI, 0.67–0.99, p = 0.04 and HR, 0.79; 95% CI, 0.70–0.88, p < .001), whereas users of ≥10 tablets/week had an increased risk of CRC-specific mortality (HR, 1.60; 95% CI, 1.07–2.40, p = .02). No statistically significant associations were found for users at other dose groups (Table 2).

The spline analysis showed a curvilinear relationship between intake dose of multivitamin supplements after CRC diagnosis and risk of CRC-specific mortality and all-cause mortality (p for nonlinear relation = <.001 and .004, respectively). The maximum risk reduction was observed at 3–5 tablets/week and no further reduction was seen at higher doses. For CRC-specific mortality, users with more than 8 tablets/week had an even higher risk of death than non-uses (Figure 1).

For deaths of other major causes, compared to non-uses, users of multivitamin supplements at a dose of 3–5 tablets/week and 7–9 tablets/week had a lower mortality of total cancer (HR, 0.68; 95% CI, 0.49–0.94 and HR, 0.76; 95% CI, 0.63–0.92, respectively), and users at a dose of 7–9 tablets/week had a lower mortality of cardiovascular disease (HR. 0.73; 95% CI, 0.57–0.93) and noncolorectal cancers (HR, 0.60; 95% CI, 0.44–0.82) (Table S1).

In the sensitivity analysis, the results remained essentially unchanged after further adjustment for dietary intake of individual vitamins and minerals, AHEI, and use of chemotherapy. We obtained similar results when stage IV CRC patients were also included in the analysis (Table S2).

Subgroup analysis

We did not observe any statistically significant difference in the association of multivitamin supplementation with CRC-specific and all-cause mortality according to tumor subsite (p for interaction = .48 and .11, respectively) or stage (p for interaction = .18 and .62, respectively), although a statistically significant inverse association was found for stage II (HR, 0.56; 95% CI, 0.34–0.93 and HR, 0.71; 95% CI, 0.57–0.88) but not stage I or III patients (Table S3). In the stratified analysis according to demographic, dietary, and lifestyle factors, and chemotherapy use, we found that the association with CRC-specific mortality was stronger among patients with low physical activity, higher AHEI, and high dietary intake of folate, calcium, and fiber (p for interaction < .05); and the inverse association with CRC-specific mortality and all-cause mortality appeared to be stronger among aspirin non-uses (p for interaction = .09) (Figure S2). However, given multiple testing, these findings should be interpreted cautiously.

Joint analysis of pre- and post-diagnostic multivitamin use

Pre- and post-diagnostic intake dose of multivitamin supplements was modestly correlated (Spearman correlation coefficient r = 0.47). In the joint analysis (Table 3), for all-cause mortality, compared to non-uses in both periods, new users after CRC diagnosis at a dose of <10 tablets/week had a lower all-cause mortality (HR, 0.81; 95% CI, 0.71–0.94, p = .005), whereas new users at a dose of ≥10 tablets/week and discontinued users had a higher risk of mortality (HR, 1.58;

TABLE 2 Multivitamin intake dose in relation to mortality among CRC patients (n = 2424).[a]

Post-diagnostic multivitamin intake	Non-user (n = 992)	1–2 tablets/week (n = 53)	3–5 tablets/week (n = 177)	6–9 tablets/week (n = 1092)	≥10 tablets/week (n = 110)	p for nonlinearity	p for overall significance
CRC-specific mortality							
Median dose, tablets/week	0	1.5	4	7.5	10		
No. of events (n = 343)	142	7	23	151	20		
No. of person-years	11,707	648	1991	11,792	1161		
Age-adjusted mortality rate (per 1000 person-years)	23.7	12.4	12.0	17.4	17.0		
Age, sex, stage-adjusted model 1[b]	1 (referent)	0.95 (0.53–1.69)	0.74 (0.51–1.07)	0.85 (0.70–1.03)	1.80 (1.24–2.62)	.002	.008
Multivariable-adjusted model 2[c]	1 (referent)	1.05 (0.57–1.92)	0.55 (0.36–0.83)	0.83 (0.66–1.04)	1.60 (1.07–2.40)	<.001	<.001
All-cause mortality							
No. of events (n = 1512)	656	28	107	644	77		
Age-adjusted mortality rate (per 1000 person-years)	62.0	45.1	60.2	49.6	65.4		
Age, sex, stage-adjusted model 1[b]	1 (referent)	0.81 (0.59–1.12)	0.93 (0.78–1.12)	0.87 (0.79–0.96)	1.20 (0.97–1.48)	.04	.03
Multivariable-adjusted model 2[c]	1 (referent)	0.79 (0.56–1.10)	0.81 (0.67–0.99)	0.79 (0.70–0.88)	1.06 (0.85–1.33)	.004	<.001

Abbreviations: BMI, body mass index; CIs, confidence intervals; CRC, colorectal cancer; HRs, hazard ratios; MET, metabolic equivalent.

[a]Post-diagnostic intake was assessed at least 6 months after diagnosis to minimize the influence of active treatment.

[b]Model 1: HRs and 95% CIs were estimated in Cox proportional hazards regression model after adjusting for age at diagnosis (continuous), sex, and cancer stage (1, 2, 3, and unspecified).

[c]Model 2: model 1+further adjusted for year of diagnosis (continuous), tumor grade of differentiation (1–3 and unspecified), subsite (proximal colon, distal colon, rectum, and unspecified), pre-diagnostic multivitamin intake (user and non-user), post-diagnostic alcohol consumption (<0.15, 0.15–1.9, 2.0–7.4, ≥7.5 g/day), pack-years of smoking (0, 1–15, 16–25, 26–45, >45), BMI (<23, 23–24.9, 25–27.4, 27.5–29.9, ≥30 kg/m^2), physical activity (women: <5, 5–11.4, 11.5–21.9, ≥22 MET-hours/week; men: <7, 7–14.9, 15–24.9, ≥25 MET-hours/week), regular use of aspirin and other nonsteroidal anti-inflammatory drugs (≥2 tablets per week), dietary consumption of red and processed meats, total fiber, marine omega-3 fatty acid, and calcium (all in quartiles), and Alternate Healthy Eating Index (in quartiles).

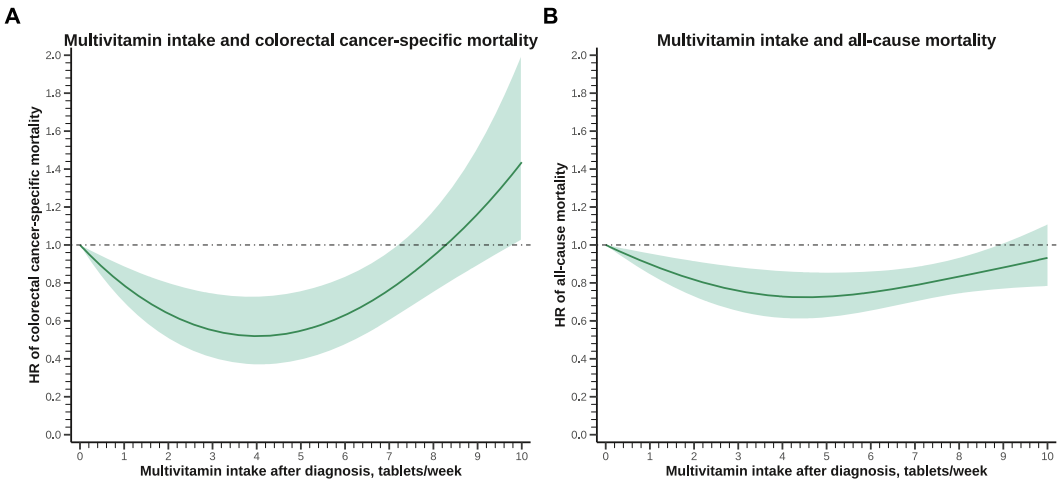

FIGURE 1 Dose–response relationship between post-diagnostic multivitamin intake and colorectal cancer-specific mortality (A) and all-cause mortality (B) among colorectal cancer patients. The cloud represents the 95% confidence intervals of the hazard ratio. Multivariable model was adjusted for the same set of covariates as in model 2 in Table 2. For colorectal cancer-specific mortality in (A), p for nonlinear relation <.001 and p for overall significance of the curve <.001. For all-cause mortality in (B), p for nonlinear relation = .004 and p for overall significance of the curve <.001.

TABLE 3 Joint association of pre- and post-diagnostic multivitamin supplement use in relation to mortality among CRC patients (n = 2424).[a,b,c]

	Post-diagnostic multivitamin intake			
	Non-user (n = 992)	<10 tablets/week (n = 1322)	≥10 tablets/week (n = 110)	p for interaction[d]
CRC-specific mortality				.01
Pre-diagnostic multivitamin				
Non-user (n = 1207)	1 (referent)	0.84 (0.63–1.12)	3.31 (1.86–5.88)	
User (n = 1217)	1.30 (0.94–1.80)	0.86 (0.67–1.09)	1.18 (0.68–2.03)	
All-cause mortality				.07
Pre-diagnostic multivitamin				
Non-user (n = 1207)	1 (referent)	0.81 (0.71–0.94)	1.58 (1.07–2.33)	
User (n = 1217)	1.35 (1.14–1.59)	1.01 (0.89–1.13)	1.20 (0.93–1.55)	

Abbreviations: BMI, body mass index; CRC, colorectal cancer; MET, metabolic equivalent.

[a]Joint multivitamin supplement was categorized by pre- and post-diagnostic multivitamin supplement. Pre-diagnostic multivitamin supplement was based on the last questionnaire reported before CRC diagnosis. Post-diagnostic multivitamin supplement was assessed at least 6 months after diagnosis to minimize the influence of active treatment.

[b]Cox proportional hazards regression model was adjusted for age at diagnosis (continuous), sex, and cancer stage (I, II, III, and unspecified), year of diagnosis (continuous), tumor grade of differentiation (1–3 and unspecified), subsite (proximal colon, distal colon, rectum, and unspecified), post-diagnostic alcohol consumption (<0.15, 0.15–1.9, 2.0–7.4, ≥7.5 g/day), pack-years of smoking (0, 1–15, 16–25, 26–45, >45), BMI (<23, 23–24.9, 25–27.4, 27.5–29.9, ≥30 kg/m^2), physical activity (women: <5, 5–11.4, 11.5–21.9, ≥22 MET-hours/week; men: <7, 7–14.9, 15–24.9, ≥25 MET-hours/week), regular use of aspirin and other nonsteroidal anti-inflammatory drugs (2 or more tablets per week), dietary consumption of red and processed meats, total fiber, marine omega-3 fatty acid, and calcium (all in quartiles), and Alternate Healthy Eating Index (in quartiles).

[c]The number of all deaths for non-users in both periods, pre-diagnostic users only, post-diagnostic users of <10 and ≥10 tablets/week, and users in both periods with post-diagnostic dose at <10 and ≥10 tablets/week was 497, 159, 250, 18, 529, and 59, respectively. The corresponding number for CRC deaths was 112, 30, 67, 7, 114, and 13, respectively.

[d]p for interaction was calculated by likelihood ratio test by comparing the model with the product term between pre- and post-diagnostic multivitamin supplement and the model without this term.

95% CI, 1.07–2.33 and HR, 1.35; 95% CI, 1.14–1.59, respectively). For CRC-specific mortality, no statistically significant associations were found in any of the combined groups, although new and continued users at a dose of <10 tablets/week had a suggestive lower risk (HR, 0.84; 95% CI, 0.63–1.12 and HR. 0.86; 95% CI, 0.67–1.09, respectively).

DISCUSSION

To our knowledge, this is the first prospective study examining the prognostic influence of multivitamin supplements among patients with stage I-III CRC. We found that users of multivitamin supplements at a dose of 3–5 and 3–9 tablets/week after CRC diagnosis had a lower CRC-specific and all-cause mortality, respectively. These associations persisted after adjusting for various potential confounding factors. The dose–response analysis showed a curvilinear relationship for both CRC-specific and all-cause mortality, with the lowest CRC-specific and all-cause mortality found for users of 3–5 tablets/week. Our findings provide novel evidence for the potential benefit of multivitamin supplements among CRC patients.

Limited but generally consistent evidence supports a beneficial association of multivitamin supplement use with lower CRC incidence. The meta-analysis by the World Cancer Research Fund/American Institute for Cancer Research reported that users had an approximately 12% lower risk of CRC than non-uses.[27] Multivitamin use in healthy individuals has been associated with 11% lower colon cancer mortality in the Cancer Prevention Study II cohort.[39] A large randomized controlled trial of male physicians has also shown that multivitamin supplementation reduces the risk of total cancer by 8%.[40] Our current study adds to the existing literature and suggests that the benefit of multivitamin supplements may extend beyond primary prevention for CRC and have a beneficial influence on prognosis in patients with established cancer.

Mechanistically, multivitamin supplementation has been shown to enhance systemic immunity.[41,42] Micronutrient components in multivitamins show antineoplastic properties in CRC xenografts,[5,11] protect the integrity of gastrointestinal epithelia,[23-26] and enhance the efficacy of chemotherapy in clinical trials.[21,22,43] Notably in the current study, the dietary intakes of many vitamins/minerals in CRC patients, such as vitamin B2, D, E, calcium, and potassium, were much lower than the Dietary Reference Intakes recommended by National Institutes of Health State-of-the-Science Conference (see Table 1).[44] Moreover, CRC and related surgical resection and chemotherapy may impair absorption of micronutrients[4,25] and lead to nutrient insufficiency or deficiency, suggesting the potential benefit of supplementation.

Once-daily multivitamin supplementation has been shown to lower prevalence of inadequacies of micronutrients, reduce risk of infections, and have a good safety profile in healthy adults.[45,46] However, the effect and optimal dose in cancer patients remain unknown. For the first time, we demonstrated a curvilinear dose–response relationship of multivitamin supplements with CRC-specific and all-cause mortality in CRC patients, such that users consuming 3–5 tablets/week had the lowest risk of both CRC-specific and all-cause mortality and the risk reduction was eroded at higher doses. Users taking more than 8 tablets/week tended to have a higher risk of CRC-specific mortality, and users with more than 10 tablets/week had a significantly higher risk of CRC-specific mortality than non-uses. These findings suggest that a dose at 3–5 tablets/week may be considered in future clinical trials to further confirm our results. Our results are consistent with the dose-related variations in effects of individual micronutrients. For example, 1.5 g/kg intravenous vitamin C every 2 weeks and 4000 IU/day oral vitamin D3 have been shown to safely improve the prognosis of advanced CRC patients.[21,22,43] Although moderate concentrations of beta-carotene and iron may benefit cancer survival[47-49] through effects on apoptosis,[50] phagocytosis,[51] insulin sensitivity,[52] immunosurveillance,[53,54] and reduced angiogenesis,[55] overly low and overly high intakes of beta-carotene[45,56,57] and iron[25,58] may have an adverse effect on cancer survival. Our findings indicate the need for further interventional studies to establish the candidate doses for micronutrients in cancer patients.

In contrast to our findings, a prior study in the CALGB 89803 trial reported no association of post-diagnostic multivitamin use with survival in patients with stage III colon cancer.[28] However, because that study only compared users to non-users and did not conduct detailed dose–response analysis, it is unknown whether the null association was driven by high-dose users (e.g., ≥10 tablets per week), for which a higher mortality was observed in our current study. Moreover, the study in CALGB 89803 trial did not account for pre-diagnostic multivitamin use. We adjusted for pre-diagnostic use in the analysis of post-diagnostic intake. Intriguingly, the joint analysis of pre- and post-diagnostic multivitamin use showed that, compared to non-users in both periods, only patients who initiated multivitamin use after CRC diagnosis at a modest dose had lower all-cause mortality, and pre-diagnostic users who discontinued use after diagnosis had even higher all-cause mortality. It is possible that the systemic alterations in CRC patients associated with the established cancer and treatment may enable a survival-prolonging benefit of post-diagnostic multivitamin supplementation, because of the anti-inflammatory[10,59,60] and endothelial function-improving properties[51,61] of antioxidant vitamins. Systemic adaptations to these properties may lead to withdrawal effect (e.g., dysregulation of the immune system) among discontinued users and negatively influence prognosis. Finally, the null results in the CALGB 89803 study may be due to their inclusion of stage III colon cancer only. Although we did not observe a statistically significant heterogeneity across tumor stage, the inverse association of multivitamin use with mortality appeared to be stronger for stage II than stage I or III patients. However, given the exploratory nature and the limited number of events in the stratified analysis, further studies are needed to confirm our findings by assessing the potential variability across CRC stage in the prognostic influence of multivitamin supplements. Our findings suggest a need for clinical trials in the postoperative settings to assess the influence of multivitamin supplements at different doses among CRC patients with different stages.

Strengths of the current study include the prospective design, detailed collection of pre- and post-diagnostic multivitamin supplement use and dose, diet and lifestyle information, standardized medical record review of CRC diagnosis and deaths, and long-term follow-up. Moreover, the detailed covariate data collected in parallel with multivitamin use allowed for rigorous control for confounding by various CRC risk factors. Our study also has some limitations. First, detailed treatment data were largely unavailable in the cohorts. However, among a subset of 516 patients who provided chemotherapy data in a supplementary questionnaire, we did not observe any difference in multivitamin supplement use according to use of chemotherapy. Moreover, during the period of the study, adjuvant treatment was largely standardized and primarily correlated with disease stage. Thus, our ability to control for stage minimized any potential confounding by treatment. Indeed, further adjustment for chemotherapy use among the subset of individuals with treatment data did not change our results and stratified analysis by chemotherapy use did not show a difference either. Second, as an observational study, residual confounding cannot be excluded, although we observed similar results through multivariable adjustment and sensitivity analyses. Third, reverse causation and recall-bias may be present. Our findings need to be validated by further studies, preferably clinical trials. Fourth, multiple testing was performed in the stratified analysis. Thus, we practiced caution when interpreting these results. Moreover, the number of events was small in some of the dosing groups and thus chance findings could not be excluded. Finally, although evidence showed a reduced risk of chemotherapy-induced peripheral neuropathy associated with multivitamin use,[62] the potential role of multivitamin in reducing chemotherapy-induced toxicity is beyond the scope of the current study.

In conclusion, use of multivitamin supplements at a moderate dose (3–5 tablets/week) after the diagnosis of nonmetastatic CRC is associated with lower CRC-specific and overall mortality, whereas a high dose (≥10 tablets/week) is associated with higher CRC-specific mortality. Further studies are needed before making clinical recommendations for multivitamin use in patients with CRC.

AUTHOR CONTRIBUTIONS

Ming-ming He: Conceptualization, methodology, data curation, formal analysis, funding acquisition, project administration, resources, writing–original draft, and writing–review and editing. **Kai Wang**: Conceptualization, data curation, formal analysis, writing–original draft, writing–review and editing, funding acquisition, project administration, methodology, and resources. **Chun-Han Lo**: Data curation, formal analysis, writing–review and editing, project administration, methodology, and resources. **Yiwen Zhang**: Data curation,

formal analysis, writing–review and editing, project administration, methodology, and resources. **Georgios Polychronidis**: Data curation, formal analysis, and writing–review and editing. **Markus D. Knudsen**: Data curation, formal analysis, and writing–review and editing. **Rong Zhong**: Data curation, formal analysis, and writing–review and editing. **Yuan Ma**: Data curation, formal analysis, and writing–review and editing. **Kana Wu**: Data curation, formal analysis, and writing–review and editing. **Andrew T. Chan**: Data curation, formal analysis, writing–review and editing, and funding acquisition. **Edward L. Giovannucci**: Data curation, formal analysis, and writing–review and editing. **Shuji Ogino**: Data curation, formal analysis, writing–review and editing, and funding acquisition. **Kimmie Ng**: Data curation, formal analysis, writing–review and editing, and funding acquisition. **Jeffrey A. Meyerhardt**: Data curation, formal analysis, and writing–review and editing. **Mingyang Song**: Conceptualization, data curation, formal analysis, writing–review and editing, funding acquisition, project administration, methodology, resources, and supervision.

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CONFLICT OF INTEREST STATEMENT

Kimmie Ng reports consulting fees from AbbVie, Bayer, Bicara Therapeutics, BioMx, CytomX, GlaxoSmithKline, Pfizer, and Seagen Inc; and grant and/or contract funding from Evergrande Group, Janssen Scientific Affairs, LLC, Pharmavite, and Revolution Medicines. Shuji Ogino reports grant and/or contract funding from the National Institutes of Health. Kana Wu reports stock holdings with Vertex Pharmaceuticals Inc. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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