Vitamin C, Vitamin E, and Multivitamin Supplement Use and Stomach Cancer Mortality in the Cancer Prevention Study II Cohort

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Abstract

Supplementation with antioxidant vitamins has been associated with decreased risk of stomach cancer or regression of precancerous lesions in high-risk areas of China and Colombia. We examined the association between stomach cancer mortality and regular use (≥15 times per month) of individual vitamin C supplements, individual vitamin E supplements, and multivitamins among 1,045,923 United States adults in the Cancer Prevention Study II (CPS-II) cohort. CPS-II participants completed a questionnaire at enrollment in 1982 and were followed for mortality through 1998. During follow-up, there were 1,725 stomach cancer deaths (1,127 in men and 598 in women). After adjustment for multiple potential stomach cancer risk factors, vitamin C use at enrollment was associated with reduced risk of stomach cancer mortality [rate ratio (RR), 0.83; 95% confidence interval (CI), 0.68–1.01]. However, this reduction in risk was observed only among participants with short duration use at enrollment (RR, 0.68; 95% CI, 0.51–0.91 for <10 years of use; RR, 1.00; 95% CI, 0.73–1.38 for ≥10 years of use). There was no association between stomach cancer mortality and regular use of vitamin E (RR, 1.02; 95% CI, 0.82–1.27) or multivitamins (RR, 0.89; 95% CI, 0.77–1.03), regardless of duration of use. Our results suggest that the use of vitamin C, vitamin E, or multivitamin supplements may not substantially reduce risk of stomach cancer mortality in North American populations in which stomach cancer rates are relatively low. Our results do not rule out effects of vitamin supplementation in areas in which stomach cancer rates are high and stomach cancer etiology may differ.

Introduction

Stomach cancer is the second most common cause of cancer mortality worldwide (1). Prevention of stomach cancer is important because at the time of diagnosis, most tumors are too advanced to be curable (2). Stomach cancer mortality rates vary widely geographically. Rates are highest in Japan, Russia, and many developing countries in Asia and South America, intermediate in western Europe, and relatively low in the United States (3). However, even in the United States, stomach cancer caused an estimated 12,800 deaths in 2001 (4). Fruits and vegetables, which contain a variety of antioxidants, are generally believed to reduce stomach cancer risk (1).

Vitamin C, an important antioxidant, may inhibit carcinogenesis in the stomach by neutralizing reactive oxygen species that can damage DNA (5) or by inhibiting the formation of carcinogenic nitrosamines (6–8). Epidemiological evidence, although limited, is consistent with a reduction in stomach cancer risk associated with high doses of supplemental vitamin C. In a recent randomized trial in a high-risk area of Colombia, vitamin C supplementation (2000 mg/day) was associated with regression of precancerous stomach lesions (9). An earlier randomized trial in Linxian (China) found no reduction in stomach cancer risk but used low doses of vitamin C (120 mg/day; 10). A multicenter population-based case-control study in the United States found vitamin C supplement use (but not use of other supplements) to be associated with a decreased risk of cancer in both the distal stomach and the gastric cardia (11). Observational studies of vitamin C serum levels and dietary intake are also consistent with a reduction in stomach cancer risk. High serum levels of vitamin C were associated with strongly decreased risk of stomach cancer or dysplasia in prospective studies in China (12) and Switzerland (13). Dietary vitamin C was associated with decreased risk of stomach cancer in 12 of 13 case-control studies, whereas there have been no cohort studies of sufficient size to be informative (1). Most of these case-control studies have found high vitamin C intake to be associated with a 30–70% decrease in stomach cancer risk (1).

Vitamin E or multivitamin supplements could plausibly decrease stomach cancer risk, although evidence for an effect of these supplements is less convincing than for vitamin C. Like vitamin C, vitamin E is an important antioxidant and could reduce stomach cancer through neutralization of free radicals (14) and inhibition of nitrosamine formation (15). A combination of vitamin E, selenium, and β-carotene reduced stomach cancer risk in the Linxian (China) trial (10), but vitamin E supplementation was not associated with stomach cancer risk in the α-Tocopherol β-Carotene (ATBC) trial among male Finnish smokers (16) or in a large multicenter population-based case-control study in the United States (11). Multivitamins typically contain low doses of vitamin C, vitamin E and other vitamins with potential for inhibiting carcinogenesis, including vitamin A and folic acid. However, multivitamin use was not associated with stomach cancer risk in either the Linxian trial (10) or a United States multicenter case-control study (11).

To our knowledge, the only prospective studies of vitamin

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supplementation and stomach cancer risk are the randomized trials described above among male Finnish smokers (16) or in very-high-risk populations within Colombia (9) and China (10). We therefore examined the association between the use of vitamin C, vitamin E, and multivitamin supplements and stomach cancer mortality in a large cohort of United States men and women. We examined the use of individual vitamin C or vitamin E supplements, rather than total intake of each of these vitamins from all dietary and supplemental sources combined. In the United States, most individual vitamin C or vitamin E supplements contain doses much higher than those typically obtained from diet or multivitamins. Therefore, users of individual vitamin C or vitamin E supplements are likely to have had substantially greater intake of these nutrients than nonusers, regardless of diet or multivitamin use. Most individual vitamin supplements in the United States contain a minimum of 250 mg of vitamin C and 200 IU of vitamin E. Mean dietary intake in the United States is about 100 mg of vitamin C and 10–15 IU of vitamin E (17–19), and multivitamins typically contain 60 mg of vitamin C and 30 IU of vitamin E.

Materials and Methods

Study Cohort and Follow-Up. Subjects in this analysis were drawn from the 1,184,622 participants (508,334 men and 676,288 women) 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 (20). 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 vital status of study participants was determined through December 31, 1998, using two approaches. American Cancer Society volunteers made personal inquiries in September 1984, 1986, and 1988 to determine whether the participants that 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 (21) extended follow-up of the entire cohort through December 31, 1998, and identified deaths among the 21,704 participants lost to follow-up between 1982 and 1988. At the completion of the follow-up in December 1998, 283,636 (24.0%) participants had died, 898,090 (75.8%) were alive, and 2,896 (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 have been obtained for 98.8% of all known deaths. The underlying cause of death was coded according to the ICD-9 (22). Stomach cancer deaths were defined as ICD-9 codes 151.0–151.9.

All of the analyses excluded participants who at enrollment reported a history of cancer other than nonmelanoma skin cancer ($n = 82,345$) or who had incomplete or uninterpretable data on vitamin supplement use ($n = 56,354$). A total of 1,045,923 participants remained (460,737 men and 585,186 women) and were included in one or more specific analyses. Analyses of each specific vitamin supplement also excluded irregular vitamin users, defined as participants reporting unquantified "occasional" or use <15 times per month. Of irregular users of each vitamin supplement, >75% reported either unquantified occasional use or use only once per month. A total of 942,993 participants remained for analyses of vitamin C use, 981,426 participants for analyses of vitamin E use, and 925,035 participants for analyses of multivitamin use. Analyses of combinations of vitamin use presented in Table 3 excluded all participants reporting irregular use of vitamin C, vitamin E, or multivitamins, leaving 841,569 participants for analysis.

Ascertainment of Vitamin Supplement Use. All of the information on vitamin use was obtained from the 1982 baseline questionnaire, which included a section asking about duration and frequency of current use of four vitamin supplements (multivitamins, vitamin A, vitamin C, and vitamin E). Participants were asked to fill in two boxes for each vitamin, 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. Participants were instructed to report occasional use of each vitamin by reporting a frequency per month of "1/2." We considered participants reporting the use of vitamin C, vitamin E, or multivitamins 15 or more times during the past month to be "regular" users of that supplement. Approximately 90% of participants meeting this definition of regular use of vitamin C, vitamin E, or multivitamins reported use at least 25 times per month, a frequency consistent with daily use. Vitamin A supplement use was uncommon and, therefore, was not examined as a main exposure. 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 stopped before study enrollment.

Statistical Analysis. We used Cox proportional hazards modeling (23) to calculate RRs for stomach cancer mortality associated with use of vitamin C, vitamin E, and multivitamin supplement use while adjusting for other potential risk factors. RRs presented compare participants with regular use (15 or more times/month) of a specific vitamin with participants reporting no use of that vitamin supplement. As noted above, participants with irregular use of a specific vitamin supplement were excluded when examining that supplement as a main exposure. The time-axis used was follow-up time since enrollment in 1982. All of the Cox models included variables for use of vitamin C, vitamin E, and multivitamins. All of the models were also adjusted for age and for several additional factors associated with risk of stomach cancer in this cohort and in other study populations (race, educational level, cigarette smoking, aspirin use, and consumption of whole grains, citrus fruits/juices, and vegetables). We examined potential confounding by vitamin A supplement use, history of ulcers or Tagamet use, smokeless tobacco use, cigar and pipe smoking, birthplace, and parents' birthplace. However, we did not adjust for these factors in the final models because such adjustments had negligible effects on our results.

All covariates except age and vitamin supplement use were modeled as dummy variables using the categories shown in Table 1. Food consumption variables were derived from the dietary portion of the questionnaire, which asked how many days per week the participant ate each of 32 common food items. The dietary portion of the questionnaire has been described previously (24). Vegetable consumption was estimated by totaling the numbers of days per week that each participant reported eating each of the six vegetable items, other than potatoes, on the questionnaire (carrots, tomatoes, squash/corn, green leafy vegetables, raw vegetables, and cabbage/broccoli/Brussels sprouts) and dividing by seven. Similarly, the high-fiber grain foods variable was derived by totaling reported consumption of three questionnaire food items (bran/corn muf-

[2] The abbreviations used are: CPS-II, Cancer Prevention Study II; ICD-9, ninth revision of the International Classification of Disease; RR, rate ratio; CI, confidence interval.

Table 1 Stomach cancer mortality risk factors by vitamin supplement use at enrollment,[a] CPS-II, 1982–1998

	Women				Men			
	No use of multivitamins, vitamin C, or vitamin E (n = 311,184) %	Vitamin C regular use[b] (n = 76,932) %	Vitamin E regular use[b] (n = 56,998) %	Multivitamin regular use[b] (n = 124,928) %	No use of multivitamins, vitamin C, or vitamin E (n = 285,743) %	Vitamin C regular use[b] (n = 49,894) %	Vitamin E regular use[b] (n = 34,905) %	Multivitamin regular use[b] (n = 76,724) %
Age (yr)								
30–39	5.4	4.4	3.3	6.0	3.8	3.0	1.9	3.9
40–49	23.0	21.0	20.6	22.9	19.3	16.3	13.6	17.1
50–59	33.2	36.9	38.9	35.7	38.0	37.9	37.3	38.0
60–69	25.0	27.3	27.2	24.8	27.4	31.4	34.5	29.8
70–79	10.9	8.9	8.6	8.6	10.0	10.1	11.3	9.7
≥80	2.6	1.6	1.4	2.0	1.6	1.3	1.3	1.6
Race								
White	91.3	95.9	95.7	95.9	93.3	96.8	96.3	96.5
Black	6.3	2.2	2.4	2.3	4.4	1.5	1.9	1.7
Other	2.4	1.9	1.9	1.7	2.3	1.8	1.8	1.8
Education								
Less than high school	16.0	8.7	10.1	8.6	18.0	9.9	11.5	10.1
High school graduate	32.3	27.0	29.3	28.0	21.8	15.5	16.9	16.1
Some college	27.2	33.5	33.2	33.1	25.8	27.5	29.0	27.6
College graduate	13.4	16.7	14.9	16.9	16.2	21.5	20.0	21.8
Graduate school	8.9	13.2	11.5	12.5	16.3	24.8	21.8	23.6
Unclassifiable	2.1	1.0	1.0	0.9	1.8	0.8	0.8	0.8
Cigarette smoking								
Never	53.2	51.9	52.5	52.3	43.4	50.1	49.0	48.5
Current	21.0	18.3	17.5	18.8	22.3	16.5	16.6	18.3
Former	18.2	24.7	24.7	23.9	29.0	30.4	31.2	30.3
Unclassifiable	7.7	5.1	5.3	5.0	5.3	3.0	3.2	2.9
Vegetables[c] (servings/day)								
<1	17.1	9.0	9.6	10.0	22.3	12.9	13.4	14.6
1–<2	26.8	22.8	23.1	25.0	33.1	30.9	30.9	32.8
2–<3	25.0	29.4	29.1	29.6	23.1	29.2	28.8	28.3
≥3	18.2	30.1	29.2	27.1	12.8	21.5	21.5	19.1
Unclassifiable	12.9	8.7	9.0	8.4	8.7	5.5	5.5	5.3
Citrus fruits/juices (servings/wk)								
<1	21.9	14.1	14.8	13.8	26.0	15.7	17.1	16.1
1–<4	16.6	13.5	13.9	13.7	20.9	17.2	17.8	16.9
4–<7	14.8	15.9	16.0	15.6	15.6	17.2	17.4	16.7
≥7	33.7	47.8	46.2	48.5	28.9	44.4	42.3	45.0
Unclassifiable	12.9	8.7	9.0	8.4	8.7	5.5	5.5	5.3
High-fiber grains[d] (servings/wk)								
<1	40.4	26.3	27.1	29.2	40.8	26.4	27.1	29.9
1–<4	19.4	18.7	19.0	19.6	21.6	20.9	20.6	21.7
4–<7	12.6	16.9	16.6	16.6	13.4	17.8	17.6	17.1
≥7	14.7	29.4	28.4	26.1	15.5	29.4	29.3	26.1
Unclassifiable	12.9	8.7	9.0	8.4	8.7	5.5	5.5	5.3
Aspirin use (times/mo)								
None	43.4	36.0	37.1	35.1	47.4	39.3	40.8	38.4
Occasional	35.4	36.2	36.1	36.9	31.2	31.5	30.7	32.2
1–9	13.7	13.9	13.5	14.2	13.9	14.8	13.8	15.0
≥10	7.4	13.8	13.2	13.8	7.4	14.4	14.7	14.5

[a] Percentages adjusted to the age distribution of the entire study population. Table does not include participants who reported only irregular vitamin use. Regular use categories for different vitamin supplements are not mutually exclusive.
[b] Regular use defined as 15 or more times per month.
[c] Based on consumption of six food items (carrots, tomatoes, squash/corn, green leafy vegetables, raw vegetables, cabbage/broccoli/Brussels sprouts).
[d] Based on consumption of three food items (bran/corn muffins, brown rice/whole wheat/barley, oatmeal/shredded wheat).

fins, brown rice/whole wheat/barley, and oatmeal/shredded wheat/bran cereals). When included in the model as a covariate rather than as the main exposure, the use of each vitamin supplement was grouped into four categories (irregular use only, regular use of <10 years, regular use of ≥10 years, and regular use of unknown duration). As noted above, irregular users of each specific vitamin supplement were excluded from the model when that supplement was examined as the main exposure. Age was adjusted for by stratifying on exact year of age at enrollment within each Cox model (25).

We also examined whether the association between each vitamin supplement and stomach cancer varied by potential effect modifiers. Specifically, we examined the association between regular use of vitamin C, vitamin E, or multivitamin

use stratified by categories of attained age, race, education, body mass index, smoking, intake of vegetables or citrus fruits/juices, family history of stomach cancer, or history of ulcers or Tagamet use. In addition to examining stratified results, we calculated two-sided *P*s for interaction between regular use of each vitamin and potential effect modifiers using the likelihood ratio statistic (26).

Results

Among participants in this analysis, 19% were regular users of multivitamins, 12% were regular users of vitamin C, and 9% were regular users of vitamin E. These percentages are generally similar to those observed among middle-aged and elderly participants in a United States nationally representative sample from a similar time period (27). Table 1 compares participants who at enrollment were regular users of vitamin C, vitamin E, or multivitamins with participants who reported no use of any of these supplements. Most participants were white and middle-aged or elderly, regardless of vitamin use. Regular users of each type of vitamin supplement (vitamin C, vitamin E, or multivitamins) were generally similar with respect to potential stomach cancer risk factors. Compared with nonusers, regular users of vitamin C, vitamin E, or multivitamins were more likely to be white, to be college educated, to be nonsmokers, to use aspirin frequently, and to report more frequent consumption of vegetables, citrus fruits/juices, and high-fiber grain foods.

As expected, many participants used more than one type of vitamin supplement. About one-half of those reporting regular use of vitamin C also reported regular use of vitamin E (50%) or multivitamins (54%). Similarly, many regular users of vitamin E were also regular users of vitamin C (69%) or multivitamins (54%). Among regular multivitamin users, a minority were regular users of vitamin C (34%) or vitamin E (25%).

We found little evidence of reduced risk of stomach cancer mortality among regular users of vitamin C, vitamin E, or multivitamins (Table 2). Regular vitamin C use at enrollment was associated with reduced risk of stomach cancer mortality (RR, 0.83; 95% CI, 0.68–1.01). However, reduced risk was observed only among participants who, at enrollment, had used vitamin C for a relatively short duration of time (RR, 0.68, and 95% CI, 0.51–0.91 for $<$10 years use; RR, 1.00, and 95% CI, 0.73–1.38 for $\geq$10 years use). There was no association between stomach cancer mortality and use of Vitamin E (RR, 1.02; 95% CI, 0.82–1.27) or multivitamins (RR, 0.89; 95% CI, 0.77–1.03), regardless of duration of use. Exclusion of participants reporting 10 or more pounds weight loss during the year before enrollment did not substantially alter these results.

The associations between vitamin supplement use and stomach cancer mortality were somewhat stronger without multivariate adjustment for potential confounders. The age and sex adjusted RRs for regular use of vitamin C, vitamin E, and multivitamins were 0.75 (95% CI, 0.64–0.88), 0.84 (95% CI, 0.70–1.00), and 0.78 (95% CI, 0.68–0.89), respectively.

Because this analysis includes 16 years of follow-up after the collection of information on vitamin use, we examined whether the association between regular vitamin use and stomach cancer mortality was attenuated over time. There were no apparent differences in results by follow-up time. During the first 8 years of follow-up (1982–1990) the RRs for vitamin C, vitamin E, and multivitamins were 0.82 (95% CI, 0.61–1.09), 1.18 (95% CI, 0.83–1.69), and 0.94 (95% CI, 0.77–1.15), respectively. During the 2nd 8 years of follow-up (1991–1998) the RRs for vitamin C, vitamin E, and multivitamins were 0.85 (95% CI, 0.64–1.13), 0.94 (95% CI, 0.65–1.37), and 0.84 (95% CI, 0.68–1.03), respectively.

Because multivitamins contain some vitamin C and vitamin E (although usually at doses many times lower than those in individual supplements), we examined the association between regular use of vitamin C and vitamin E among nonusers of multivitamins. Neither regular vitamin C use (RR, 0.83; 95% CI, 0.63–1.08) nor vitamin E use (RR, 1.27; 95% CI, 0.96–1.68) was associated with stomach cancer mortality among nonusers of multivitamins.

Any effect of vitamin supplementation may be limited to those with diets low in specific vitamins. We, therefore, examined the association between stomach cancer mortality and the use of vitamin C, vitamin E, and multivitamins stratified by intake of citrus fruit (a major source of vitamin C) and by vegetable intake (a source of many vitamins). Vitamin C use was associated with reduced risk among participants with high intake (four or more times per week) of citrus fruits/juices (RR, 0.68; 95% CI 0.51–0.90), but not among participants with lower intake of citrus fruits/juices (RR, 1.08; 95% CI 0.78–1.51), although this difference could plausibly be attributable to chance ($P = 0.15$ for interaction). We found no other evidence that the associations between vitamin use and stomach cancer mortality differed by citrus or vegetable intake.

In additional subgroup analyses, regular vitamin C use was associated with decreased risk of stomach cancer mortality among former cigarette smokers (RR, 0.57; 95% CI, 0.38–0.85) but not among never smokers (RR, 0.88; 95% CI, 0.61–1.25) or current cigarette smokers (RR, 1.11; 95% CI, 0.72–1.71; $P = 0.30$ for interaction by smoking status, cigar and pipe smokers excluded). We found no evidence that the association between stomach cancer mortality and vitamin C, vitamin E, or multivitamin use was modified by age, race, education, body mass index, family history of stomach cancer, or a personal history of peptic ulcers or Tagamet use.

Table 3 shows RRs for stomach cancer mortality associated with each possible combination of regular use at enrollment of vitamin C, vitamin E, and multivitamins compared with no use of any of these supplements. Simultaneous use of vitamin C, vitamin E, and multivitamins at enrollment was associated with decreased risk (RR, 0.68; 95% CI, 0.48–0.95). However, use of various combinations of two vitamin supplements did not suggest synergistic effects. For example, use of vitamin C alone was associated with decreased risk (RR, 0.72; 95% CI, 0.50–1.03) whereas use of vitamin C and E together was associated with increased risk (RR, 1.23; 95% CI, 0.93–1.62).

To estimate the continuity of vitamin supplement use during the follow-up period, we compared use reported on the 1982 baseline CPS-II questionnaire with use reported on a 1992–93 follow-up questionnaire completed by a subgroup of ~184,000 CPS-II participants from 21 selected states. This subgroup of respondents to the 1992–93 questionnaire may have been somewhat more likely to continue or initiate vitamin use than participants in the cohort as a whole. Most users of each specific vitamin supplement in 1982 reported continued use of the same supplement ~10 years later, and relatively few nonusers in 1982 had begun using a new vitamin supplement. Among participants reporting regular use of a specific vitamin supplement in 1982, the prevalence of regular use of the same vitamin in 1992–93 was 55% for vitamin C, 50% for vitamin E, and 58% for multivitamins. Among participants reporting no use of a specific vitamin supplement in 1982, the prevalence of regular use of that vitamin supplement in 1992–93 was 10% for vitamin C, 9% for vitamin E, and 18% for multivitamins.

Table 2 RRs and 95% CIs for stomach cancer mortality associated with regular use of vitamin C, vitamin E, and multivitamin supplements at cohort enrollment[a] CPS-II, 1982–1998

	Men and women combined	Men only	Women only
Vitamin C use			
At enrollment			
Nonuser			
RR (95% CI)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Deaths/participants	1,403/816,167	924/370,332	479/445,835
Regular user			
RR (95% CI)	0.83 (0.68–1.01)	0.82 (0.64–1.06)	0.84 (0.61–1.17)
Deaths/participants	162/126,826	102/49,894	60/76,932
Duration of use at enrollment (yr)			
<10			
RR (95% CI)	0.68 (0.51–0.91)	0.71 (0.50–1.01)	0.64 (0.40–1.04)
Deaths/participants	66/65,268	43/25,361	23/39,907
≥10			
RR (95% CI)	1.00 (0.73–1.38)	1.04 (0.71–1.53)	0.94 (0.54–1.64)
Deaths/participants	65/41,565	44/17,381	21/24,184
Unknown years			
RR (95% CI)	0.97 (0.63–1.49)	0.76 (0.40–1.44)	1.20 (0.67–2.14)
Deaths/participants	31/19,993	15/7,152	16/12,841
Vitamin E use			
At enrollment			
Nonuser			
RR (95% CI)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Deaths/participants	1,476/889,523	972/401,373	504/488,150
Regular user			
RR (95% CI)	1.02 (0.82–1.27)	1.08 (0.82–1.42)	0.93 (0.65–1.34)
Deaths/participants	130/91,903	84/34,905	46/56,998
Duration of use at enrollment (yr)			
<10			
RR (95% CI)	1.11 (0.84–1.46)	1.12 (0.79–1.58)	1.11 (0.71–1.75)
Deaths/participants	71/55,167	45/19,763	26/35,404
≥10			
RR (95% CI)	0.99 (0.66–1.47)	0.92 (0.56–1.50)	1.14 (0.57–2.26)
Deaths/participants	38/22,467	25/10,007	13/12,460
Unknown years			
RR (95% CI)	0.82 (0.49–1.37)	1.26 (0.65–2.42)	0.48 (0.21–1.12)
Deaths/participants	21/14,269	14/5,135	7/9,134
Multivitamin use			
At enrollment			
Nonuser			
RR (95% CI)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Deaths/participants	1,297/723,383	854/338,206	443/385,177
Regular user			
RR (95% CI)	0.89 (0.77–1.03)	0.91 (0.76–1.09)	0.87 (0.69–1.10)
Deaths/participants	259/201,652	159/76,724	100/124,928
Duration of use at enrollment (years)			
<10			
RR (95% CI)	0.93 (0.75–1.14)	1.00 (0.77–1.29)	0.81 (0.57–1.15)
Deaths/participants	105/88,682	69/33,566	36/55,116
≥10			
RR (95% CI)	0.93 (0.75–1.14)	0.99 (0.76–1.29)	0.83 (0.58–1.19)
Deaths/participants	111/79,408	73/31,471	38/47,937
Unknown years			
RR (95% CI)	0.77 (0.56–1.06)	0.54 (0.33–0.90)	1.04 (0.69–1.58)
Deaths/participants	43/33,562	17/11,687	26/21,875

[a] Regular vitamin use defined as 15 or more times per month. RRs adjusted for age, sex (for combined sex results), race, education, smoking, consumption of vegetables, citrus fruits/juices, and high-fiber grains, and use of aspirin and vitamin supplements (vitamin C, vitamin E, and multivitamin supplements).

Discussion

In this large prospective study of United States adults, we found little association between use of vitamin C, vitamin E, or multivitamin supplements and risk of stomach cancer mortality. Our results are of interest because, despite promising results from trials in exceptionally high-risk populations in developing countries (9, 10), few studies have examined the potential effect of vitamin supplementation in populations from lower-risk populations in more developed countries.

In the CPS-II cohort, regular vitamin C use at enrollment was associated with slightly decreased risk of stomach cancer mortality (RR, 0.83; 95% CI, 0.68–1.01). However, this reduction in risk was observed solely for short duration vitamin C use. We know of no clear explanation, other than chance, for a

Table 3 RRs and 95% CIs for stomach cancer mortality associated with combinations of regular use of vitamin C, vitamin E, and multivitamin supplements at cohort enrollment,[a] men and women combined, CPS-II, 1982–1998

	Stomach cancer deaths	Participants	RR (95% CI)
No use	1,068	596,927	1.00 (ref)
Vitamin C only	30	24,644	0.72 (0.50–1.03)
Vitamin E only	22	11,703	1.07 (0.70–1.63)
Multivitamin only	152	106,367	0.94 (0.79–1.12)
Vitamin C and vitamin E	53	24,831	1.23 (0.93–1.62)
Vitamin C and multivitamin	36	29,434	0.90 (0.65–1.26)
Multivitamin and vitamin E	14	11,747	0.78 (0.46–1.32)
Vitamin C, vitamin E, and multivitamin	35	35,916	0.68 (0.48–0.95)

[a] Regular vitamin use defined as 15 or more times per month. Irregular users of vitamin C, vitamin E, or multivitamins excluded. RRs adjusted for age, sex, race, education, smoking, consumption of vegetables, citrus fruits/juices and high-fiber grains, and aspirin use.

reduction in risk limited to short duration use. Only three previous studies have examined the association between vitamin C supplement use and stomach cancer or its precursor lesions, and results have been inconsistent. A recent United States multicenter population-based case-control study included cases of both incident cardia and noncardia stomach cancer (11). This case-control study found vitamin C supplement use (at least weekly) was associated with decreased risk of both cardia (RR, 0.60; 95% CI, 0.41–0.88) and noncardia (RR, 0.71; 95% CI, 0.48–1.07) stomach cancer. Two randomized trials in high-risk populations have reported somewhat different results. In a large multifactorial trial in Linxian (China), participants were randomized to receive vitamin C (120 mg/day) in combination with molybdenum (10). After 5 years of supplementation and follow-up, vitamin C and molybdenum treatment was not associated with a risk of incident stomach cancer (RR, 1.09; 95% CI, 0.88–1.36). In contrast, results from a trial in a very high-risk Andean area of Colombia suggested some inhibition of stomach carcinogenesis with vitamin C treatment (9). Precancerous stomach lesions were significantly more likely to regress in participants randomized to receive 2000 mg/day of vitamin C for 6 years than in participants receiving a placebo (20% regression *versus* 7%).

We found no association between regular use of either multivitamins or vitamin E and risk of stomach cancer mortality. These results are consistent with results from the limited number of previous studies in both high- and lower-risk populations. Multivitamin use was not associated with stomach cancer risk in either the multicenter United States case-control study (11) or a small randomized trial in Linxian among individuals with esophageal dysplasia (28). Vitamin E supplement use was not associated with stomach cancer incidence in the multicenter United States case-control study (11). Low-dose vitamin E (30 mg α-tocopherol/day) was not associated with stomach cancer incidence in the α-Tocopherol β-Carotene trial among Finnish male smokers (16). In the large multifactorial Linxian trial, a combined regimen of low-dose Vitamin E (30 mg α-tocopherol/day), β-carotene, and selenium significantly reduced risk of stomach cancer incidence and mortality (10), but this reduction in risk cannot be attributed to vitamin E alone.

In subgroup analyses, regular use at enrollment of all three vitamin supplements (vitamin C, vitamin E, and multivitamins) was associated with modestly reduced risk of stomach cancer mortality (RR, 0.68; 95% CI, 0.48–0.95). However, the lack of reduced risk among participants using any of the combinations of two vitamin supplements argues against synergism between vitamin C, vitamin E, and multivitamins. The reduced risk among participants using all three vitamin supplements should also be interpreted cautiously because these individuals may have been likely to use additional vitamin supplements not measured on the questionnaire or to practice other health conscious behaviors.

Strengths of this analysis are its prospective design and exceptionally large size. The size of this study allowed us to obtain informative risk estimates for vitamin supplement use even when adjusting for multiple potential confounders. In addition, we were able to examine the role of potentially important effect modifiers.

Several limitations in our measurement of vitamin supplements could have caused bias toward the null, obscuring a modest effect of vitamin use. We had no information about past use of any specific vitamin for participants who were former vitamin users of that vitamin at enrollment. Our referent group, therefore, included some former vitamin users. We also did not have information on changes in use after enrollment and, therefore, could not take into account the fact that many participants may have started or stopped vitamin use after enrollment. Finally, we had no information on vitamin dosage. However, it is likely that the doses of vitamins 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 Nurses' 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 Nurses' 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]

Another limitation of our study is that we had no information on type of stomach cancer and, therefore, could not examine whether the association between vitamin supplement use and stomach cancer differed by anatomical subsite (cardia *versus* noncardia). Cancers of the gastric cardia, historically uncommon, have recently increased in incidence in the United States and now account for about one-half of all stomach cancers in white males and one-quarter of all stomach cancers in white females (29). Cardia and noncardia stomach cancers may have considerably different etiologies. In particular, obesity has been implicated as a risk factor for cardia but not noncardia stomach cancers (30). Only the United States multicenter case-control study has examined the association between supplement use and stomach cancer by anatomical subsite (11). Results were similar for cardia and noncardia cancers, which suggests that the association between supplement use and stomach cancer does not differ substantially by anatomical subsite.

It should be noted that our study examined stomach cancer mortality, rather than incidence. However, more than three-quarters of stomach cancer patients die of their disease within 5 years (2), so associations of risk factors with stomach cancer mortality and with stomach cancer incidence are likely to be similar.

As in any observational study, the effects of potential

[3] Meir Stampfer (Harvard University), 2000, personal communication.

confounding factors need to be considered. This is particularly true for analyses of vitamin supplement use because regular vitamin users are likely to have more 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 *Helicobacter pylori* infection, and only relatively crude measures of diet. However, any confounding by these factors would be expected to result in vitamin supplement use being associated with reduced risk of stomach cancer mortality; we found little evidence of such a reduction in risk.

In conclusion, results from this large prospective study of United States adults suggest that supplementation with vitamin C, vitamin E, or multivitamins may not substantially reduce risk of stomach cancer mortality in lower-risk, relatively well-nourished populations. The effect of vitamin supplementation may differ in higher-risk populations from developing countries, where factors such as childhood infection with *H. pylori* and nutritional deficiencies may play a larger role in stomach cancer etiology.

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