

# A Prospective Study on Supplemental Vitamin E Intake and Risk of Colon Cancer in Women and Men<sup>1</sup>

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## Abstract

**We conducted a prospective study on the association between supplemental vitamin E and colon cancer in 87,998 females from the Nurses' Health Study and 47,344 males from the Health Professionals Follow-up Study. There was some suggestion that men with supplemental vitamin E intake of 300 IU/day or more may be at lower risk for colon cancer when compared with never users [multivariate relative risk (RR), 300–500 IU/day versus never users, 0.73 (95% confidence interval (CI), 0.52–1.03); ≥600 IU/day versus never users = 0.70 (95% CI = 0.38–1.29)], but CIs included 1. In women, there was no evidence for an inverse association between vitamin E supplementation and risk of colon cancer. Our findings do not provide consistent support for an inverse association between supplemental vitamin E and colon cancer risk. Considering the paucity of epidemiological data on this association, further studies of vitamin E and colon cancer are warranted.**

## Introduction

In the United States, colon cancer is the third leading cause of cancer mortality in both men and women and second for both sexes combined (1). Dietary factors may influence colon cancer risk (2–4), and among the nutrients hypothesized to be beneficial is the lipid soluble antioxidant vitamin E (5). Vitamin E has been hypothesized to prevent oxidative DNA damage by scavenging free radicals and inhibiting lipid peroxidation in biological membranes (6, 7), even though a recent randomized clinical trial showed no benefit of vitamin E supplementation on lipid peroxidation in 30 healthy adults (8). Other hypothesized anticarcinogenic mechanisms of vitamin E include its

ability to reduce nitrite, a potential carcinogen, (9) and to enhance immune response (7).

Few observational studies have investigated the relationship of vitamin E to the risk of colon cancer (10–15), and findings have been inconsistent. In a pooled analysis using data from five nested case-control studies, a 30% reduction of colon cancer risk was found for participants in the highest quartile of serum  $\alpha$ -tocopherol levels when compared with those in the lowest quartile, but results were not statistically significant (12). Data from one prospective study suggest an inverse association between vitamin E and colon cancer risk in women, but only with the high levels of intake usually attained with vitamin E supplements (10). In the  $\alpha$ -Tocopherol,  $\beta$ -Carotene Cancer Prevention Study, a randomized trial conducted among 29,133 male smokers, supplementation with 50 mg vitamin E for 5–8 years was also associated with a 22%, albeit nonsignificantly, decreased risk of colorectal cancer (16). On the other hand, another randomized clinical trial by Greenberg *et al.* (17) found no association between daily supplementation with 400 mg of vitamin E and the risk of colorectal adenomas. Some (13–15), but not all, studies (11), have suggested that inverse associations between vitamin E and colon cancer may be stronger in women than in men.

The lack of repeated dietary measurements, which may have led to misclassification of long-term nutrient intake or insufficient statistical power, may have contributed to inconsistent findings from epidemiological studies. Using repeated dietary information from multiple food frequency questionnaires, we prospectively examined the relationship of vitamin E supplement use to colon cancer risk in two large ongoing cohorts of United States men and women, the HPFS<sup>3</sup> and the NHS.

## Materials and Methods

**HPFS Cohort.** The HPFS cohort was started in 1986, when 51,129 male health professionals ages 40–75 years, all residing in the United States, were asked to respond to a mailed questionnaire (18). Since then, biennial follow-up questionnaires have been sent to surviving participants to update information on exposure and medical history. The 1986 questionnaire included a 131-item semiquantitative food-frequency questionnaire similar to those administered in the NHS. Dietary information was updated with subsequent food-frequency questionnaires in 1990 and 1994.

**NHS Cohort.** In brief, the NHS cohort was initiated in 1976 when 121,700 registered female United States nurses ages 30–55 years completed a mailed questionnaire requesting information on exposures and medical diagnoses (19). Follow-up

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<sup>3</sup> The abbreviations used are: HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; RR, relative risk; OR, odds ratio; CI, confidence interval.

questionnaires updating this information were mailed every 2 years. In 1980, 98,462 women completed a 61-item semiquantitative food-frequency questionnaire that had been added to the mailed questionnaires. More detailed food-frequency questionnaires, containing between 121 and 136 items, were part of the 1984, 1986, 1990, and 1994 mailings.

**Diet and Vitamin Supplement Assessment.** On the food-frequency questionnaire, participants were asked to report the average frequency of use of common foods and beverages during the past year. Intakes of nutrients were calculated by multiplying the frequency response with the nutrient content of each food or beverage and summing the contributions of all items. Energy-adjusted nutrient intake values were derived using residuals from the regression of nutrient intake on total calorie intake (20). The reproducibility and validity of the food-frequency questionnaires applied in both cohorts have been reported previously (21–25). Total vitamin E intake (from supplemental and dietary sources combined) calculated from the food-frequency questionnaires was reasonably correlated with the average intake of two 1-week diet records [Pearson correlation coefficient  $r = 0.87$  ( $n = 127$  men); Ref. 22] as well as with plasma tocopherol concentrations [ $r = 0.51$  ( $n = 121$  men);  $r = 0.41$  ( $n = 186$  women; Ref. 26).

Current use and dosage of vitamin supplementation (including multivitamins and individual vitamins) were evaluated in each biennial questionnaire cycle. Participants were also asked to write in the usual brand and type of multivitamins. With regard to the dosage of individual vitamin E supplements, participants were given five choices (<100 IU/day, 100–250 IU/day, 300–500 IU/day,  $\geq 600$  IU/day, and don't know). The 1980 NHS questionnaire and the 1986 HPFS questionnaire also inquired about the duration of vitamin supplement use. Information on past use of vitamins was obtained from the 1986 HPFS baseline questionnaire, but not the 1980 NHS questionnaire. In each questionnaire, participants were also asked to provide the brand and type of their multivitamin, which was then used to calculate the amount of vitamin E from multivitamins. Multivitamins contributed only relatively small amounts of vitamin E relative to vitamin supplements; in the NHS, the mode dose of vitamin E from multivitamins was 15 IU in 1980, 1984, and 1986, and 30 IU in 1990 and 1994. In men, the mode dose was 30 IU in 1986, 1990, and 1994. Because information on calculated amounts of vitamin E from multivitamins was not available for the non-diet questionnaire cycles (*i.e.*, in 1982, 1988, and 1992 for the NHS cohort and in 1988 and 1992 for the HPFS cohort), respondents reporting current use of multivitamins on those questionnaires were assigned the computed amount of vitamin E from the most previous diet cycle.

For participants who did not return one or more of the follow-up questionnaires, information on vitamin E supplementation (from either multivitamins and/or individual vitamin E pills) from the most recently completed questionnaire was carried forward. A participant who indicated current use of vitamin E, but did not provide information on dose, was assumed to have a dose of 400 IU/day, the mode dose for supplement users. Total supplemental vitamin E intake was calculated as the sum of supplemental vitamin E from multivitamins and from vitamin E supplements.

**Exclusion of Participants at Baseline.** Only participants who had completed the baseline food-frequency questionnaires (*i.e.*, in 1980 for the female cohort and 1986 for the male cohort) were included in this study. Of those, we excluded respondents with implausibly high (>3500 calories for women; >4200

calories for men) or low intakes (<600 calories for women; <800 calories for men) or who had left a high number of items blank (>10 items for women; >70 items for men). Individuals who reported a history of ulcerative colitis or previous cancer (except for nonmelanoma skin cancer) were also excluded. Thus, 87,998 women and 47,344 men remained for follow-up (from 1980 to 1996 for women and from 1986 to 1996 for men).

**Case and Death Ascertainment.** On each biennial follow-up questionnaire, participants were asked whether they had been diagnosed with colon or rectal cancer in the previous 2 years. If a participant had reported a diagnosis of colon or rectal cancer, he or she was contacted, and authorization to obtain and evaluate hospital and pathology reports was requested. For reported cases of cancers of the colon and rectum, we were able to confirm through medical record review 88% of cases. For remaining cases, confirmation was based on additional information from the participants or family members. Physicians reviewed those records and extracted information on histology, anatomical location, and stage of cancer. Among eligible women, 626 incident colon cancer cases were documented, among eligible men, 399 colon cancer cases were documented. Of these 1025 female and male colon cancer cases, 842 (82%) had anatomical site definitely confirmed by medical records. For the vast majority of the remaining cases, confirmation was based on corroborating information on treatment or diagnosis from the participants (*e.g.*, through telephone interview). Because definitive medical record information was available for 82%, and the corroborating information was provided by highly educated health professional participants for the remaining, it is probable that only a relatively small number of the cases misclassified rectal cancer cases as colon cancers. In any case, results were similar when we considered only the 842 individuals with definitive medical record information on anatomical site.

Deaths were usually reported by family members or the postal service, and the National Death Index was also used to identify deaths among nonrespondent participants. For participants who died from cancer that had not already been reported, permission to review medical records was requested from next of kin, and these were similarly reviewed.

**Statistical Analysis.** Participants contributed follow-up time from the month they returned their baseline questionnaires to the month of diagnosis of cancer, the date of death, or the end of the study period (May 31, 1996, for the NHS cohort; January 31, 1996, for the HPFS cohort) if they were noncases. We computed incidence rates by dividing the number of incident cases by the number of total person-years within each level of exposure. RRs were calculated by dividing the incidence rates among supplement users by the incidence rates among non-supplement users. We also investigated the associations between dietary vitamin E intake and the risk of colon cancer in nonusers of supplements by comparing incidence rates in each quintile of intake with those in the lowest quintile. Adjustment for age and other possible confounders was performed applying the Mantel-Haenzel estimator (27) and pooled logistic regression (28, 29) using 2-year follow-up intervals. Known and suspected nondietary risk factors [age, family history, body mass index, physical activity, pack-years of smoking before age 30, aspirin use, menopausal status and hormone use (for NHS only), as well as red meat and alcohol consumption] were included into all multivariate models. We also investigated possible confounding effects of nutrients such as total fat, fiber, iron, methionine, folate, calcium, vitamin D, vitamin C, total vitamin A, and total carotene by controlling for these nutrients

Table 1 Baseline characteristics of study population, by categories of vitamin E supplementation from vitamin E pills: HPFS, 1986 and NHS, 1980

Characteristics <sup>a</sup>	HPFS, 1986					NHS, 1980 <sup>b</sup>			
	Never users	≤250 IU	300–500 IU	≥600 IU	Past users <sup>b</sup>	Never users	≤250 IU	300–500 IU	≥600 IU
Participants no.	32,553	2,572	4,931	1,518	5,770	76,475	3,923	5,900	1,700
Mean age (yr)	54.0	55.3	57.2	56.9	53.8	46.4	47.7	49.1	49.5
Mean pack-years of smoking before age 30	5.4	4.9	5.2	5.8	5.5	3.0	2.8	3.1	3.2
Aspirin user (%)	27.3	34.5	35.5	35.3	32.1	32.4	35.4	35.6	37.7
Family history of colorectal cancer (%)	8.3	8.3	8.8	8.8	8.8	7.8	8.9	8.0	7.4
Previous polyps (%)	3.4	3.6	3.6	3.5	3.9	0.9	0.9	0.8	1.1
Previous endoscopy (%)	25.1	27.2	27.7	25.9	27.7	9.6	11.5	11.3	11.5
Postmenopausal (%) <sup>c</sup>	NA <sup>d</sup>	NA	NA	NA	NA	32.9	32.9	33.7	34.0
Age at menarche (yr)	NA	NA	NA	NA	NA	12.4	12.4	12.4	12.3
Physical activity <sup>f</sup>	20.2	22.8	23.8	25.6	20.9	10.1%	14.3%	13.5%	13.4%
Mean BMI (kg/m <sup>2</sup> ) <sup>e</sup>	25.6	25.2	25.2	25.5	25.6	24.5	23.9	24.2	24.3
Current multivitamin supplementation (%)	31.3	83.0	79.5	80.1	39.8	28.8	70.2	70.7	69.5
Regular Vitamin C supplementation (%)	10.7	70.2	71.3	80.9	20.2	11.1	72.1	75.0	77.2
Mean vitamin E intake from multivitamins (IU)	5.6	17.8	21.2	26.1	7.8	4.7	13.9	15.2	17.9
Mean daily intake <sup>g</sup>									
Total vitamin E (IU)	16.9	190	457	895	19.7	11.4	194	440	1,042
Calories (kcal)	1,987	2,027	1,956	1,921	1,990	1,566	1,573	1,565	1,556
Total fat (g)	72.1	69.2	68.8	68.9	70.4	70.0	68.5	67.7	67.6
Folate (μg)	426	672	676	769	466	342	503	533	572
Methionine (g)	2.2	2.2	2.2	2.3	2.2	1.9	1.9	1.9	2.0
Alcohol (g)	11.4	11.1	11.3	12.4	11.0	6.3	6.3	6.5	6.7
Vitamin C (mg)	290	806	923	1,294	405	223	652	847	1,365
Total carotene (IU)	9,308	11,525	11,877	13,294	10,198	7,910	8,957	9,173	9,755
Vitamin D (IU)	302	574	588	693	342	265	437	479	529
Calcium (mg)	837	1,093	1,102	1,282	886	722	800	801	819
Total fiber (g)	20.5	22.6	22.6	23.2	21.8	13.5	14.7	15.0	15.0
Beef, pork, or lamb as main dish (servings/day)	0.3	0.2	0.2	0.2	0.2	0.4	0.3	0.3	0.3

<sup>a</sup> Standardized for age at baseline.

<sup>b</sup> No information on past vitamin use was available from 1980 Nurses' questionnaire; past use is defined as past vitamin E pill use (either with or without multivitamin use).

<sup>c</sup> Percentage of hormone users among postmenopausal women only.

<sup>d</sup> NA, not available

<sup>e</sup> BMI, body mass index.

<sup>f</sup> Physical activity at baseline for the HPFS is calculated as metabolic equivalents/week (mets/week) using information from the baseline questionnaire in 1986; for the NHS physical activity is calculated as the percentage of women in the highest category of physical activity since for the NHS information on mets/week is not available from the baseline questionnaire (1980 questionnaire).

<sup>g</sup> Nutrients are adjusted for total energy intake.

one-at-a-time. Trend tests were calculated by using median vitamin intake in each category (for vitamin E supplementation) or quintile (for dietary vitamin E intake) as continuous exposure scores in the logistic models. All *P*s are two sided.

Long-term intake of dietary vitamin E intake was assessed by calculating a cumulative average of dietary vitamin E intake (*i.e.*, the average of all of the available nutrient intakes for a participant up to the beginning of each 2-year follow-up cycle; Ref. 30).

Possible effects of short-term intake of vitamin E supplements on colon cancer risk were evaluated by using only information from the most recent biennial questionnaire to estimate cancer risk during the following 2 years (30). Participants who had stopped taking vitamin E supplements during follow-up, but had reported vitamin E supplementation on one or more previous questionnaires, were considered past users.

## Results

Table 1 shows age-standardized baseline characteristics by dose of vitamin E supplementation in the HPFS and the NHS cohorts. Most nondietary baseline characteristics were similar between vitamin E supplement users and never users. Compared with never users, a higher proportion of vitamin E supplement users were also aspirin users. Vitamin E supplement users were also more physically active than never users. The

majority of vitamin E supplement users consumed multivitamin and vitamin C supplements, which contributed to higher total intakes of folate, vitamin C, vitamin D, and total carotene. In addition, supplement users also had lower daily intakes of total fat and red meat and higher intakes of dietary fiber and calcium compared with never users, although the differences were relatively modest.

Associations between the risk of colon cancer and the dietary intake of vitamin E (after exclusion of multivitamin and vitamin E supplement users) at baseline and using the cumulative average measurements using the cumulative average measurements are depicted in Table 2. Among men, there was no association between higher dietary vitamin E intake and colon cancer risk. Higher dietary intake of vitamin E was associated with a slightly, albeit not statistically significant, reduced risk of colon cancer among women.

Compared with intake from vitamin E supplements, the amount of vitamin E obtained from foods alone was low (median intake in 1986: 10.2 IU in men, 8.6 IU in women). Therefore, we concentrated our further analysis on the association between supplemental intake of vitamin E and colon cancer risk.

Age- and multivariate-adjusted RRs of colon cancer according to baseline supplemental intake of vitamin E in both cohorts are shown in Table 3. Among men, results were sug-

Table 2 Age-adjusted and multivariate RRs and 95% CI of colon cancer according to baseline and updated dietary intake of vitamin E in both cohorts among participants not taking supplemental vitamin E

	HPFS			NHS		
	Cases/person years	Age-adjusted RR (95% CI)	Multivariate <sup>a</sup> RR (95% CI)	Cases/person years	Age-adjusted RR (95% CI)	Multivariate <sup>a</sup> RR (95% CI)
At baseline, <sup>b</sup> dietary intake vitamin E						
Q <sup>c</sup> 1	49/47,282	1.00	1.00	96/166,553	1.00	1.00
Q2	35/47,137	0.68 (0.44–1.05)	0.74 (0.48–1.15)	75/180,667	0.70 (0.52–0.95)	0.74 (0.54–1.00)
Q3	41/49,390	0.72 (0.47–1.09)	0.81 (0.53–1.23)	67/165,976	0.65 (0.48–0.89)	0.70 (0.51–0.96)
Q4	46/45,614	0.81 (0.54–1.21)	0.95 (0.62–1.44)	86/164,628	0.81 (0.61–1.09)	0.87 (0.64–1.18)
Q5	50/47,314	0.79 (0.53–1.18)	0.97 (0.64–1.46)	90/166,241	0.79 (0.59–1.05)	0.86 (0.63–1.17)
		$P_{\text{trend}} = 0.58$	$P_{\text{trend}} = 0.69$		$P_{\text{trend}} = 0.39$	$P_{\text{trend}} = 0.78$
Cumulative average update, <sup>b</sup> dietary intake vitamin E						
Q1	39/45,840	1.00	1.00	70/148,656	1.00	1.00
Q2	38/46,294	0.91 (0.58–1.42)	1.03 (0.66–1.62)	71/157,444	0.92 (0.66–1.29)	0.97 (0.70–1.36)
Q3	40/47,690	0.88 (0.56–1.36)	1.04 (0.67–1.63)	63/153,370	0.79 (0.56–1.12)	0.85 (0.60–1.21)
Q4	42/45,555	0.85 (0.55–1.32)	1.08 (0.69–1.69)	69/153,629	0.82 (0.59–1.15)	0.89 (0.63–1.25)
Q5	48/46,496	0.91 (0.60–1.38)	1.18 (0.76–1.83)	63/153,693	0.71 (0.50–1.00)	0.78 (0.55–1.11)
		$P_{\text{trend}} = 0.76$	$P_{\text{trend}} = 0.41$		$P_{\text{trend}} = 0.02$	$P_{\text{trend}} = 0.16$

<sup>a</sup> Multivariate adjusted for: age, family history of colorectal cancer, body mass index (at baseline), physical activity (at baseline), pack-years of smoking before age 30, aspirin use (at baseline), red meat intake (as beef, pork, or lamb as main dish at baseline), alcohol consumption (at baseline); multivariate models for NHS also included postmenopausal hormone use and menopausal status.

<sup>b</sup> Baseline variables denote information obtained in 1986 (HPFS) and in 1980 (NHS); updated variables denote information from all questionnaire cycles 1986–1994 (HPFS) and 1980–1994 (NHS); dietary vitamin E was updated using cumulative average update (see Materials and Methods).

<sup>c</sup> Q, quintile.

Table 3 Age-adjusted and multivariate RRs of colon cancer according to baseline supplemental intake of vitamin E in both cohorts<sup>a</sup>

	HPFS			NHS		
	Cases/person years	Age-adjusted RR (95% CI)	Multivariate <sup>b</sup> RR (95% CI)	Cases/person years	Age-adjusted RR (95% CI)	Multivariate <sup>b</sup> RR (95% CI)
At baseline <sup>c</sup>						
Type of vitamin supplementation						
Never users	150/152,068	1.00	1.00	414/844,063	1.00	1.00
Vitamin E only	15/16,055	0.74 (0.43–1.27)	0.79 (0.46–1.34)	26/54,735	0.77 (0.52–1.15)	0.80 (0.54–1.19)
Multivitamin only	105/114,256	0.92 (0.72–1.18)	0.97 (0.75–1.24)	129/341,313	0.78 (0.64–0.95)	0.83 (0.68–1.01)
Vitamin E and multivitamin	58/66,352	0.76 (0.56–1.03)	0.82 (0.60–1.11)	57/122,953	0.82 (0.62–1.09)	0.88 (0.66–1.16)
Total supplemental vitamin E						
Never users	160/158,622	1.00	1.00	414/857,142	1.00	1.00
0.1–15 IU	56/59,843	0.91 (0.67–1.23)	0.96 (0.71–1.30)	82/217,670	0.79 (0.62–1.00)	0.84 (0.66–1.06)
15.1–99.0 IU	45/50,992	0.86 (0.62–1.20)	0.90 (0.65–1.26)	50/118,354	0.88 (0.66–1.19)	0.93 (0.69–1.25)
>99 IU	67/77,743	0.71 (0.54–0.95)	0.77 (0.57–1.02)	80/169,898	0.83 (0.65–1.05)	0.87 (0.68–1.11)
		$P_{\text{trend}} = 0.03$	$P_{\text{trend}} = 0.06$		$P_{\text{trend}} = 0.21$	$P_{\text{trend}} = 0.37$
Vitamin E supplementation from vitamin E pills only						
Never users	282/298,081	1.00	1.00	543/1,185,377	1.00	1.00
≤250 IU	25/23,620	1.01 (0.67–1.52)	1.09 (0.72–1.64)	28/60,817	0.91 (0.62–1.33)	0.95 (0.65–1.39)
300–500 IU	37/44,960	0.69 (0.49–0.97)	0.73 (0.52–1.03)	44/90,917	0.87 (0.64–1.18)	0.90 (0.66–1.22)
≥600 IU	11/13,826	0.69 (0.38–1.25)	0.70 (0.38–1.29)	11/25,954	0.74 (0.41–1.35)	0.78 (0.43–1.42)
		$P_{\text{trend}} = 0.03$	$P_{\text{trend}} = 0.06$		$P_{\text{trend}} = 0.18$	$P_{\text{trend}} = 0.29$

<sup>a</sup> Relative risks for past supplement users (information on past supplement use at baseline only available for HPFS) are not shown in table 3 (for more information refer to Results). All trend tests were calculated after exclusion of past users.

<sup>b</sup> Multivariate adjusted for: age, family history of colorectal cancer, body mass index (at baseline), physical activity (at baseline), pack-years of smoking before age 30, aspirin use (at baseline), red meat intake (as beef, pork, or lamb as main dish at baseline), alcohol consumption (at baseline); multivariate models for NHS also included postmenopausal hormone use and menopausal status.

<sup>c</sup> Baseline variables denote information obtained in 1986 (HPFS) and in 1980 (NHS).

gestive of an inverse association between high intake of supplemental vitamin E (>99 IU) and the risk of colon cancer, but the CIs included one. When examining specific vitamin E supplements alone, a lower risk among men was suggested only at intakes of at least 300 IU vitamin E per day. In women, there was no evidence for an inverse association between vitamin E supplementation and risk of colon cancer. In both men and women, associations between vitamin E supplementation, using the biennially updated information, and colon cancer were similar to the findings for baseline supplemental vitamin E

intake (data not shown). Inclusion of multivitamin use in the final multivariate models did not change the results in either cohort. Results were also basically unchanged when other nutrients such as total fat, fiber, iron, methionine, folate, calcium, vitamin D, total vitamin A, and total carotene were added separately to the multivariate models. When vitamin C intake was added separately to the models, associations were unchanged for men; however, results for vitamin E were attenuated for women (data not shown). In both cohorts, the past use of supplemental vitamin E was not significantly associated with

Table 4 Multivariate RR of colon cancer and 95% CI by duration of high-dose vitamin E supplementation in both cohorts using updated information

	HPFS		NHS	
	Cases/person years	Multivariate <sup>a</sup> RR (95% CI)	Cases/person years	Multivariate <sup>a</sup> RR (95% CI)
Duration of vitamin E supplementation <sup>b</sup>				
Never users	266/278,350	1.00	448/1,005,303	1.00
Users				
1–4 yr	47/68,980	0.71 (0.52–0.98)	72/146,103	1.06 (0.82–1.37)
5–9 yr	23/26,756	0.85 (0.56–1.31)	42/86,069	0.98 (0.71–1.35)
≥10 yr	34/35,616	0.77 (0.54–1.11)	37/70,091	0.87 (0.61–1.22)
		$P_{\text{trend}} = 0.08$		$P_{\text{trend}} = 0.50$

<sup>a</sup> Multivariate adjusted for variables as denoted in Table 3.

<sup>b</sup> Low-dose vitamin E supplement users (*i.e.*, ≤250 IU supplementation per day) were excluded from analysis.

colon cancer risk (data not shown). Because the amount of vitamin E supplements obtained from multivitamins is generally low (median among supplement users at baseline: 15 IU for both men and women), all further analysis was focused on specific vitamin E pills only, unless otherwise noted.

Table 4 shows RRs of colon cancer by duration of vitamin E supplementation using the biennially updated information. Participants with doses of vitamin E supplement use ≤250 IU/day were excluded. In men, all duration categories showed risk estimates below one, but there was no evidence that risk decreased with longer duration. In women, there was also no evidence for an inverse association between the duration of vitamin use and colon cancer risk.

We investigated whether the association between vitamin E supplements and colon cancer risk differed by tertiles of dietary vitamin E intake. Among men, inverse associations between vitamin E supplementation and colon cancer risk was largely restricted to those in the highest tertile of dietary vitamin E intake. In women, we did not observe a stronger association for vitamin E supplementation on colon cancer risk with lower dietary vitamin E intake (data not shown).

We included a product term consisting of vitamin E supplementation (at baseline) as a binary variable (never and low-dose users combined *versus* supplemental intake ≥300 IU) and age (at baseline) as a continuous variable into the final multivariate models, but did not find evidence for a significant interaction between age and supplemental vitamin E intake (HPFS:  $P_{\text{interaction}} = 0.58$ ; NHS:  $P_{\text{interaction}} = 0.38$ ).

Relationships between vitamin E and colon cancer risk were also studied after stratification by menopausal status. Findings for both premenopausal women and postmenopausal women (after excluding postmenopausal women with current hormone use) were similar to those observed in the total NHS cohort (data not shown).

## Discussion

Findings from these two large United States cohorts do not provide consistent support for an inverse association between vitamin E supplementation and the risk of colon cancer. There was some suggestion that men with supplemental vitamin E intake of 300 IU/day or more may be at lower risk for colon cancer, but CIs included 1. Major strengths of this prospective study include the long follow-up period, the relatively large number of cases, the ability to control for various potential confounders, and the ability to investigate possible temporal relationships using repeated dietary measurements.

Relatively few observational studies have investigated an association between vitamin E and colon cancer risk (10–15),

including some case-control studies that have studied these associations separately for men and women. Gender-specific results have been conflicting. In one case-control study, an inverse association between supplemental vitamin E and colon cancer was stronger in women (comparing supplemental vitamin E of at least 200 IU to never users: OR, 0.27; 95% CI, 0.12–0.59) than in men (OR, 0.59; 95% CI, 0.30–1.18; Ref. 15). Another case-control study found an inverse association between dietary  $\alpha$ -tocopherol intake and colon cancer among men only [comparing highest quartile of intake to the lowest: OR in men, 0.44 (95% CI, 0.24–0.80); OR in women, 1.03 ( $P = 0.9$ ); Ref. 11].

Findings from nested case-control studies based on prediagnostic serum  $\alpha$ -tocopherol levels provide only limited support for a protective effect of serum  $\alpha$ -tocopherol on colon cancer risk. In a pooled analysis using data from five nested case-control studies, with 206 colon cancer cases and 938 controls, participants in the highest quartile of serum  $\alpha$ -tocopherol levels had a 30% lower risk of colon cancer than those in the lowest quartile (OR, 0.7; 95% CI, 0.4–1.3) but results were not statistically significant (12).

In a prospective study on 11,580 residents of a retirement community in California (Leisure World, Laguna Hills), who had been followed for 8 years, vitamin E supplementation (users *versus* nonusers) was associated with a slightly, albeit not statistically significant, decreased risk of colon cancer in women (RR, 0.76; 95% CI, 0.52–1.12) but not in men (RR, 1.01; 95% CI, 0.68–1.51; Ref. 13). Some potential limitations of that study include a relatively small number of colon cancer cases (96 male and 103 female cases), the lack of control for potential risk factors for colon cancer, and the use of a single baseline assessment of diet. Furthermore, the participants were considerably older (mean age in females, 73.8 years; mean age in males, 74.9 years) than our participants. In the prospective Iowa Women's Health study, 35,215 postmenopausal women between 55 and 69 years of age were followed for 4 years, during which 212 colon cancer cases were identified. Women in the highest quintile of total vitamin E intake had a 58% decrease in colon cancer risk when compared with women in the lowest quintile (RR, 0.42; 95% CI, 0.22–0.78), and women ages 55–59 years had a 84% decreased risk (RR, 0.16; 95% CI, 0.04–0.70; Ref. 10). In contrast, we did not find evidence for an interaction between supplemental vitamin E and age with regard to colon cancer risk.

Findings from recent clinical trials on supplemental vitamin E on the risk of colorectal adenomas are not conclusive (17, 31–33). In the  $\alpha$ -Tocopherol,  $\beta$ -Carotene Cancer Prevention Study, a randomized trial conducted among 29,133 male smok-

ers, supplementation with 50 mg of vitamin E for 5–8 years was associated with a 22%, albeit nonsignificantly, decreased risk of colorectal cancer (16); however, supplemental vitamin E was also statistically significantly associated with a higher risk of colorectal adenomas (RR, 1.66; 95% CI, 1.19–2.32; Ref. 33). In a large multicenter clinical trial, supplementation with 400 mg of vitamin E and 1 g of vitamin C per day over a period of 4 years was not related to risk of recurrent colorectal adenoma (RR, 1.1; 95% CI, 0.9–1.3; Ref. 17). In contrast, another trial from Italy observed a reduced risk of recurrent adenomas after daily supplementation with the vitamins A, C, and E (32). However, patients in these trials were followed for a short time period, precluding inferences about possible long-term effects. Furthermore, only a small fraction of all colorectal adenomas will evolve into colorectal cancer, and relationships may differ for adenomas that develop into colorectal cancer (2, 34).

Our data provide only limited evidence for an inverse association between the duration of vitamin E supplementation and colon cancer risk. The strongest association was seen among men who had used high-dose vitamin E supplements for up to 4 years, but the observed RR estimates were below 1 in all duration categories. A recent prospective study on the large American Cancer Society Cohort also failed to observe a relationship between long-term supplemental vitamin E and colorectal cancer mortality [ $<10$  years of supplemental vitamin E *versus* none: rate ratio, 0.87 (95% CI, 0.73–1.03);  $\geq 10$  years of supplemental vitamin E *versus* none: rate ratio = 1.08 (95% CI, 0.85–1.38); Ref. 35].

Some limitations in our study design are apparent. Potential interactions between supplemental intake of vitamin E and selenium, a cofactor for the antioxidant enzyme glutathione peroxidase, that also plays an important role in decreasing lipid peroxidation (36), could not be evaluated in this study. Information on selenium intake was not available because selenium contents of ingested foods vary with regional soil conditions (36). In addition, we cannot exclude the possibility that an unidentified variable related to high-dose supplemental vitamin E intake may have led to our observed associations in men. However, adjustment for variables that are commonly associated with healthier lifestyles such as physical activity, multivitamin supplementation, body mass index, various dietary factors, or smoking did not change our observed associations. Furthermore, in this study we focused only on  $\alpha$ -tocopherol, because vitamin E supplements contain only this form. However, it has been suggested that  $\gamma$ -tocopherol may also play a role in colon carcinogenesis (5).

In conclusion, our findings do not provide consistent support for an inverse association between supplemental vitamin E and colon cancer risk. Considering the paucity of epidemiological data on this association, we think that additional studies of vitamin E and colon cancer are warranted.

## References

- Greenlee, R. T., Hill-Harmon, M. B., Murray, T., and Thun, M. Cancer statistics, 2001. *CA Cancer J. Clin.*, *51*: 15–36, 2001.
- Greenberg, E. R. Preventing colorectal cancer. *Recent Results Cancer Res.*, *142*: 9–18, 1996.
- Giovannucci, E., and Willett, W. C. Dietary factors and risk of colon cancer. *Ann. Med.*, *26*: 443–452, 1994.
- Potter, J. D. Nutrition and colorectal cancer. *Cancer Causes Control*, *7*: 127–146, 1996.
- Stone, W. L., and Papas, A. M. Tocopherols and the etiology of colon cancer. *J. Natl. Cancer Inst. (Bethesda)*, *89*: 1006–1014, 1997.
- Packer, L. Protective role of vitamin E in biological systems. *Am. J. Clin. Nutr.*, *53*: 1050S–1055S, 1991.
- Meydani, M. Vitamin E [see comments]. *Lancet*, *345*: 170–175, 1995.
- Meagher, E. A., Barry, O. P., Lawson, J. A., Rokach, J., and Fitzgerald, G. A. Effects of vitamin E on lipid peroxidation in healthy persons. *J. Am. Med. Assoc.*, *285*: 1178–1182, 2001.
- Mirvish, S. S. Effects of vitamins C and E on *N*-nitroso compound formation, carcinogenesis, and cancer. *Cancer (Phila.)*, *58*: 1842–1850, 1986.
- Bostick, R. M., Potter, J. D., McKenzie, D. R., Sellers, T. A., Kushi, L. H., Steinmetz, K. A., and Folsom, A. R. Reduced risk of colon cancer with high intake of vitamin E: the Iowa Women's Health Study. *Cancer Res.*, *53*: 4230–4237, 1993.
- Ghadirian, P., Lacroix, A., Maisonneuve, P., Perret, C., Potvin, C., Gravel, D., Bernard, D., and Boyle, P. Nutritional factors and colon carcinoma: a case-control study involving French Canadians in Montreal, Quebec, Canada. *Cancer (Phila.)*, *80*: 858–864, 1997.
- Longnecker, M. P., Martin-Moreno, J. M., Knekt, P., Nomura, A. M., Schober, S. E., Stahelin, H. B., Wald, N. J., Gey, K. F., and Willett, W. C. Serum  $\alpha$ -tocopherol concentration in relation to subsequent colorectal cancer: pooled data from five cohorts. *J. Natl. Cancer Inst. (Bethesda)*, *84*: 430–435, 1992.
- Shibata, A., Paganini-Hill, A., Ross, R. K., and Henderson, B. E. Intake of vegetables, fruits,  $\beta$ -carotene, vitamin C and vitamin supplements and cancer incidence among the elderly: a prospective study. *Br. J. Cancer*, *66*: 673–679, 1992.
- Slattery, M. L., Edwards, S. L., Anderson, K., and Caan, B. Vitamin E and colon cancer: is there an association? *Nutr. Cancer*, *30*: 201–206, 1998.
- White, E., Shannon, J. S., and Patterson, R. E. Relationship between vitamin and calcium supplement use and colon cancer. *Cancer Epidemiol. Biomark. Prev.*, *6*: 769–774, 1997.
- Albanes, D., Malila, N., Taylor, P. R., Huttunen, J. K., Virtamo, J., Edwards, B. K., Rautalahti, M., Hartman, A. M., Barrett, M. J., Pietinen, P., Hartman, T. J., Sipponen, P., Lewin, K., Teerenhovi, L., Hietanen, P., Tangrea, J. A., Virtanen, M., and Heinonen, O. P. Effects of supplemental  $\alpha$ -tocopherol and  $\beta$ -carotene on colorectal cancer: results from a controlled trial (Finland). *Cancer Causes Control*, *11*: 197–205, 2000.
- Greenberg, E. R., Baron, J. A., Tosteson, T. D., Freeman, D. H., Jr. Beck, G. J., Bond, J. H., Colacchio, T. A., Collier, J. A., Frankl, H. D., Haile, R. W., et al. A clinical trial of antioxidant vitamins to prevent colorectal adenoma. Polyp Prevention Study Group [see comments]. *N. Engl. J. Med.*, *331*: 141–147, 1994.
- Rimm, E. B., Giovannucci, E. L., Willett, W. C., Colditz, G. A., Ascherio, A., Rosner, B., and Stampfer, M. J. Prospective study of alcohol consumption and risk of coronary disease in men [see comments]. *Lancet*, *338*: 464–468, 1991.
- Willett, W. C., Stampfer, M. J., Colditz, G. A., Rosner, B. A., Hennekens, C. H., and Speizer, F. E. Dietary fat and the risk of breast cancer. *N. Engl. J. Med.*, *316*: 22–28, 1987.
- Willett, W. C., and Stampfer, M. J. Implications of total energy intake for epidemiologic analyses. In: W. C. Willett (ed.), *Nutritional Epidemiology*, pp. 273–301. New York: Oxford University Press, 1998.
- Feskaniich, D., Rimm, E. B., Giovannucci, E. L., Colditz, G. A., Stampfer, M. J., Litin, L. B., and Willett, W. C. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. *J. Am. Diet. Assoc.*, *93*: 790–796, 1993.
- Rimm, E. B., Giovannucci, E. L., Stampfer, M. J., Colditz, G. A., Litin, L. B., and Willett, W. C. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *Am. J. Epidemiol.*, *135*: 1114–1126; discussion, 1127–1136, 1992.
- Salvini, S., Hunter, D. J., Sampson, L., Stampfer, M. J., Colditz, G. A., Rosner, B., and Willett, W. C. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. *Int. J. Epidemiol.*, *18*: 858–867, 1989.
- Willett, W. C., Sampson, L., Stampfer, M. J., Rosner, B., Bain, C., Witschi, J., Hennekens, C. H., and Speizer, F. E. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am. J. Epidemiol.*, *122*: 51–65, 1985.
- Willett, W. C., Reynolds, R. D., Cottrell-Hoehner, S., Sampson, L., and Browne, M. L. Validation of a semi-quantitative food frequency questionnaire: comparison with a 1-year diet record. *J. Am. Diet. Assoc.*, *87*: 43–47, 1987.
- Ascherio, A., Stampfer, M. J., Colditz, G. A., Rimm, E. B., Litin, L., and Willett, W. C. Correlations of vitamin A and E intakes with the plasma concentrations of carotenoids and tocopherols among American men and women. *J. Nutr.*, *122*: 1792–1801, 1992.
- Greenland, S., and Rothman, K. J. Introduction to stratified analysis. In: Rothman, K. J., and Sander, G. (eds.) *Modern epidemiology* 2<sup>nd</sup> ed., pp. 253–279. Philadelphia, PA: Lippincott-Raven Publishers, 1998.
- Cupples, L. A., D'Agostino, R. B., Anderson, K., and Kannel, W. B. Comparison of baseline and repeated measure covariate techniques in the Framingham Heart Study. *Stat. Med.*, *7*: 205–222, 1988.

29. D'Agostino, R. B., Lee, M. L., Belanger, A. J., Cupples, L. A., Anderson, K., and Kannel, W. B. Relation of pooled logistic regression to time dependent Cox regression analysis: the Framingham Heart Study. *Stat. Med.*, *9*: 1501–1515, 1990.
30. Willett, W. C. Issues in analysis and presentation of dietary data. *In*: W. C. Willett (ed.), *Nutritional Epidemiology*, pp. 321–345. New York: Oxford University Press, 1998.
31. McKeown-Eyssen, G., Holloway, C., Jazmaji, V., Bright-See, E., Dion, P., and Bruce, W. R. A randomized trial of vitamins C and E in the prevention of recurrence of colorectal polyps. *Cancer Res.*, *48*: 4701–4705, 1988.
32. Roncucci, L., Di Donato, P., Carati, L., Ferrari, A., Perini, M., Bertoni, G., Bedogni, G., Paris, B., Svanoni, F., Girola, M., *et al.* Antioxidant vitamins or lactulose for the prevention of the recurrence of colorectal adenomas. Colorectal Cancer Study Group of the University of Modena and the Health Care District 16. *Dis. Colon Rectum*, *36*: 227–234, 1993.
33. Malila, N., Virtamo, J., Virtanen, M., Albanes, D., Tangrea, J. A., and Huttunen, J. K. The effect of  $\alpha$ -tocopherol and  $\beta$ -carotene supplementation on colorectal adenomas in middle-aged male smokers. *Cancer Epidemiol. Biomark. Prev.*, *8*: 489–493, 1999.
34. Konings, E., and Greenberg, E. R. Antioxidant supplements and colorectal cancer [editorial]. *Nutrition*, *14*: 245–247, 1998.
35. Jacobs, E. J., Connell, C. J., Patel, A. V., Chao, A., Rodriguez, C., Seymour, J., McCullough, M. L., Calle, E. E., and Thun, M. J. Vitamin C and vitamin E supplement use and colorectal cancer mortality in a large American Cancer Society cohort. *Cancer Epidemiol. Biomark. Prev.*, *10*: 17–23, 2001.
36. Levander, O. A., and Burk, R. F. Selenium. *In*: M. L. Brown (ed.), *Present Knowledge in Nutrition*, pp. 268–273. Washington, DC: International Life Sciences Institute, Nutrition Foundation, 1990.

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