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Article

The Associations of Multivitamin and Antioxidant Use With Mortality Among Women and Men Diagnosed With Colorectal Cancer

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Abstract

Background: Colorectal cancer survivors often use multivitamins and other over-the-counter dietary supplements, but evidence is limited regarding their potential associations with mortality. **Methods:** This prospective analysis included women and men from the Cancer Prevention Study-II Nutrition Cohort who were cancer-free at baseline (1992 or 1993) and diagnosed with colorectal cancer through June 2015. Detailed information on multivitamin use, vitamin C supplements, and vitamin E supplements was self-reported on questionnaires at baseline, in 1997, and every 2 years thereafter. Pre- and postdiagnosis data were available for 3176 and 2006 colorectal cancer survivors, respectively, among whom 2116 (648 from colorectal cancer) and 1256 (242 from colorectal cancer) died. Multivariable-adjusted Cox proportional hazards regression models examined associations. All statistical tests were 2-sided. **Results:** Among colorectal cancer survivors, 49.7% and 58.5% reported multivitamin use before and after diagnosis, respectively (vitamin C use before and after diagnosis: 27.8% and 28.1%; vitamin E use before and after diagnosis: 27.5% and 29.4%, respectively). There were no statistically significant associations of pre- or postdiagnosis multivitamin use with all-cause, colorectal cancer-specific, or noncolorectal cancer mortality. Vitamin C was also not associated with any mortality outcomes. However, prediagnosis vitamin E use was associated with a nonstatistically significant increased risk of all-cause mortality (multivariable adjusted hazard ratio = 1.08, 95% confidence intervals = 0.96 to 1.23) and all other noncolorectal cancer mortality (multivariable adjusted hazard ratio = 1.13, 95% confidence intervals = 0.97 to 1.31). **Conclusions:** These results suggest that multivitamin use before or after diagnosis is not associated with mortality in colorectal cancer survivors. However, vitamin E use may be associated with increased risk of mortality and merits further investigation.

Colorectal cancer survivors have expressed a need for evidence-based information on diet and nutrition choices potentially influencing their prognosis and long-term quality of life (1,2), but there is limited data on the impact of dietary supplements on clinical outcomes (3,4). The World Cancer Research Fund (WCRF) and American Institute for Cancer Research 2018 report on colorectal cancer concluded that there is limited but generally consistent evidence that multivitamin supplements are associated with lower risk of colorectal cancer incidence (5). The report also concluded that there is probable evidence for an inverse association with calcium supplements and colorectal cancer incidence but insufficient evidence for the role of many other vitamins and supplements, such as vitamins A, C, E, and beta-carotene, with the development of colorectal cancer (5). Despite these potential inverse associations (5), the WCRF and American Institute for Cancer Research recommends "eating a healthy diet rather than relying on supplements to protect against cancer" (5). Gaziano et al. (6) found that daily multivitamin use was associated with a statistically significantly lower risk of all cancers among men, especially those with a history of cancer, but not specifically associated with colorectal cancer risk or mortality, although their sample sizes were small for colorectal cancer-specific analyses. The influence of multivitamin and other supplements on survival outcomes after a colorectal cancer diagnosis is much less studied,

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despite a clear need for this information for the approximately 1.8 million survivors of colorectal cancer worldwide (7).

Despite the lack of evidence suggesting potential health-related benefits, studies have shown that people diagnosed with cancer are more likely to use multivitamins and other dietary supplements than the general population. Between 64% and 81% of cancer survivors reported using any vitamin or mineral supplements, with 14% to 32% of those patients initiating supplement use after their cancer diagnosis (8). Two-thirds of physicians are unaware of supplement use among their patients (8). Because of the high prevalence of vitamin and other supplement use among men and women with cancer, it is important to identify potential benefits or harms of these supplements with cancer survival. For example, it has been suggested that folate supplementation can increase recurrence of adenoma with high malignant potential (9). Other supplements may interact with treatment efficacy and promote carcinogenesis (10). Vitamin E was associated with an increased risk of hemorrhagic stroke in a randomized, controlled clinical trial of apparently healthy men aged 50 years and older (11).

To date, most of the research on multivitamin and supplement use among individuals with colorectal cancer is descriptive (12-14). Ng et al. (15) used observational data from 1038 stage III colon cancer patients to show that multivitamin use during treatment and 6 months after chemotherapy completion was not associated with recurrence-free (hazard ratio [HR] = 0.93, 95% confidence interval [CI] = 0.75 to 1.15) or overall survival (HR = 0.92, 95% CI = 0.74 to 1.16). Overall, large-scale, randomized cancer prevention trials have been null with respect to supplement use and colorectal cancer incidence, with some notable adverse effects (16).

We used data from the Cancer Prevention Study-II (CPS-II) Nutrition Cohort to examine the associations of pre- and postdiagnosis use of multivitamins, vitamin E, and vitamin C with colorectal cancer-specific and all-cause mortality among colorectal cancer survivors. This study was conducted to better inform clinicians and colorectal cancer survivors about the potential benefits and/or harms of vitamins and supplements.

Methods

Study Participants

The analytic cohort for this analysis began with 4753 participants in the CPS-II Nutrition Cohort who were free from colorectal cancer at baseline and who were subsequently diagnosed with invasive colon (International Classification of Diseases [ICD]–10: C18) or rectal cancer (ICD-10: C19-C20) after baseline (1992 or 1993) enrollment and before the end of incidence follow-up (June 30, 2015). The institutional review board at Emory University approved the CPS-II Nutrition Cohort study. Participants were followed for mortality outcomes through December 31, 2018. Exclusions were made for the following reasons: cases identified through the National Death Index that could not be verified with cancer registries (n = 302), cases with a prior diagnosis of cancer at baseline other than nonmelanoma skin cancer (n = 457), cases with an implausible diagnosis date (n = 16), cases with an unknown cancer stage at diagnosis (n = 172), cases with a nonadenocarcinoma colorectal cancer histology (n = 62), cases who were diagnosed with colorectal cancer and died on the same day (n = 2), and cases missing vitamin and/or supplement data on the prediagnosis questionnaire (n = 32). We also excluded persons diagnosed with distant metastatic staged disease (n = 534) in our primary mortality analyses because we anticipated the poor prognosis associated with distant metastatic disease would not be materially influenced by supplement use, similar to our previous observations with other lifestyle and behavioral factors in this cohort (17-22). Therefore, we had 3176 participants for prediagnosis analyses. Among these colorectal cancer survivors, 2116 deaths occurred (648 from colorectal cancer and 1468 from all other causes). A total of 2106 participants returned a valid postdiagnosis questionnaire that included supplement information. We excluded cases who died within 1 year of returning their postdiagnosis questionnaire (n = 100) because of plausible biases from reverse causation, leaving 2006 participants for postdiagnosis analyses. In this postdiagnosis group, 1256 deaths occurred (242 from colorectal cancer and 1014 from all other causes).

Assessment of Multivitamin and Other Vitamin Use

Information on use of individual and multivitamin supplements was assessed at baseline (1992 or 1993), again in 1997, and biennially thereafter through 2017. The reference period for prediagnosis analyses was the questionnaire preceding diagnosis, whereas the postdiagnosis reference period was the questionnaire immediately afterward. Supplements of primary interest in this study were multivitamins (eg, One A Day, Stresstabs, therapeutic), vitamin C, and vitamin E. Vitamin D and calcium were included in a previous CPS-II publication when combined with dietary intakes (21) and are not included in this analysis. Exposure levels were characterized as follows for multivitamins: nonusers (ie, responded “no” to “Do you currently take a multivitamin?”), less than daily users (ie, responded “yes” to “Do you currently take a multivitamin?” and indicated taking less than 6 pills per week), and daily users (ie, responded “yes” to “Do you currently take a multivitamin?” and indicated taking 6 or more pills per week). Use of vitamins C and E were categorized as no use or any use (ie, responded “yes” to “Not counting multivitamins, do you regularly take any of the following supplements, individually or in combinations?”). Daily use of multivitamins was used in an analysis that examined pre- to postdiagnosis change in use. Postdiagnosis use was defined as supplement use at least 1 year after diagnosis, to avoid potential biases associated with treatment and potential healthy user effects.

Vital status, cause of death, and date of death were determined through linkage to the National Death Index through December 31, 2018. Cause of death was obtained for 99.3% of all known deaths in the CPS-II Nutrition Cohort. The primary outcome of interest was defined as overall mortality. We also examined colorectal cancer–specific mortality (ICD-10, codes C18 to C20) and all other causes of death.

Statistical Analysis

Hazard ratios and 95% confidence intervals were estimated using Cox proportional hazards models. Time since diagnosis was used as the underlying time axis. For analyses of prediagnosis use, each participant contributed person-time starting on their diagnosis date. For analyses of postdiagnosis use, each participant contributed person-time starting on a date 1 year after the completion date of their postdiagnosis questionnaire (using delayed-entry Cox model procedures), to reduce potential biases from reverse causation and other factors. Follow-up continued until death or the administrative end of follow-up on December

31, 2018. All proportional hazards assumptions were tested by modeling a multiplicative interaction term between time (in months) and each supplement variable. The statistical significance of the interaction term was assessed using the log likelihood ratio test. No violations of the proportional hazards assumptions were identified.

All covariables in the Cox proportional hazards models were decided a priori; the full Cox models included sex, age at diagnosis, year of diagnosis, treatment, disease stage, education, physical activity, body mass index, American Cancer Society diet score [(19), based on consumption of fruits and vegetables, whole grains moreso than refined grains, and avoidance of red and processed meats], smoking, and use of nonsteroidal anti-inflammatory drugs, calcium supplements, vitamin D supplements, vitamin E supplements, vitamin C supplements, and multivitamins. Postdiagnosis models also included weight change between the prediagnosis and postdiagnosis questionnaires. The potential confounding variables in the multivariable models were selected based on previous CPS-II analyses (17-22) of variables known to associate with colorectal cancer survival that may plausibly correlate with the main supplement exposures of interest. Missing data for covariates were modeled as an "unknown or missing" category for categorical variables.

We examined associations of pre- and postdiagnosis total and specific supplement use with survival stratified by age at diagnosis (aged younger than 70 years vs 70 years and older) and sex (men vs women). No differences between these strata were observed (data not shown).

Results

Baseline characteristics for the prediagnosis period are shown in Table 1 according to multivitamin use. Mean age at colorectal cancer diagnosis was 73.8 (7.3) years. Nonsupplement users were more likely to be men, younger than age 65 years, and nonaspirin users and have a body mass index of 30 kg/m^2 or more and a low American Cancer Society diet score ($P < .001$). Associations of characteristics with postdiagnosis use were similar (Supplementary Table 1). Among supplement users, multivitamins were the most common supplement reported from the pre- and postdiagnosis surveys (49.7% and 58.5%, respectively) followed by vitamin C use (27.8% and 28.1%, respectively) and vitamin E use (27.5% and 29.4%, respectively). Multivitamin use in combination with calcium (prediagnosis: 24.1%, postdiagnosis: 28.1%), vitamin C (prediagnosis: 20.1%, postdiagnosis: 21.5%), and vitamin E (prediagnosis: 19.9%, postdiagnosis: 23.1%) were the most frequent pairings.

Daily multivitamin use in the prediagnosis period was not associated with all-cause (multivariable-adjusted [MV]-HR = 1.06, 95% CI = 0.96 to 1.17), colorectal cancer-specific (MV-HR = 0.98, 95% CI = 0.81 to 1.18), or all other cause mortality (MV-HR = 1.10, 95% CI = 0.98 to 1.24; Table 2). Postdiagnosis multivitamin use was also not associated with mortality (all-cause MV-HR = 0.97, 95% CI = 0.85 to 1.11; colorectal cancer-specific MV-HR = 1.00, 95% CI = 0.74 to 1.35; and all other causes MV-HR = 0.96, 95% CI = 0.83 to 1.12) (Table 2). Similarly, vitamin C was not statistically significantly associated with mortality in the pre- and postdiagnosis periods. However, prediagnosis vitamin E use was associated with a non-statistically significant increased risk of all-cause mortality (MV-HR = 1.08, 95% CI = 0.96 to 1.23) and all noncolorectal cancer mortality (MV-HR = 1.13, 95% CI = 0.97 to 1.31). Estimates for postdiagnosis use of vitamin E remained positive but were also not statistically significant (all-cause MV-HR = 1.07, 95% CI = 0.92 to 1.25; colorectal cancer-specific MV-HR = 1.06, 95% CI = 0.73 to 1.54; and all other causes MV-HR = 1.09, 95% CI = 0.92 to 1.30). Changes in multivitamin user status after colorectal cancer diagnosis was also not statistically significantly associated with mortality; however, compared with consistent nonusers in the pre- to postdiagnosis period, persons who used MVs in the prediagnosis period and stopped using them in the postdiagnosis period saw a suggestively increased risk of all-cause (MV-HR = 1.26, 95% CI = 0.99 to 1.61) and all other cause mortality (MV-HR = 1.29, 95% CI = 0.98 to 1.71) (Table 3).

Discussion

In this prospective cohort study of more than 3100 colorectal cancer survivors followed for up to 26 (mean follow-up: 9.9) years, multivitamins, vitamin C, and vitamin E supplements used either before or after colorectal cancer diagnosis were not associated with benefit or with harm regarding mortality outcomes. Future studies should examine vitamin E use and the influence of quitting multivitamin use in similar contexts as analyzed here to identify whether our non-statistically significant findings suggestive of increased mortality are replicated in other study populations.

There is currently no strong evidence for benefits from multivitamin or antioxidant supplement use with respect to recurrence or death among colorectal cancer survivors (15,23,24). Some evidence of lower risk of death among patients with colorectal cancer taking calcium supplements after diagnosis has been reported (25). Despite strong preclinical (26) and observational data (26-29), supplementation with vitamin D did not result in a lower incidence of death from colorectal cancer (HR = 1.09, 95% CI = 0.73 to 1.62) in the Vitamin D and Omega-3 Trial (30). Some evidence suggests high levels of omega-3 are associated with longer time to cancer progression (31) and lower colorectal cancer-specific mortality (32). However, findings from Vitamin D and Omega-3 Trial did not identify an association with death from total cancer (HR = 0.97, 95% CI = 0.79 to 1.20) (33). Results from the CALGB study also reported no association between multivitamins and recurrence or mortality during and after chemotherapy in stage III colon cancer patients (15). To our knowledge, no previous study has investigated pre- to postdiagnosis changes in supplement use with mortality outcomes in colorectal cancer survivors. Therefore, our finding of a suggestive increased risk of mortality from stopping supplement use should be interpreted cautiously, and this finding may simply reflect illness associated with quitting supplement use (eg, reverse causation) during this period. In summary, limited evidence supports the use of multivitamins and other over-the-counter dietary supplements in colorectal cancer survivors to improve mortality outcomes.

One limitation of our analysis is missing data. We relied on self-reported supplement use; therefore, misclassification of the exposure is possible. Patients who consume supplements often engage in other healthful behaviors, and there is some possibility of residual confounding. More complete and accurate covariate assessments would only likely move these results closer to the null hypothesis, however. Interestingly, our results modestly suggested potential harm with vitamin E and, especially, with noncolorectal cancer causes of death, although our results were not statistically significant. Given that the Physicians' Health Study II (PHS-II) (11) reported higher risks of hemorrhagic stroke in the vitamin E intervention arm compared

Table 1. Descriptive characteristics of study population in the Cancer Prevention Study-II by strata of prediagnostic supplement use

Characteristic	Nonuser, No. (%)	Less than daily user, No. (%)	Daily user, No. (%)	P[a]
Total No.	1596	258	1322	
Age at diagnosis, y				
< 65	230 (68.2)	17 (5.0)	90 (26.7)	<.001
65 to < 70	309 (54.7)	52 (9.2)	204 (36.1)	
70 to < 75	405 (53.5)	57 (7.5)	295 (39.0)	
75 to < 80	369 (45.3)	75 (9.2)	371 (45.5)	
80 to < 85	196 (41.5)	35 (7.4)	241 (51.1)	
85 and older	87 (37.8)	22 (9.6)	121 (52.6)	
Sex				
Female	650 (44.5)	146 (10.0)	666 (45.6)	<.001
Male	946 (55.2)	112 (6.5)	656 (38.3)	
Race				
Black	24 (58.5)	4 (9.8)	13 (31.7)	.59
Other/Unknown[b]	16 (42.1)	3 (7.9)	19 (50.0)	
White	1556 (50.2)	251 (8.1)	1290 (41.7)	
Education				
<High school	124 (54.9)	22 (9.7)	80 (35.4)	.002
High school graduate	493 (55.7)	68 (7.7)	324 (36.6)	
Some college	456 (48.6)	77 (8.2)	406 (43.2)	
College graduate	514 (46.3)	90 (8.1)	507 (45.6)	
Unknown	9 (60.0)	1 (6.7)	5 (33.3)	
Stage				
Local	809 (50.3)	122 (7.6)	677 (42.1)	.51
Regional	787 (50.2)	136 (8.7)	645 (41.1)	
BMI, kg/m^2				
<18.5	22 (40.0)	6 (10.9)	27 (49.1)	.001
18.5 to <25	553 (45.5)	114 (9.4)	549 (45.1)	
25 to <30	660 (51.5)	99 (7.7)	523 (40.8)	
≥30	342 (57.7)	36 (6.1)	215 (36.3)	
Unknown	19 (63.3)	3 (10.0)	8 (26.7)	
Smoking				
Never	649 (50.5)	100 (7.8)	535 (41.7)	.14
Current	103 (60.6)	11 (6.5)	56 (32.9)	
Former	839 (48.9)	147 (8.6)	728 (42.5)	
Unknown	5 (62.5)	0 (0)	3 (37.5)	
Alcohol consumption				
None	656 (49.8)	112 (8.5)	549 (41.7)	.91
<1 drink per day	523 (50.2)	86 (8.3)	433 (41.6)	
≥1 drink per day	305 (52.1)	41 (7.0)	239 (40.9)	
Unknown	112 (48.3)	19 (8.2)	101 (43.5)	
Physical activity, MVPA MET-h/wk				
0 to <3.5	285 (53.1)	45 (8.4)	207 (38.5)	.40
3.5 to <4.5	327 (52.7)	53 (8.5)	241 (38.8)	
4.5 to <14	335 (50.1)	54 (8.1)	280 (41.9)	
14 to <21.5	295 (47.4)	48 (7.7)	280 (44.9)	
≥21.5	300 (47.9)	48 (7.7)	278 (44.4)	
Unknown	54 (54.0)	10 (10.0)	36 (36.0)	
NSAID use				
No recent use	593 (60.3)	67 (6.8)	323 (32.9)	<.001
Less than regular use	251 (51.1)	48 (9.8)	192 (39.1)	
Current regular use	619 (43.9)	106 (7.5)	685 (48.6)	
Unknown	133 (45.5)	37 (12.7)	122 (41.8)	
ACS diet score				
0-2	629 (62.1)	70 (6.9)	314 (31.0)	<.001
3-4	556 (48.0)	99 (8.5)	503 (43.4)	
5-9	329 (38.3)	76 (8.8)	455 (52.9)	
Unknown	82 (56.6)	13 (9.0)	50 (34.5)	

[a] χ^2 2-sided test. ACS = American Cancer Society; BMI = body mass index; MET-h/wk = metabolic equivalent hours per week; MVPA = moderate intensity physical activity; NSAID = nonsteroidal anti-inflammatory drugs.

[b] "Other" race category includes Hispanic, Asian, more than 1 racial group, and all other self-identified racial and ethnic groups not listed on the questionnaire.

Table 2. Hazard ratios for the relationship between pre- and postdiagnosis multivitamin, vitamin C, and vitamin E supplement use with mortality among men and women with colorectal cancer

	Multivitamin			Vitamin C		Vitamin E	
Model	Nonuser	Less than daily user	Daily user	Nonuser	User	Nonuser	User
Prediagnosis use[a]							
All-cause mortality							
No. of deaths/No. of CRCs	1094/1596	158/258	864/1322	1524/2294	574/882	1533/2283	583/893
HR (95% CI)	1.00 (Referent)	0.86 (0.73 to 1.03)	1.06 (0.96 to 1.17)	1.00 (Referent)	0.95 (0.84 to 1.08)	1.00 (Referent)	1.08 (0.96 to 1.23)
CRC-specific mortality							
No. of deaths/No. of CRCs	337/1596	57/258	254/1322	468/2294	180/882	476/2283	172/893
HR (95% CI)	1.00 (Referent)	1.01 (0.75 to 1.36)	0.98 (0.81 to 1.18)	1.00 (Referent)	1.03 (0.82 to 1.30)	1.00 (Referent)	1.01 (0.80 to 1.27)
All other mortality							
No. of deaths/No. of CRCs	757/1596	101/258	610/1322	1074/2294	394/882	1057/2283	411/893
HR (95% CI)	1.00 (Referent)	0.80 (0.65 to 1.00)	1.10 (0.98 to 1.24)	1.00 (Referent)	0.90 (0.78 to 1.05)	1.00 (Referent)	1.13 (0.97 to 1.31)
Postdiagnosis use[b]							
All-cause mortality							
No. of deaths/No. of CRCs	555/832	105/182	596/992	887/1432	369/574	847/1373	409/633
HR (95% CI)	1.00 (Referent)	0.92 (0.73 to 1.15)	0.97 (0.85 to 1.11)	1.00 (Referent)	1.05 (0.89 to 1.23)	1.00 (Referent)	1.07 (0.92 to 1.25)
CRC-specific mortality							
No. of deaths/No. of CRCs	103/832	24/182	115/992	180/1432	62/574	172/1373	70/633
HR (95% CI)	1.00 (Referent)	1.20 (0.74 to 1.96)	1.00 (0.74 to 1.35)	1.00 (Referent)	0.89 (0.61 to 1.31)	1.00 (Referent)	1.06 (0.73 to 1.54)
All other mortality							
No. of deaths/No. of CRCs	452/832	81/182	481/992	707/1432	307/574	675/1373	339/633
HR (95% CI)	1.00 (Referent)	0.87 (0.67 to 1.12)	0.96 (0.83 to 1.12)	1.00 (Referent)	1.08 (0.90 to 1.29)	1.00 (Referent)	1.09 (0.92 to 1.30)

[a]Adjusted for sex, age at diagnosis, year of diagnosis, treatment, stage, education, physical activity (prediagnosis), BMI (prediagnosis), ACS diet score (prediagnosis), smoking (prediagnosis), NSAIDs (prediagnosis), calcium supplements (prediagnosis), vitamin D supplements (prediagnosis), vitamin E supplements (prediagnosis), vitamin C supplements (prediagnosis), and use of multivitamins (prediagnosis). ACS = American Cancer Society; BMI = body mass index; CI = confidence interval; CRC = colorectal cancer; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drugs.

[b]Adjusted for sex, age at diagnosis, year of diagnosis, treatment, stage, education, physical activity (postdiagnosis), BMI (postdiagnosis), ACS diet score (postdiagnosis), smoking (postdiagnosis), NSAIDs (postdiagnosis), calcium supplements (postdiagnosis), vitamin D supplements (postdiagnosis), vitamin E supplements (postdiagnosis), vitamin C supplements (postdiagnosis), and use of multivitamins (postdiagnosis). Also includes additional adjustment for change in weight from pre- to postdiagnosis.

Table 3. Hazard ratios for pre- to postdiagnosis change in multivitamin use with mortality among men and women with colorectal cancer

Model	Pre- and Postdiagnosis multivitamin use				
	Non to non	Non to daily user	Daily user to non	Daily user to daily user	Other change
All-cause mortality					
No. of deaths/Total No. CRCs	446/677	175/284	86/118	379/627	170/300
HR (95% CI)	1.00 (Referent)	0.99 (0.82 to 1.20)	1.26 (0.99 to 1.61)	1.04 (0.89 to 1.21)	0.89 (0.73 to 1.07)
CRC-specific mortality					
No. of deaths/Total No. CRCs	78/677	39/284	19/118	68/627	38/300
HR (95% CI)	1.00 (Referent)	1.17 (0.77 to 1.76)	1.26 (0.73 to 2.17)	1.00 (0.69 to 1.46)	1.14 (0.75 to 1.75)
All other mortality					
No. of deaths/Total No. CRCs	368/677	136/284	67/118	311/627	132/300
HR (95% CI)	1.00 (Referent)	0.95 (0.77 to 1.17)	1.29 (0.98 to 1.71)	1.05 (0.88 to 1.25)	0.84 (0.68 to 1.05)

[a]All statistical models are adjusted for sex, age at diagnosis, year of diagnosis, treatment, stage, education, physical activity (postdiagnosis), BMI (postdiagnosis), ACS diet score (postdiagnosis), smoking (postdiagnosis), NSAIDs (postdiagnosis), calcium supplements (postdiagnosis), vitamin D supplements (postdiagnosis), vitamin E supplements (postdiagnosis), vitamin C supplements (postdiagnosis), and change in weight from pre- to postdiagnosis. ACS = American Cancer Society; BMI = body mass index; CI = confidence interval; CRC = colorectal cancer; HR = hazard ratio; non = nonuser; NSAID = nonsteroidal anti-inflammatory drugs.

with placebo, a potential harm from vitamin E cannot be ruled out. In post hoc analyses, we lacked sufficient outcomes to investigate the previous Physicians' Health Study II finding in detail, most notably for deaths attributed to hemorrhagic stroke. Future studies should reexamine this research question.

An important strength of our study is the ability to examine different types of supplements in the pre- and postdiagnosis periods, enabling the assessment of behavior change after a cancer diagnosis. Further, to our knowledge, studies have focused primarily on single supplements, and we evaluated common supplement combinations. This line of research has important clinical implications because many people tend to take multiple types of supplements together. A more complete understanding of the patterns of supplement use during treatment and posttreatment is needed.

Altogether these data suggest that multivitamin supplement use is not associated with benefit or harm with respect to mortality outcomes among colorectal cancer survivors, in line with the WCRF recommendation of eating a healthy diet and not relying on supplements to protect against cancer incidence. Future work needs to consider potential harm from vitamin E supplements in the context of cancer survival.

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Data Availability

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

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