Vitamin C and Vitamin E Supplement Use and Colorectal Cancer Mortality in a Large American Cancer Society Cohort

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Abstract

Some recent epidemiological studies have suggested that use of vitamin C or vitamin E supplements, both of which are important antioxidants, may substantially reduce the risk of colon or colorectal cancer. We examined the association between colorectal cancer mortality and use of individual vitamin C and E supplements in the American Cancer Society's Cancer Prevention Study II cohort. We used proportional hazards modeling to estimate rate ratios among 711,891 men and women in the United States who completed a self-administered questionnaire at study enrollment in 1982, had no history of cancer, and were followed for mortality through 1996. During the 14 years of follow-up, 4404 deaths from colorectal cancer occurred. After adjustment for multiple colorectal cancer risk factors, regular use of vitamin C or E supplements, even long-term use, was not associated with colorectal cancer mortality. The combined-sex rate ratios were 0.89 [95% confidence interval (CI), 0.73–1.09] for 10 or more years of vitamin C use and 1.08 (95% CI, 0.85–1.38) for 10 or more years of vitamin E use. In subgroup analyses, use of vitamin C supplements for 10 or more years was associated with decreased risk of colorectal cancer mortality before age 65 years (rate ratio = 0.48; 95% CI, 0.28–0.81) and decreased risk of rectal cancer mortality at any age (rate ratio = 0.40; 95% CI, 0.20–0.80). Our results do not support a substantial effect of vitamin C or E supplement use on overall colorectal cancer mortality.

Introduction

Vitamin C and vitamin E, both important antioxidants, may reduce the risk of cancer by neutralizing reactive oxygen species or other free radicals that can damage DNA (1–3). With respect to colorectal cancer, vitamin C and E inhibit colorectal cancer in rodent models (4–6), and supplementation with vitamin C or E decreases fecal mutagenicity in humans (7). If vitamin C or E supplement use substantially reduces the risk of colorectal cancer, there could be important public health implications because vitamin supplements are relatively inexpensive and easy to use and because colorectal cancer is the third most common cause of cancer death in men and women in the United States (8). Only three prospective studies have examined the association between colon or colorectal cancer and use of vitamin C or E supplements (9–11). Some results from these prospective studies suggest a reduction in risk, particularly for vitamin E supplementation. However, none of these studies reported results by duration of vitamin supplement use. We therefore examined the association between colorectal cancer mortality and the use of individual vitamin C or E supplements, particularly long-term use, in a large prospective study of adults in the United States.

This analysis focuses on vitamin C or E intake specifically from individual vitamin C or E supplements, rather than intake from diet, multivitamins, or from all sources combined. Most individual vitamin C or E supplements contain doses several times greater than those typically obtained from diet or multivitamins.

Materials and Methods

Study Cohort and Follow-Up. Subjects in this analysis were drawn from the 508,351 male participants and 676,306 female participants in CPS-II.[2] These participants were enrolled in 1982 by American Cancer Society volunteers in all 50 states of the United States, the District of Columbia, and Puerto Rico as described previously (12). Participants completed a four-page baseline self-administered questionnaire in 1982 that included information on demographic characteristics and various behavioral, environmental, occupational, and dietary factors. The median age at enrollment was 57 years for men and 56 years for women; no participants were younger than 30 years.

The vital status of study participants was determined through December 31, 1996 using two approaches. American Cancer Society volunteers made personal inquiries in September 1984, 1986, and 1988 to determine whether the participants they had enrolled were alive or dead and to record the date and place of all deaths. Reported deaths were verified by obtaining death certificates. Automated linkage using the National Death Index (13) extended follow-up of the entire cohort through December 31, 1996 and identified deaths among the 21,704 participants lost to follow-up between 1982 and 1988. At the completion of follow-up in December 1996, 237,452 participants had died (20.0%), 944,313 were alive (79.7%), and 2,892 (0.2%) had follow-up truncated on September 1, 1988 because of insufficient data for National Death Index linkage. Death certificates or codes for cause of death were obtained for 98.6%

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[2] The abbreviations used are: CPS-II, Cancer Prevention Study II; RR, rate ratio; CI, confidence interval; BMI, body mass index; OR, odds ratio.

of all deaths. The underlying cause of death was coded from death certificates according to the ninth revision of the International Classification of Disease (ICD-9; Ref. 14). Colorectal cancer deaths were defined as ICD-9 codes 153.0–153.9 (colon cancer) or 154.0–154.9 (rectal cancer).

We excluded participants who reported a history of cancer other than nonmelanoma skin cancer (n = 82,349) or did not provide complete information on frequency and duration of use for all four vitamin supplements (vitamin A, vitamin C, vitamin E, and multivitamins) listed on the questionnaire (n = 158,180). We also excluded participants who reported less than weekly use of one or more of the vitamin supplements (n = 110,684) because it is unclear whether such irregular use at enrollment is likely to have adequately represented long-term patterns of vitamin use. In addition, we excluded 17,628 participants who reported identical frequency and duration for all four vitamin supplements because it is possible that many of these participants were reporting components of their multivitamin on the questions intended to measure use of individual vitamin supplements. Finally, we excluded 103,925 participants with missing information on diet, education, or BMI. Analyses are based on the remaining 711,891 participants (334,125 men and 377,766 women).

Ascertainment of Vitamin Supplement Use. Vitamin supplement use was ascertained from the 1982 baseline questionnaire, which included a section asking about duration and frequency of current use of four vitamin supplements (vitamin A, vitamin C, vitamin E, and multivitamins). Specifically, participants were asked to fill in two boxes for each vitamin, with the first box reporting the number of times in the last month they had used this vitamin, and the second box reporting the number of years of use. In this analysis, we considered participants reporting use of a particular vitamin 25 or more times during the past month to be "daily users." No information was collected on the dose or brand of vitamin supplements, use of any other dietary supplements, or any past vitamin supplement use that had been discontinued before study enrollment.

Statistical Analysis. We used Cox proportional hazards modeling to examine the association of vitamin C and E supplement use with colorectal cancer mortality while adjusting for other potential risk factors. The time-axis used was follow-up time since enrollment in 1982. Age adjustment was accomplished by stratifying on exact year of age at enrollment within each Cox model (15). All Cox models were also adjusted for educational level, BMI, use of aspirin and estrogen replacement therapy, and consumption of two food groups (vegetables and high-fiber grain foods) associated with decreased risk of colorectal cancer mortality in this cohort (16). All covariates, other than age, were modeled as dummy variables using the categories shown in Table 1. Women who left all of the questions on postmenopausal estrogen use blank were categorized as never users. Food consumption variables were derived from items on the questionnaire that asked about the frequency of consumption of 32 common food items. The derivation of food group variables from this questionnaire has been described previously (16). Of particular relevance to this analysis, the vegetable variable was derived by summing the numbers of days per week that each participant reported eating each of the seven vegetable items on the questionnaire (carrots, tomatoes, potatoes, squash/corn, green leafy vegetables, raw vegetables, and cabbage/broccoli/brussels sprouts). Similarly, the high-fiber grain foods variable was derived by summing reported consumption of three food items (bran/corn muffins, brown rice/whole wheat/barley, and oatmeal/shredded wheat/bran cereals). In combined sex models, we also included interaction terms between sex and each BMI category to account for the somewhat different association of BMI with colorectal cancer mortality by sex in this cohort (17). Race, marital status, cigarette smoking, cigar and pipe smoking, alcohol use, exercise level, consumption of citrus fruits/juices, consumption of low fat meats (fish and chicken), consumption of high fat meats (red meat), family history of colorectal cancer, and personal history of colorectal polyps, diabetes, heart disease, or hypertension were also examined as potential confounders. However, we did not adjust for these factors in final models because such adjustment had virtually no effect on our results. All models also included dummy variables for each combination of frequency ($<$25 times per month, $\geq$25 times per month) and duration of use ($<$10 years, $\geq$10 years) of multivitamins, vitamin A, vitamin C, and vitamin E.

To determine whether the association of vitamin supplement use with colorectal cancer mortality was modified by demographic factors or factors that may affect nutrient status, we examined results stratified by attained age, sex, education level, BMI, multivitamin use, cigarette smoking, and alcohol consumption. We also examined results stratified by subsite (colon *versus* rectum) and follow-up year. In addition to examining stratified results, we calculated two-sided P*s* to examine whether the RRs associated with long-term vitamin C or E use and colorectal cancer differed by subsite or any of the potential effect modifiers listed above. *P*s were calculated using the Wald's test statistic when examining differences in associations by subsite and attained age and using the likelihood ratio statistic associated with an interaction term for all other potential effect modifiers (18).

We did not examine results stratified by dietary intake of vitamin C or E for two reasons. First, our dietary data may not be sufficiently detailed to provide accurate estimates of these micronutrients. Second, for an analysis stratified by dietary intake of vitamin C or E to be meaningful, we would first need to exclude users of multivitamins, which contain considerable amounts of vitamin C and E. After this exclusion, our statistical power to investigate the effects of vitamin C or E would be limited because many vitamin C or E supplement users also used multivitamins.

Results

During the 14 years of follow-up (1982–1996), there were 4404 deaths from colorectal cancer among participants included in this analysis. Of these deaths, 2468 occurred in men, and 1936 occurred in women.

Table 1 compares baseline characteristics of participants who were daily users of individual vitamin C or E supplements with baseline characteristics of participants who reported no use of either vitamin C or E supplements. The great majority of participants were white and middle-aged or elderly, regardless of vitamin use. However, daily users of vitamin C or E supplements were slightly more likely than nonusers to be white. Compared with nonusers, daily vitamin C or E users were much more likely to use multivitamins and slightly more likely to be well educated, to have low BMI, to report frequent consumption of vegetables and high-fiber grain foods, and to use aspirin regularly. Male daily vitamin C or E users were slightly less likely to be current cigarette smokers, and female daily vitamin C or E users were somewhat more likely to be former cigarette smokers. Female daily vitamin C or E users were also more likely than nonusers to be current or former users of estrogen replacement therapy. In this cohort, as in other epidemiological studies, aspirin use (19), estrogen replacement therapy (20),

Table 1 Colorectal cancer mortality risk factors by use of vitamin C and vitamin E supplements at cohort enrollment[a]: CPS-II, 1982–1996

	Women			Men		
	No vitamin C or E use (n = 310,166) %	Vitamin C daily use (n = 46,037)[b] %	Vitamin E daily use (n = 33,833)[c] %	No vitamin C or E use (n = 286,376) %	Vitamin C daily use (n = 32,597)[b] %	Vitamin E daily use (n = 22,274)[c] %
Age (yrs)						
30–39	5.9	4.4	3.3	3.9	2.7	1.6
40–49	24.3	21.5	21.1	19.6	16.2	13.2
50–59	34.4	38.6	40.6	38.6	38.8	38.4
60–69	24.2	26.9	26.8	27.3	31.8	35.1
70–79	9.2	7.5	7.2	9.1	9.5	10.6
≥80	2.1	1.2	1.0	1.4	1.1	1.1
Race						
White	93.2	96.6	96.6	94.5	97.2	96.9
Black	4.7	1.7	1.8	3.4	1.2	1.4
Other	2.1	1.7	1.7	2.0	1.6	1.6
Education						
Less than high school	13.8	7.8	9.0	16.2	9.0	10.7
High school graduate	32.6	27.6	30.0	21.4	15.5	17.0
Some college	29.0	33.7	33.5	26.8	27.4	29.2
College graduate	14.8	17.3	15.5	17.6	22.4	20.6
Graduate school	9.9	13.6	12.0	18.0	25.8	22.5
BMI (kg/m^2)						
<20.0	9.4	12.1	11.4	2.3	2.1	1.9
20.0–<22.5	24.8	31.1	30.6	9.8	12.1	10.8
22.5–<25.0	25.5	26.1	26.6	26.0	31.3	29.7
25.0–<27.5	18.5	16.0	16.1	33.9	33.6	34.8
27.5–<30.0	9.2	6.7	7.0	16.7	13.3	14.3
≥30.0	12.7	8.0	8.3	11.2	7.6	8.6
Exercise level						
None	2.4	1.6	1.5	2.3	1.6	1.5
Slight	24.8	23.8	22.7	22.3	22.2	21.4
Moderate	65.6	67.4	68.5	62.8	63.5	63.6
Heavy	5.6	6.0	6.2	11.7	12.0	12.7
Unclassifiable	1.6	1.2	1.2	0.9	0.8	0.7
Vegetable consumption (servings/day)[d]						
<1	13.6	6.9	7.4	14.9	8.2	8.7
1–<2	24.6	19.2	19.7	30.3	25.4	25.4
2–<3	30.4	30.8	30.4	30.7	32.2	32.2
≥3	31.4	43.2	42.6	24.1	34.1	33.6
High-fiber grain foods[e] (servings/week)						
<1	44.1	28.6	29.7	43.1	28.2	28.6
1–<3	15.2	13.2	13.4	16.8	15.0	14.9
3–<6	18.3	20.4	20.2	18.0	19.8	19.8
≥6	22.3	37.9	36.7	22.1	36.9	36.7
Multivitamin use						
None	83.6	39.3	40.8	87.7	43.2	43.4
Less than daily						
<10 yrs	1.6	1.4	1.3	1.2	1.5	1.1
≥10 yrs	1.0	1.0	0.7	0.9	1.1	0.8
Daily						
<10 yrs	7.7	28.5	29.2	5.3	26.3	27.2
≥10 yrs	6.1	29.8	28.0	4.9	27.9	27.4
Cigarette smoking						
Never	53.5	51.1	51.7	44.5	50.2	49.2
Current	20.9	18.7	18.0	22.0	16.5	16.3
Former	19.6	26.2	26.1	29.5	30.9	31.9
Unclassifiable	6.0	4.0	4.2	4.1	2.4	2.6
Aspirin use (times/month)						
None	40.1	35.4	36.4	45.0	38.3	40.2
Occasional	36.6	35.8	35.6	32.0	31.1	29.9
1–9	14.5	14.1	13.7	14.5	15.0	13.8
≥10	8.8	14.8	14.3	8.5	15.6	16.1
Estrogen replacement therapy						
Never	70.0	59.1	58.0			
Current use						
<5 yrs	2.6	3.5	3.7			
≥5 yrs	5.0	8.4	8.4			
Former use						
<5 yrs	9.5	11.8	11.8			
≥5 yrs	5.3	8.2	8.5			
Ever use unspecified	7.6	9.0	9.5			

[a] Percentages adjusted to the age distribution of the entire study population.
[b] Includes users of vitamin E or other vitamin supplements.
[c] Includes users of vitamin C or other vitamin supplements.
[d] Based on consumption of seven food items (carrots, tomatoes, potatoes, squash/corn, green leafy vegetables, raw vegetables, and cabbage/broccoli/Brussels sprouts).
[e] Based on consumption of three food items (bran/corn muffins, brown rice/whole wheat/barley, and oatmeal/shredded wheat/bran cereals).

Table 2 RRs and 95% CIs for colorectal cancer mortality associated with daily use of vitamin C or vitamin E supplements at cohort enrollment[a]: CPS-II, 1982–1996

	Men and women combined	Men only	Women only
Vitamin C use			
Nonuser			
RR	1.00 (ref)	1.00 (ref)	1.00 (ref)
Deaths/participants	3,914/615,867	2,200/293,821	1,714/322,046
<10 yrs			
RR	0.99	1.15	0.84
95% CI	0.85–1.15	0.94–1.40	0.67–1.05
Deaths/participants	252/48,139	146/19,346	106/28,793
≥10 yrs			
RR	0.89	0.75	1.05
95% CI	0.73–1.09	0.57–1.00	0.80–1.38
Deaths/participants	169/30,495	80/13,251	89/17,244
Vitamin E use			
Nonuser			
RR	1.00 (ref)	1.00 (ref)	1.00 (ref)
Deaths/participants	4,035/642,761	2,272/306,374	1,763/336,387
<10 yrs			
RR	0.87	0.82	0.92
95% CI	0.73–1.03	0.64–1.04	0.72–1.17
Deaths/participants	193/39,757	99/14,719	94/25,038
≥10 yrs			
RR	1.08	1.13	1.05
95% CI	0.85–1.38	0.82–1.57	0.73–1.49
Deaths/participants	108/16,350	59/7,555	49/8,795

[a] Adjusted for age, sex (for combined sex results), education, BMI, vegetable consumption, consumption of high-fiber grain foods, vitamin supplement use (vitamins A, C, or E and multivitamin supplements), and use of aspirin and estrogen replacement therapy.

physical activity, and consumption of vegetables and high-fiber grains (16) are associated with reduced risk of colon cancer mortality, whereas high BMI is associated with increased risk (17).

Overall, we found no evidence of reduced risk of colorectal cancer mortality associated with daily use of individual vitamin C or E supplements, even for long-term use (Table 2). However, there was a suggestion of decreased risk for men with daily vitamin C use of 10 or more years at enrollment (RR = 0.75; 95% CI, 0.57–1.00), but not for women (RR = 1.05; 95% CI, 0.80–1.38). There were few participants who reported less than daily vitamin supplement use (<25 uses per month). Therefore, results for less-than-daily vitamin supplement use were not informative and are not shown. Results were similar when we excluded participants reporting weight loss of 10 or more pounds during the year before study enrollment or when we excluded the first 2 years of follow-up (data not shown). RRs adjusted only for age and sex were somewhat lower than the multivariate adjusted RRs shown in Table 2 [age- and sex-adjusted RR = 0.77 (95% CI, 0.66–0.90) for ≥10 years of vitamin C use; age- and sex-adjusted RR = 0.86 (95% CI, 0.71–1.04) for ≥10 years of vitamin E use].

Table 3 shows multivariate-adjusted RRs for colorectal cancer mortality associated with vitamin C and vitamin E supplement use by attained age, multivitamin use, follow-up year, and tumor subsite (colon or rectum). Long-term use (10 or more years) of vitamin C was associated with substantially decreased risk of colorectal cancer mortality before age 65 years (RR = 0.48; 95% CI, 0.28–0.81), but not at age 65 years or after (RR = 1.02; 95% CI, 0.83–1.26; $P = 0.009$ for interaction by age group). Long-term vitamin C use was also associated with decreased risk of rectal cancer mortality at all ages (RR = 0.40; 95% CI, 0.20–0.80) but was not associated with decreased risk of colon cancer mortality (RR = 0.98; 95% CI, 0.80–1.20; $P = 0.01$ for difference by subsite). There was some suggestion that long-term vitamin E use was associated with decreased risk of colorectal cancer mortality in participants who were current cigarette smokers at enrollment (RR = 0.60; 95% CI, 0.31–1.16) but not in never or former cigarette smokers, although the interaction between cigarette smoking and long-term vitamin E use was not statistically significant ($P = 0.13$). Otherwise, we found little evidence of differences in the association between colorectal cancer mortality and vitamin C or E supplement use by age, multivitamin use, follow-up year, or subsite (Table 3) or by education level, BMI, cigarette smoking status, or alcohol use (results not shown). In addition, we found little evidence of interaction between daily vitamin C and daily vitamin E use, regardless of whether or not users of multivitamins (which contain lower doses of vitamin C and E) were included or excluded.

To estimate the continuity of vitamin supplement use during the follow-up period, we compared vitamin supplement use reported on the baseline 1982 CPS-II questionnaire with use reported on a 1992–1993 follow-up questionnaire completed by a subgroup of CPS-II participants from 21 selected states. Among the 112,698 participants included in this analysis who also completed the 1992–1993 questionnaire, the proportion of daily vitamin supplement users in 1982 who were using the same vitamin supplement in 1992 was similar in men and women and relatively high for use of individual vitamin C supplements (58% reported daily use, and 68% reported at least weekly use) and individual vitamin E supplements (54% reported daily use, and 63% reported at least weekly use). The proportion of participants reporting no use of a particular vitamin supplement in 1982 but at least weekly use of this vitamin supplement on the 1992–1993 questionnaire was 13% for vitamin C and 11% for vitamin E.

Discussion

In this large prospective study, we found little association between use of either vitamin C or E supplements and risk of colorectal cancer, despite being able to examine long-term supplement use. Our generally null results are important given that some recent study results have suggested a substantial protective effect of these antioxidant supplements. For example, vitamin E supplement use was associated with a 50% decrease in risk of colon cancer in the Iowa Women's Health Study (10).

Our results concerning vitamin C supplement use (RR = 0.89; 95% CI, 0.73–1.09 for ≥10 years of use) are generally consistent with results from two cohort studies of supplemental vitamin C and colon cancer incidence, each of which included about 200 cases. In the Iowa Women's Health Study cohort (follow-up from 1986–1990; Ref. 10), high average daily intake of supplemental vitamin C (predominantly from individual vitamin C supplements) at study baseline was not associated with colon cancer risk after adjustment for potential confounders, including vitamin E intake. In the California Leisure World retirement community cohort (follow-up from 1981–1989), intake of any supplemental vitamin C (from either multivitamins or individual vitamin C supplements) at baseline was not associated with colon cancer risk in men but was associated with modestly decreased risk in women (RR = 0.67; 95% CI, 0.45–0.99; Ref. 9). In contrast, two population-based case-control studies, a study of colon cancer incidence in the Seattle

Table 3 RRs and 95% CIs for colorectal cancer mortality associated with daily use of vitamin C or vitamin E supplements by attained age, multivitamin use, follow-up year, and tumor subsite[a]: CPS-II, 1982–1996

	Vitamin C supplements		Vitamin E supplements	
	<10 years of use	≥10 years of use	<10 years of use	≥10 years of use
Attained age (yrs)				
<65				
RR (95% CI)	0.75 (0.54–1.05)	0.48 (0.28–0.81)	0.81 (0.56–1.17)	1.52 (0.86–2.70)
Deaths[b]	54	23	42	19
≥65				
RR (95% CI)	1.08 (0.91–1.28)	1.02 (0.83–1.26)	0.89 (0.73–1.08)	1.00 (0.77–1.31)
Deaths[b]	198	146	151	89
Multivitamin use[c]				
No use				
RR (95% CI)	1.02 (0.84–1.25)	0.91 (0.67–1.21)	0.84 (0.66–1.07)	1.23 (0.86–1.77)
Deaths[b]	135	70	97	48
Daily use				
RR (95% CI)	0.96 (0.76–1.21)	0.89 (0.68–1.17)	0.89 (0.70–1.15)	1.02 (0.74–1.42)
Deaths[b]	113	93	93	58
Follow-up year				
1982–1989				
RR (95% CI)	0.91 (0.71–1.16)	0.77 (0.56–1.07)	0.71 (0.53–0.95)	1.08 (0.74–1.58)
Deaths[b]	90	63	63	43
1990–1996				
RR (95% CI)	1.05 (0.87–1.27)	0.98 (0.76–1.26)	0.98 (0.79–1.21)	1.09 (0.80–1.49)
Deaths[b]	162	106	130	65
Subsite				
Colon				
RR (95% CI)	0.98 (0.83–1.15)	0.98 (0.80–1.20)	0.91 (0.76–1.10)	1.02 (0.79–1.31)
Deaths[b]	215	156	171	93
Rectum				
RR (95% CI)	1.08 (0.73–1.62)	0.40 (0.20–0.80)	0.61 (0.37–1.01)	1.78 (0.94–3.35)
Deaths[b]	37	13	22	15

[a] This includes both sexes. Adjusted for age, sex, education, BMI, vegetable consumption, consumption of high-fiber grain foods, vitamin supplement use (vitamins A, C, or E and multivitamin supplements), and use of aspirin and estrogen replacement therapy.
[b] Deaths among users of specified vitamin supplement only.
[c] Multivitamin use at study baseline, less than daily multivitamin users excluded.

area with about 400 cases (21) and a study of colorectal cancer incidence in Australia with about 700 cases (22), found high average daily intake of supplemental vitamin C (likely predominantly from individual vitamin C supplements) to be associated with decreased risk in both sexes. It is possible that the reduced risk associated with vitamin C supplement use observed in some of these studies may be due at least in part to confounding by use of other dietary supplements because only the Iowa Women's Health Study analysis (10) presented risk estimates adjusted for use of any other supplemental vitamins.

In subanalyses, we found that long-term vitamin C supplement use was associated with decreased risk of colorectal cancer mortality in men and in both sexes before age 65 years. Results from these subanalyses should be interpreted cautiously. No previous study has suggested that vitamin C supplement use is associated with a stronger reduction in risk for men than for women or for younger rather than older people.

In additional subanalyses, we found that long-term vitamin C supplement use was associated with substantially decreased risk of rectal cancer mortality but not colon cancer mortality. The Australian case-control study found significantly decreased risk of both rectal and colon cancer incidence associated with vitamin C use (22). No other study has examined the effect of vitamin supplements of any type specifically on rectal cancer. We know of no reason to expect a specific effect of vitamin C on rectal rather than colon cancer. When interpreting subsite results, it should be acknowledged that death certificates often misclassify deaths due to rectal cancer as being due to colon cancer and (somewhat less frequently) misclassify colon cancer deaths as being due to rectal cancer (23). However, such misclassification would be expected to result in an underestimate of any effects that are limited to either the colon or rectum.

We found no association between vitamin E supplement use and risk of colorectal cancer mortality (RR = 1.08; 95% CI, 0.85–1.38 for ≥10 years of use). Results from previous epidemiological studies have been inconsistent. Two of four studies of colon cancer incidence (9–11, 21), the Iowa Women's Health Study cohort (10) and the Seattle area case-control study (21), found substantial reductions in risk of colon cancer associated with high daily intake of supplemental vitamin E (predominantly from individual vitamin E supplements). In the Seattle case-control study (21), high average daily intake of supplemental vitamin E over a 10-year period before the reference date was associated with an OR of 0.4 (95% CI, 0.3–0.7). Similarly, in the Iowa Women's Health Study cohort (10), high daily intake of supplemental vitamin E at study baseline was associated with a RR of 0.5 (95% CI, 0.3–0.9). In contrast, there was no association between vitamin E supplement use and colon cancer incidence in the California Leisure World cohort (supplement use measured at study baseline; Ref. 9) or in a large United States multisite case-control study with nearly 2000 cases (supplement use measured at reference date; Ref. 24). A randomized trial in Finnish male smokers (11) reported a RR of 0.78 (95% CI, 0.55–1.09) for colorectal cancer incidence after an average of 6 years of supplementation and follow-up, but these results may be of limited relevance due to

the short duration of exposure and the use of relatively low doses of vitamin E (50 IU/day).

Our results for both vitamin C and E supplement use are consistent with results from randomized trials examining the occurrence of new colorectal polyps after colonoscopy. Although an Italian trial found combined vitamin A, C, and E supplementation was associated with decreased risk of colorectal polyps (25), a Canadian trial (26) and a large United States trial (27) found no reduction in risk after combined supplementation with vitamin C and vitamin E.

There are several possible explanations that should be considered that might explain why we found little association between vitamin C or E supplement use and either colon or colorectal cancer, whereas some previous studies have found substantially decreased risk. First, we examined mortality rather than incidence. In theory, poorer survival from colorectal cancer among vitamin supplement users than among nonusers could account for the lack of association observed in our mortality study, although we know of no reason to expect such a difference. Second, any association between vitamin C or E supplement use and colorectal cancer could be stronger among younger people and therefore less evident in our older study population, in which the median age at death from colorectal cancer was 72 years. This hypothesis is consistent with the reduced risk of colorectal cancer mortality before age 65 years associated with vitamin C supplement use in our study but is less consistent with our results for vitamin E supplement use. Third, there could have been important differences in the dose or duration of vitamin C or E supplement use in our cohort compared with other study populations. However, we know of no reason to believe that vitamin supplement dose varied substantially between our nationwide study population and the other United States study populations, which were studied during similar time periods. Differences in duration of vitamin supplement use also seem to be an unlikely explanation for the lack of association in our study, given that we specifically examined long-term use and found little association. Finally, the differences in results between studies could be due to chance. However, given the large size of our study, it is unlikely that chance alone could have obscured a strong effect of vitamin C or E supplement use.

As in any observational study, the effect of potential confounding factors needs to be considered. This is particularly true for analyses of vitamin supplement use because vitamin users may be more likely to have health conscious behaviors. Although we were able to adjust (or determine that adjustment was unnecessary) for many potential confounding factors, we had no information on colorectal cancer screening or use of dietary supplements other than vitamins A, C, and E or multivitamins. In addition, we had only relatively crude measures of diet and physical activity. However, any confounding from these factors would be expected to bias our results toward finding vitamin supplement use to be associated with reduced of risk of colorectal cancer mortality; we observed little evidence of such a reduction in risk.

One limitation of this analysis was that we had no information about past use of vitamin supplements for participants who were former vitamin supplement users at baseline. Our referent group therefore likely included some former vitamin C and E supplement users. Our results could be biased toward the null if a large proportion of our participants were former vitamin C or E users who had used these supplements for a long enough period of time to affect the risk of colorectal cancer mortality. However, such bias is not likely to have obscured a strong effect of vitamin C or E supplement use.

A second limitation was that we had no updated information on vitamin use after study baseline. If vitamin C or E supplement use affects later stages of colorectal carcinogenesis, the lack of updated vitamin use information could have biased our results toward the null during later years of the 14-year follow-up period. However, we found no association between either vitamin C or E supplement use and colorectal cancer mortality during the first 7 years of follow-up, when the lack of updated vitamin use information would not be expected to substantially effect results.

An additional limitation of this analysis is that we had no information on vitamin dose. However, it is likely that the doses of vitamin C and E obtained from individual supplements in our United States study population were similar to those reported during the same time period in the Nurse's Health Study, which also included participants from throughout the United States. In 1982 (the year the CPS-II questionnaire was administered), 80% of the participants in the Nurse's Health Study who were taking vitamin C supplements (and knew their dose) reported a dose of 400 mg or more. Similarly, 88% of nurses who were taking vitamin E supplements (and knew their dose) reported a dose of 200 IU or more.[3] Regardless of the exact supplement doses used, it is likely that most of our individual vitamin C or E supplement users had total vitamin C and E intakes several times higher than those receiving vitamin C or E only from diet and/or multivitamins. Mean daily dietary intake in the United States is approximately 100 mg of vitamin C and 10–15 IU of vitamin E (28–30), and multivitamins typically contain 60 mg of vitamin C and 30 IU of vitamin E.

Important strengths of this analysis are its prospective design, large size, and the availability of information on duration of supplement use. The large size of this study allowed us to examine the effect of vitamin supplements stratified by potentially important effect modifiers, such as age, multivitamin use, and follow-up time. In addition, we were able to obtain fairly precise estimates for long-term use of each type of vitamin supplement, even when adjusting for use of other vitamin supplements. No previous prospective study has examined the association between long-term use of vitamin C and E supplements and colorectal cancer.

In conclusion, our results do not support a substantial effect of even relatively long-term use of vitamin C or vitamin E supplements on risk of colorectal cancer mortality. However, our data cannot rule out effects in populations with poor nutrition or effects that are modest or limited to specific subgroups.

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