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Vitamin C and Vitamin E Supplement Use and Bladder Cancer Mortality in a Large Cohort of US Men and Women

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Some epidemiologic studies suggest that use of vitamin C or vitamin E supplements, both potent antioxidants, may reduce the risk of bladder cancer. The authors examined the association between use of individual vitamin C and vitamin E supplements and bladder cancer mortality among 991,522 US adults in the Cancer Prevention Study II (CPS-II) cohort. CPS-II participants completed a self-administered questionnaire at enrollment in 1982 and were followed regarding mortality through 1998. During follow-up, 1,289 bladder cancer deaths occurred (962 in men and 327 in women). Rate ratios were adjusted for age, sex, cigarette smoking, education, and consumption of citrus fruits and vegetables. Regular vitamin C supplement use (≥15 times per month) was not associated with bladder cancer mortality, regardless of duration (rate ratio (RR) = 0.91, 95% confidence interval (CI): 0.68, 1.20 for <10 years' use; RR = 1.25, 95% CI: 0.91, 1.72 for ≥10 years' use). Regular vitamin E supplement use for ≥10 years was associated with a reduced risk of bladder cancer mortality (RR = 0.60, 95% CI: 0.37, 0.96), but regular use of shorter duration was not (RR = 1.04, 95% CI: 0.77, 1.40). Results support the hypothesis that long-duration vitamin E supplement use may reduce the risk of bladder cancer mortality.

ascorbic acid; bladder neoplasms; dietary supplements; prospective studies; vitamin E; vitamins

Abbreviations: ATBC, Alpha-Tocopherol Beta-Carotene; CI, confidence interval; CPS-II, Cancer Prevention Study II; RR, rate ratio.

Approximately 56,500 new cases of bladder cancer and 12,600 bladder cancer deaths are expected in the United States in 2002, accounting for 4.4 percent of all incident cancers and 2.3 percent of all cancer deaths (1). Cigarette smoking is a known cause of bladder cancer, with cigarette smokers experiencing a twofold-to-threefold increased risk compared with never smokers (2). Consumption of fruits and/or vegetables may reduce the risk of bladder cancer, although there have been few prospective studies, and results have been inconsistent (3–5).

Vitamins C and E are potent antioxidants and could inhibit carcinogenesis in the bladder by neutralizing reactive oxygen species that can damage DNA (6) or by inhibiting the formation of nitrosamines (7), which may be bladder carcinogens (8). Vitamins C and E could also plausibly reduce bladder cancer risk by enhancing immune function (9, 10).

Few epidemiologic studies have examined the association between use of individual vitamin C or E supplements and bladder cancer (11–15). In a cohort of US men (the Health Professionals Follow-up Study), use of individual vitamin C supplements and use of individual vitamin E supplements for 10 or more years were both associated with a modestly decreased risk of incident bladder cancer (vitamin C: rate ratio (RR) = 0.73, 95 percent confidence interval (CI): 0.52, 1.03; vitamin E: RR = 0.68, 95 percent CI: 0.45, 1.03) (14). No other cohort studies are known to have examined the association between individual vitamin C or vitamin E supplements and bladder cancer. The Alpha-Tocopherol Beta-Carotene (ATBC) randomized trial among Finnish male smokers found no association between vitamin E supplementation and bladder cancer incidence after a median of 6 years of supplementation and follow-up (15). However, the ATBC trial used a low dose of vitamin E (50 IU/day) and could not examine long-duration use. Use of individual vitamin C supplements has been examined in three case-control studies of bladder cancer (11–13). Results

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from these studies are generally consistent with a modest reduction in risk associated with use of vitamin C supplements, although only one of these studies reported a statistically significant reduction in risk (13).

We examined the association between use of vitamin C and vitamin E supplements and bladder cancer mortality in a large cohort of US men and women. We studied 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, individual vitamin C or vitamin E supplements typically contain doses much higher than those obtained from diet or multivitamin supplements. Most individual vitamin supplements in the United States contain a minimum of 250 mg of vitamin C and 200 IU of vitamin E, whereas mean dietary intake is about 100 mg of vitamin C and 10–15 IU of vitamin E (16, 17), and multivitamins typically contain 60 mg of vitamin C and 30 IU of vitamin E. Therefore, regardless of diet or multivitamin use, users of individual vitamin C or vitamin E supplements are likely to have a much higher intake of these nutrients than nonusers. Note that this analysis examines only the potential effects of the high doses of vitamin C and vitamin E obtained from individual vitamin supplements, not the potential effects of the lower doses of vitamin C or vitamin E obtainable from diet or multivitamins.

MATERIALS AND METHODS

Study cohort and follow-up

Subjects for this analysis were drawn from the 1,184,622 participants (508,334 men and 676,288 women) in the Cancer Prevention Study II (CPS-II). Participants were enrolled in 1982 by American Cancer Society volunteers in all 50 US states, the District of Columbia, and Puerto Rico, as described previously (18). 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, by 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 then verified by obtaining death certificates (19). At completion of the 1988 follow-up based on American Cancer Society volunteer reports, vital status was known for 98.2 percent of the cohort (19). Automated linkage using the National Death Index then extended follow-up of the entire cohort from September 1988 through December 31, 1998, and also identified deaths among the 21,704 participants lost to follow-up between 1982 and 1988 (19). At the completion of follow-up in December 1998, 283,636 participants had died (23.9 percent), 898,090 were alive (75.8 percent), and 2,896 (0.2 percent) had follow-up truncated on September 1, 1988, because insufficient data were available to perform linkage with the National Death Index. Death certificates or codes for cause of death have been obtained for 98.8 percent of all known deaths. The underlying cause of death was coded according to the *International Classification of Diseases*, Ninth Revision (20); bladder cancer deaths were defined as codes 188.0–188.9, which included all known bladder cancer deaths in this cohort.

All aspects of the CPS-II cohort are approved by the Emory University School of Medicine Human Investigations Committee (Atlanta, Georgia). Informed consent to participate was implied by returning a completed self-administered questionnaire in 1982.

All analyses excluded participants who, at enrollment, reported a history of cancer other than nonmelanoma skin cancer (n = 82,345) or for whom data on vitamin supplement use (n = 56,354) or on cigarette smoking (n = 54,401) were incomplete or uninterpretable. A total of 991,522 participants (446,227 men and 545,295 women) remained for analysis.

Ascertainment of vitamin supplement use

All information on vitamin use was obtained from the 1982 baseline questionnaire, which included a section 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 reporting the number of times in the last month that they had used this vitamin and the second reporting the number of years of use. Participants were instructed to write "1/2" in the times-per-month box if they used a vitamin only occasionally. 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. The 1982 baseline questionnaire is available on the Internet at the American Cancer Society's Web site (www.cancer.org).

Statistical analysis

We used Cox proportional hazards modeling (21) to calculate rate ratios for bladder cancer mortality associated with vitamin C and vitamin E supplement use while adjusting for other potential risk factors. The time axis used was follow-up time since enrollment in 1982.

Participants reporting use of vitamin C or vitamin E supplements 15 or more times a month were categorized as "regular" users of that vitamin supplement. Approximately 90 percent of regular vitamin C users and regular vitamin E users reported use at least 25 times per month, a frequency consistent with daily use. Participants reporting unquantified "occasional" use or use 1–14 times per month were categorized as "occasional" users of that vitamin supplement. Over 75 percent of occasional vitamin C users and occasional vitamin E users reported only unquantified "occasional" use or use only once per month.

All Cox models included variables for use of vitamin C and vitamin E supplements. In addition, the models were adjusted for age, sex, and several additional factors associated with risk of bladder cancer in this cohort and/or other study populations (cigarette smoking, education, and consumption of citrus fruits/juices and vegetables).

All covariates except age, cigarette smoking, and vitamin supplement use were modeled as dummy variables by using the categories shown in table 1. Age was adjusted for by stratifying on exact year of age at enrollment in each Cox model (22). Cigarette smoking was adjusted for by using dummy variables for combinations of smoking status (never, current, former) and number of cigarette pack-years of smoking (<20, 20–<40, 40–<60, ≥60, unknown). In the main analyses, vitamin C and vitamin E supplement use were modeled by using six categories (occasional use of <10 years, occasional use of ≥10 years, occasional use of unknown duration, regular use of <10 years, regular use of ≥10 years, and regular use of unknown duration). In stratified analyses, occasional users of each vitamin supplement were combined into one category, regardless of duration of use, because of the small number of occasional users who reported long-duration use. Food consumption variables were derived from the dietary portion of the questionnaire, which asked how many days per week participants ate each of 32 common food items. The dietary portion of the questionnaire has been described previously (23). The variable for daily vegetable servings was estimated by summing the numbers of days per week that each participant reported on the questionnaire that they ate each of the six vegetable items, other than potatoes (carrots, tomatoes, squash/corn, green leafy vegetables, raw vegetables, and cabbage/broccoli/brussels sprouts) and dividing by seven.

We examined potential confounding by multivitamin use, vitamin A supplement use, exposure to gasoline and diesel exhaust, and cigar and pipe smoking. However, we did not adjust for these factors in the final models because such adjustment had negligible effects on our results. We had no data on fluid consumption.

We analyzed whether the association between use of each vitamin supplement and bladder cancer varied by potential effect modifiers. Specifically, we examined the association between regular vitamin C and regular vitamin E use stratified by categories of cigarette smoking, multivitamin use, vegetable consumption, and consumption of citrus fruits/juices. All p values presented are two sided for heterogeneity of the rate ratios calculated by using the likelihood ratio statistic (24).

RESULTS

Among participants in this analysis, approximately 12 percent were regular users of vitamin C and 9 percent were regular users of vitamin E supplements. These percentages are generally similar to those observed among middle-aged and elderly participants in a US nationally representative sample from a similar time period (25).

Table 1 compares participants who, at enrollment, were regular users of vitamin C or vitamin E with participants who did not use either vitamin C or vitamin E supplements. Most participants were White and were middle-aged or elderly, regardless of vitamin use. Regular users of vitamin C or vitamin E supplements were similar to each other with respect to bladder cancer risk factors. Compared with participants who did not use either vitamin C or vitamin E, regular users of vitamin C or vitamin E supplements were less likely to be current cigarette smokers and more likely to be White, to be college educated, and to report frequent consumption of vegetables and citrus fruits/juices.

There was considerable overlap between use of vitamin C and vitamin E supplements. About half of those reporting regular use of vitamin C also reported regular use of vitamin E (50 percent). Most regular users of vitamin E were also regular users of vitamin C (69 percent).

Table 2 presents the association between vitamin C and vitamin E supplement use at enrollment and bladder cancer mortality. Vitamin C use, even regular long-duration use (≥10 years at enrollment), was not associated with bladder cancer mortality (RR = 1.25, 95 percent CI: 0.91, 1.72). Regular long-duration vitamin E use was associated with a reduced risk of bladder cancer mortality (RR = 0.60, 95 percent CI: 0.37, 0.96), while no reduction in risk was found with occasional use or regular use of shorter duration. When adjusted for age and sex only (rather than multivariate adjusted, as in table 2), the rate ratio for regular long-duration vitamin C use was 0.95 (95 percent CI: 0.72, 1.24), and the rate ratio for regular long-duration vitamin E use was 0.66 (95 percent CI: 0.44, 0.99).

Because cigarette smoking is an important cause of bladder cancer, we examined the association between vitamin C and vitamin E use and bladder cancer mortality stratified by cigarette smoking status (table 3). We found no association between regular vitamin C use and bladder cancer mortality, regardless of smoking status. The reduced risk associated with regular long-duration vitamin E use (≥10 years at enrollment) was more apparent among current cigarette smokers at enrollment (RR = 0.31, 95 percent CI: 0.10, 0.89) than among former cigarette smokers (RR = 0.69, 95 percent CI: 0.35, 1.36) or never cigarette smokers (RR = 0.84, 95 percent CI: 0.36, 1.93), although this difference could have been due to chance ($p = 0.52$ for heterogeneity of the rate ratios by smoking status).

Multivitamins contain some vitamin C and vitamin E (although usually at doses many times lower than those in individual supplements); therefore, we examined the association between regular use of vitamin C and vitamin E and bladder cancer mortality stratified by multivitamin use (which was not itself associated with risk of bladder cancer mortality). Results were similar among nonusers and regular users of multivitamins (occasional multivitamin users were excluded from this analysis). Among nonusers of multivitamins, the rate ratio for regular long-duration vitamin C use (≥10 years at enrollment) was 1.38 (95 percent CI: 0.85, 2.23), and the rate ratio for regular long-duration vitamin E use was 0.54 (95 percent CI: 0.25, 1.15). Among regular multivitamin users, the rate ratio for regular long-duration vitamin C use was 1.12 (95 percent CI: 0.72, 1.76), and the rate ratio for regular long-duration vitamin E use was 0.52 (95 percent CI: 0.27, 1.00).

Any effect of vitamin supplementation may be limited to those whose diets are low in specific vitamins or antioxidants. We therefore examined the association between bladder cancer mortality and regular use of vitamin C and vitamin E supplements stratified by intake of citrus fruit/juices (a major source of vitamin C) and by vegetable intake (a source of many vitamins and antioxidants). We found no

TABLE 1. Selected demographic and bladder cancer mortality risk factors (%) by vitamin C and vitamin E supplement use at enrollment,* Cancer Prevention Study II, United States, 1982–1998

	Women			Men		
	No vitamin C or vitamin E use (*n* = 388,611)	Vitamin C regular use† (*n* = 73,009)	Vitamin E regular use† (*n* = 53,992)	No vitamin C or vitamin E use (*n* = 342,335)	Vitamin C regular use† (*n* = 48,871)	Vitamin E regular use† (*n* = 34,115)
Age (years)						
<40	5.9	4.5	3.3	4.0	3.0	2.0
40–49	23.9	21.2	20.8	19.2	16.4	13.7
50–59	33.8	37.2	39.1	38.1	38.1	37.5
60–69	24.2	27.1	27.1	27.4	31.3	34.5
70–79	9.9	8.6	8.3	9.7	9.9	11.1
≥80	2.3	1.5	1.3	1.6	1.2	1.3
Race						
White	92.6	96.0	95.8	94.0	96.8	96.3
Black	5.2	2.2	2.3	3.8	1.5	1.8
Other	2.2	1.8	1.9	2.2	1.7	1.8
Educational level						
Less than high school	13.8	8.3	9.7	16.5	9.7	11.3
High school graduate	31.7	27.0	29.2	21.0	15.5	16.8
Some college	28.8	33.7	33.4	26.4	27.4	29.0
College graduate	14.4	16.8	15.1	17.2	21.6	20.1
Graduate school	9.8	13.3	11.6	17.5	25.0	22.0
Unclassifiable	1.5	0.9	1.0	1.4	0.7	0.8
Cigarette smoking						
Never smoker	57.1	54.6	55.4	33.8	37.0	36.1
Current smoker	22.4	19.3	18.6	25.9	19.7	19.9
Former smoker	20.5	26.0	26.1	40.4	43.3	44.1
Multivitamin use						
None	73.8	38.6	39.7	80.5	42.7	42.7
Occasional	10.4	5.1	4.3	7.6	4.7	4.0
Regular	15.7	56.3	55.9	11.9	52.7	53.4
Citrus fruit/juices (servings/week)						
<1	20.2	13.9	14.7	24.5	15.7	17.0
1–<4	16.5	13.6	14.0	20.7	17.3	17.8
4–<7	15.4	15.9	16.1	15.9	17.1	17.3
≥7	36.9	48.2	46.5	31.2	44.5	42.5
Unclassifiable	11.0	8.4	8.7	7.7	5.4	5.4
Vegetables (servings/day)						
<1	15.6	8.8	9.3	21.2	12.8	13.3
1–<2	27.2	22.9	23.2	33.6	31.0	30.9
2–<3	26.4	29.6	29.4	24.0	29.3	28.8
≥3	19.7	30.3	29.5	13.5	21.6	21.5
Unclassifiable	11.0	8.4	8.7	7.7	5.4	5.4

* Percentages were adjusted to the age distribution of the entire study population. Regular-use categories for vitamin E and vitamin C supplements are not mutually exclusive.

† Reported use ≥15 times per month.

evidence that the associations of vitamin C and vitamin E supplement use with bladder cancer mortality differed by citrus or vegetable intake.

Vitamin C and vitamin E have been hypothesized to act synergistically because vitamin C may regenerate the antioxidant activity of vitamin E (9). Therefore, we examined the

TABLE 2. Multivariate-adjusted rate ratios and 95% confidence intervals for bladder cancer mortality associated with frequency and duration of vitamin C and vitamin E supplement use,* Cancer Prevention Study II, United States, 1982–1998

	Men only	Women only	Men and women combined
Vitamin C use at enrollment			
No use			
RR† (95% CI†)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Deaths/participants	782/357,989	254/413,854	1,036/771,843
Occasional use‡			
<10 years			
RR (95% CI)	1.37 (0.94, 1.98)	1.10 (0.57, 2.14)	1.29 (0.94, 1.79)
Deaths/participants	36/13,999	11/20,667	47/34,666
≥10 years			
RR (95% CI)	0.83 (0.49, 1.41)	0.37 (0.11, 1.27)	0.70 (0.43, 1.14)
Deaths/participants	16/11,774	3/14,125	19/25,899
Unknown no. of years			
RR (95% CI)	0.72 (0.45, 1.16)	0.90 (0.50, 1.64)	0.79 (0.54, 1.14)
Deaths/participants	21/13,594	14/23,640	35/37,234
Regular use§			
<10 years			
RR (95% CI)	1.02 (0.73, 1.41)	0.67 (0.38, 1.21)	0.91 (0.68, 1.20)
Deaths/participants	50/24,925	15/38,196	65/63,121
≥10 years			
RR (95% CI)	1.22 (0.84, 1.78)	1.32 (0.74, 2.36)	1.25 (0.91, 1.72)
Deaths/participants	40/17,074	16/23,091	56/40,165
Unknown no. of years			
RR (95% CI)	0.98 (0.54, 1.75)	1.51 (0.78, 2.91)	1.17 (0.76, 1.81)
Deaths/participants	17/6,872	14/11,722	31/18,594
Vitamin E use at enrollment			
No use			
RR (95% CI)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Deaths/participants	843/388,419	273/454,146	1,116/842,565
Occasional use‡			
<10 years			
RR (95% CI)	0.97 (0.63, 1.50)	0.95 (0.44, 2.05)	0.96 (0.66, 1.40)
Deaths/participants	26/10,767	8/17,225	34/27,992
≥10 years			
RR (95% CI)	0.52 (0.22, 1.23)	1.34 (0.39, 4.62)	0.67 (0.33, 1.36)
Deaths/participants	6/5,162	3/5,869	9/11,031
Unknown no. of years			
RR (95% CI)	0.85 (0.48, 1.51)	1.15 (0.57, 2.32)	0.94 (0.61, 1.47)
Deaths/participants	14/7,764	10/14,063	24/21,827
Regular use§			
<10 years			
RR (95% CI)	0.94 (0.66, 1.35)	1.30 (0.77, 2.20)	1.04 (0.77, 1.40)
Deaths/participants	41/19,374	19/33,829	60/53,203
≥10 years			
RR (95% CI)	0.63 (0.37, 1.08)	0.52 (0.19, 1.40)	0.60 (0.37, 0.96)
Deaths/participants	19/9,823	5/11,876	24/21,699
Unknown no. of years			
RR (95% CI)	1.02 (0.53, 1.99)	1.08 (0.48, 2.43)	1.03 (0.61, 1.72)
Deaths/participants	13/4,918	9/8,287	22/13,205

* Adjusted for age, sex (in combined-sex models), educational level, cigarette smoking (current or former status and number of pack-years), consumption of citrus fruits/juices, consumption of vegetables, and vitamin C and vitamin E supplement use.
† RR, rate ratio; CI, confidence interval.
‡ Reported unquantified "occasional" use, or use 1–14 times per month.
§ Reported use ≥15 times per month.

TABLE 3. Combined-sex multivariate-adjusted rate ratios and 95% confidence intervals for bladder cancer mortality associated with vitamin C and vitamin E supplement use by cigarette smoking status,* Cancer Prevention Study II, United States, 1982–1998

	Never cigarette smoker	Former cigarette smoker	Current cigarette smoker
Vitamin C use at enrollment			
No use			
RR† (95% CI†)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Deaths/participants	303/357,450	373/230,213	360/184,180
Occasional use‡			
RR (95% CI)	0.84 (0.56, 1.26)	1.23 (0.88, 1.73)	0.66 (0.41, 1.06)
Deaths/participants	33/47,498	47/29,319	21/20,982
Regular use§			
<10 years			
RR (95% CI)	0.71 (0.39, 1.28)	0.88 (0.56, 1.37)	1.13 (0.71, 1.81)
Deaths/participants	14/29,279	27/21,091	24/12,751
≥10 years			
RR (95% CI)	1.00 (0.54, 1.87)	1.19 (0.73, 1.95)	1.61 (0.94, 2.75)
Deaths/participants	15/18,825	24/13,953	17/7,387
Unknown no. of years			
RR (95% CI)	1.84 (1.02, 3.33)	1.03 (0.48, 2.20)	0.45 (0.13, 1.59)
Deaths/participants	18/9,634	10/5,423	3/3,537
Vitamin E use at enrollment			
No use			
RR (95% CI)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Deaths/participants	324/391,350	406/252,051	386/199,164
Occasional use‡			
RR (95% CI)	1.24 (0.79, 1.92)	0.78 (0.50, 1.22)	0.72 (0.40, 1.27)
Deaths/participants	27/29,336	26/18,392	14/13,122
Regular use§			
<10 years			
RR (95% CI)	0.88 (0.47, 1.63)	1.22 (0.79, 1.89)	0.95 (0.56, 1.64)
Deaths/participants	13/25,229	29/17,827	18/10,147
≥10 years			
RR (95% CI)	0.84 (0.36, 1.93)	0.69 (0.35, 1.36)	0.31 (0.10, 0.89)
Deaths/participants	8/9,915	12/7,838	4/3,946
Unknown no. of years			
RR (95% CI)	1.05 (0.50, 2.23)	1.08 (0.46, 2.52)	0.86 (0.24, 3.07)
Deaths/participants	11/6,856	8/3,891	3/2,458

* Adjusted for age, sex (in combined-sex models), educational level, number of cigarette pack-years (among current or former smokers), consumption of citrus fruits/juices, consumption of vegetables, and vitamin C and vitamin E supplement use.

† RR, rate ratio; CI, confidence interval.

‡ Reported unquantified "occasional" use, or use 1–14 times per month.

§ Reported use ≥15 times per month.

association of combinations of regular long-duration vitamin C and vitamin E supplement use with bladder cancer mortality. When we excluded occasional and short- or unknown-duration users of vitamin C or vitamin E, rate ratios were 1.34 (95 percent CI: 0.92, 1.96) for regular long-duration use of vitamin C alone, 0.77 (95 percent CI: 0.32, 1.86) for regular long-duration use of vitamin E alone, and 0.77 (95 percent CI: 0.49, 1.21) for regular long-duration use of both vitamin C and vitamin E supplements.

We had no updated information on vitamin supplement use during the 18 years of follow-up. To estimate the continuity of vitamin supplement use patterns during follow-up, we compared use reported on the 1982 baseline CPS-II questionnaire with use reported on a 1992–1993 follow-up ques-

tionnaire completed by a subgroup of approximately 184,000 CPS-II participants from 21 selected US states (26). This subgroup of respondents to the 1992–1993 questionnaire may have been somewhat more likely to continue or initiate vitamin use than participants in the cohort as a whole. Sixty percent of regular vitamin C users and 56 percent of regular vitamin E users in 1982 reported continued use of the same vitamin supplement in 1992–1993. Among participants reporting no vitamin C use in 1982, approximately 11 percent were using vitamin C in 1992–1993. Similarly, 10 percent of participants reporting no vitamin E use in 1982 were using vitamin E in 1992–1993.

DISCUSSION

In this large cohort of US men and women, regular long-duration use of vitamin E supplements was associated with a reduced risk of bladder cancer mortality. Shorter-duration vitamin E supplement use as well as vitamin C supplement use (regardless of duration) were not associated with bladder cancer mortality.

The association between individual vitamin E supplement use and bladder cancer has been examined in two previous studies, a cohort study of US men (the Health Professionals Follow-up Study (14)) and a randomized trial among Finnish male smokers (the ATBC trial (15)). Studies of bladder cancer that categorized subjects who may have used only multivitamins as users of "supplemental vitamin E" have produced mixed results (13, 27, 28) but are of limited relevance in determining the potential effects of the high doses of vitamin E contained in individual vitamin E supplements.

In the Health Professionals Follow-up Study cohort, use of vitamin E supplements for 10 or more years was associated with a modestly reduced bladder cancer incidence (RR = 0.68, 95 percent CI: 0.45, 1.03 for ≥10 years' use; p-trend = 0.03 for increasing duration of use) (14). In the ATBC trial, participants in the intervention arm received 50 IU of vitamin E (alpha-tocopherol) per day for 5–8 years. Follow-up continued for the same 5–8-year period, and no reduction in bladder cancer incidence was observed (RR = 1.1, 95 percent CI: 0.8, 1.5) (15). The reduced risk associated with use of individual vitamin E supplements observed in the two US observational cohort studies (our CPS-II cohort and the Health Professionals Follow-up Study cohort (14)) could be a result of confounding not present in the randomized ATBC trial. Alternatively, the absence of reduced risk in the ATBC trial could be due to differences in duration or dose. Only short-duration vitamin E use could be examined in the ATBC trial. In addition, the 50-IU dose of vitamin E used in the ATBC trial is several times lower than the 200–1,000 IU typically contained in individual vitamin E supplements in the United States.

In the CPS-II cohort, regular vitamin E supplement use of 10 or more years was associated with the greatest reduction in bladder cancer mortality among participants who were cigarette smokers at enrollment, whereas smaller, nonstatistically significant reductions in risk were observed among never or former smokers. Vitamin E supplement use could plausibly have stronger effects on bladder carcinogenesis in cigarette smokers if vitamin E inhibits the action of carcinogens in tobacco smoke. However, the differences in rate ratios by smoking status that we observed could easily have been due to chance. In the Health Professionals Follow-up Study cohort, vitamin E use was associated with a statistically significant reduction in risk among former smokers only, not among current or never smokers, although statistical power to examine differences by smoking status was limited (14). Additional data will be needed to determine whether potential effects of long-duration vitamin E supplement use on bladder cancer differ by smoking status. Regardless of whether vitamin E supplement use reduces bladder cancer risk for cigarette smokers, our results do not suggest that cigarette smokers can meaningfully reduce their overall disease risk by using vitamin E supplements. Smoking greatly increases the risk of many common and serious diseases, including lung cancer, cardiovascular disease, and respiratory disease (29). Quitting smoking is by far the best way for smokers to prevent both bladder cancer and many other serious diseases (30).

If high doses of supplemental vitamin E do inhibit bladder carcinogenesis, there could be potential implications for bladder cancer treatment as well as for primary prevention. In a randomized trial among 65 patients with superficial bladder tumors (those that have not invaded the muscle wall), a combination of high doses of vitamin E (400 IU/day), vitamin A (40,000 IU/day), vitamin C (2,000 mg/day), and vitamin B_6 (100 mg/day) resulted in substantially reduced rates of bladder tumor recurrence (31). However, such vitamin supplementation is not used in the treatment of bladder cancer patients, possibly because of concerns about the toxicity of high doses of vitamin A. Our results, together with those from the Health Professionals Follow-up Study cohort (14), suggest that vitamin E, which has low toxicity (32), could have contributed to the reduction in tumor recurrence observed in the randomized trial. The possibility that vitamin E supplementation could inhibit later stages of carcinogenesis is supported by the ability of vitamin E supplementation (at 800 IU/day) to cause regression of precancerous oral lesions (33). Because more than half of bladder tumors recur within 5 years (34), randomized trials of the effect of vitamin E supplementation on bladder cancer recurrence could be conducted relatively quickly.

We found no association between bladder cancer mortality and vitamin C use, even regular long-duration use. The few epidemiologic studies of bladder cancer and vitamin C use have produced mixed results. In the Health Professionals Follow-up Study cohort, vitamin C use of 10 or more years was associated with a modestly reduced bladder cancer incidence (RR = 0.73, 95 percent CI: 0.52, 1.03) (14). Of three case-control studies of incident bladder cancer, one reported that vitamin C supplement use was associated with a strongly reduced risk (RR = 0.40, 95 percent CI: 0.21, 0.76) (13), one reported a weaker reduction in risk (odds ratio = 0.7, 95 percent CI: 0.4, 1.3) (11), and one reported a reduced risk for women (odds ratio = 0.5, 95 percent CI: 0.3, 1.1) but not men (odds ratio = 1.2, 95 percent CI: 0.8, 1.8) (12).

We examined mortality from bladder cancer rather than incidence of bladder cancer. Only a relatively small proportion of incident bladder cancers result in mortality. The 5-year relative survival rate for bladder cancer is 81 percent

(35). Therefore, risk factors for bladder cancer mortality may be substantially different from those for bladder cancer incidence. However, our results with respect to regular long-duration vitamin E supplement use and bladder cancer mortality are similar to those reported for bladder cancer incidence in the Health Professionals Follow-up Study cohort (14).

As in any observational study, the effects of potential confounding factors need to be considered, which is particularly true in analyses of vitamin supplement use because regular vitamin users are generally more likely to practice "health-conscious" behaviors. Although we were able to adjust (or determine that adjustment was unnecessary) for several potential confounding factors, we cannot rule out residual confounding. However, in this cohort, regular vitamin C and vitamin E users were very similar with respect to measured health-related behaviors and characteristics such as smoking, education, and vegetable consumption. If there were important confounding by health-conscious behaviors associated with vitamin supplement use, we would have expected to observe a reduced risk associated with both vitamin C and vitamin E supplement use. Instead, we observed a reduced risk associated with only regular long-duration vitamin E use and not with vitamin C use.

Several limitations in our measure of vitamin supplement use could have contributed to an underestimate of any beneficial effects of vitamin C or vitamin E supplement use. Our referent group undoubtedly included some former vitamin users because participants who did not report current vitamin supplement use at enrollment were not asked about their past vitamin supplement use. We did not have information on changes in vitamin supplement use after enrollment and therefore could examine duration of vitamin use only as reported at enrollment. In addition, some participants who did not use vitamin supplements at enrollment are likely to have started vitamin use during follow-up. We also had no information on vitamin dose. However, it is likely that the doses of vitamin C and vitamin E obtained from individual supplements in our US 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 in which the CPS-II questionnaire was administered), 80 percent of the participants in the Nurses' Health Study who were using vitamin C supplements (and knew their dose) reported a dose of 400 mg or more. Similarly, 88 percent of nurses who were using vitamin E supplements (and knew their dose) reported a dose of 200 IU or more (Meir Stampfer, Harvard University, personal communication, 2000).

Strengths of this analysis include its prospective design and exceptionally large size. The size of this study enabled us to examine the role of potentially important effect modifiers, such as cigarette smoking.

In summary, our results, together with those from the Health Professionals Follow-up Study cohort (14), provide some support for the hypothesis that long-duration vitamin E supplementation may reduce bladder cancer risk. However, further confirmation is needed.

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