Vitamins E and C in the Prevention of Prostate and Total Cancer in Men: The Physicians' Health Study II Randomized Controlled Trial

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Vitamins E and C in the Prevention of Prostate and Total Cancer in Men

The Physicians' Health Study II Randomized Controlled Trial

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Context Many individuals take vitamins in the hopes of preventing chronic diseases such as cancer, and vitamins E and C are among the most common individual supplements. A large-scale randomized trial suggested that vitamin E may reduce risk of prostate cancer; however, few trials have been powered to address this relationship. No previous trial in men at usual risk has examined vitamin C alone in the prevention of cancer.

Objective To evaluate whether long-term vitamin E or C supplementation decreases risk of prostate and total cancer events among men.

Design, Setting, and Participants The Physicians' Health Study II is a randomized, double-blind, placebo-controlled factorial trial of vitamins E and C that began in 1997 and continued until its scheduled completion on August 31, 2007. A total of 14 641 male physicians in the United States initially aged 50 years or older, including 1307 men with a history of prior cancer at randomization, were enrolled.

Intervention Individual supplements of 400 IU of vitamin E every other day and 500 mg of vitamin C daily.

Main Outcome Measures Prostate and total cancer.

Results During a mean follow-up of 8.0 years, there were 1008 confirmed incident cases of prostate cancer and 1943 total cancers. Compared with placebo, vitamin E had no effect on the incidence of prostate cancer (active and placebo vitamin E groups, 9.1 and 9.5 events per 1000 person-years; hazard ratio [HR], 0.97; 95% confidence interval [CI], 0.85-1.09; $P=.58$) or total cancer (active and placebo vitamin E groups, 17.8 and 17.3 cases per 1000 person-years; HR, 1.04; 95% CI, 0.95-1.13; $P=.41$). There was also no significant effect of vitamin C on total cancer (active and placebo vitamin C groups, 17.6 and 17.5 events per 1000 person-years; HR, 1.01; 95% CI, 0.92-1.10; $P=.86$) or prostate cancer (active and placebo vitamin C groups, 9.4 and 9.2 cases per 1000 person-years; HR, 1.02; 95% CI, 0.90-1.15; $P=.80$). Neither vitamin E nor vitamin C had a significant effect on colorectal, lung, or other site-specific cancers. Adjustment for adherence and exclusion of the first 4 or 6 years of follow-up did not alter the results. Stratification by various cancer risk factors demonstrated no significant modification of the effect of vitamin E on prostate cancer risk or either agent on total cancer risk.

Conclusions In this large, long-term trial of male physicians, neither vitamin E nor C supplementation reduced the risk of prostate or total cancer. These data provide no support for the use of these supplements for the prevention of cancer in middle-aged and older men.

Trial Registration clinicaltrials.gov Identifier: NCT00270647

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IN SOME OBSERVATIONAL STUDIES, INtake or blood levels of vitamins E and C have been associated with reduced risk of certain cancers.[1] Basic research has provided plausible mechanisms by which antioxidant micronutrients such as vitamin E and vitamin C may delay various steps in carcinogenesis.[2-4] However, definitive proof that vitamins E and C can reduce the risk of overall or site-specific cancers must rely on large-scale randomized trials.

A number of trials have addressed the potential role of vitamins in the prevention of cancer; however, the results from these trials have not been consistent. Some[5-8] but not all[9-16] have supported a role for various antioxidants in the prevention of total or site-specific cancers. The most compelling data supporting a role of vitamin E in the prevention of prostate cancer have come from the Finnish ATBC (α-Tocopherol, Beta Carotene) Cancer Prevention Trial.[9] This trial was designed

See also related articles.

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to test the effect of vitamin E and beta carotene on lung cancer risk among current and past smokers. Although there was no reduction in risk of lung cancer with either agent, men assigned to active α-tocopherol had a 34% reduction in the hazard of prostate cancer (HR, 0.66; 95% CI, 0.52-0.86).[17] The HOPE-TOO (Heart Outcomes Prevention Evaluation–The Ongoing Outcomes) trial reported no reduction in prostate cancer among those treated with vitamin E compared with placebo for an average of 7 years (HR, 0.98; 95% CI, 0.76-1.26).[16]

Other trials of vitamin E were not designed specifically to address prostate cancer risk, and most of these trials were of just a few years' duration, which may be too short to detect longer-term effects on cancer. Vitamin C alone has been less well studied in large-scale trials. One other recently completed study evaluated vitamin C (500 mg daily) supplementation and total and site-specific cancer risk among women.[18]

Despite uncertainty about the long-term health effects or benefits, more than half of US adults take vitamin supplements, and vitamins E and C are among the most popular individual supplements.[19] Given this widespread use, the gaps in knowledge about the role of these agents in cancer prevention, and the uncertainties about other long-term health effects of vitamins E and C, we conducted the Physicians' Health Study (PHS) II, a randomized, double-blind, placebo-controlled factorial trial designed to provide clinically relevant information on the individual effects of vitamin E and vitamin C on total and prostate cancer among 14 641 male physicians treated and followed up for an average of 8.0 years. In this article, we present the findings on prostate, total, and other common cancers. The effects of these agents on cardiovascular events were recently published.[20]

METHODS

Study Design

The PHS II is a randomized, double-blind, placebo-controlled, 2×2×2×2 factorial trial evaluating the balance of risks and benefits of vitamin E (400-IU synthetic α-tocopherol or its placebo on alternate days; BASF Corporation, Florham Park, New Jersey), vitamin C (500-mg synthetic ascorbic acid or its placebo daily; BASF Corporation), and a multivitamin (Centrum Silver or its placebo daily; Wyeth Pharmaceuticals, Madison, New Jersey) in the prevention of cancer and cardiovascular disease among 14 641 male physicians 50 years or older.[21] A fourth randomized component, beta carotene (50-mg Lurotin or placebo on alternate days; BASF Corporation), was terminated on schedule in March 2003. The multivitamin component is continuing at the recommendation of the data and safety monitoring committee.

The PHS II study design has previously been described.[20,21] In brief, recruitment, enrollment, and randomization of men into PHS II occurred in 2 phases (FIGURE 1). Starting in July 1997, 18 763 PHS I participants[10,22] were invited to participate in PHS II. Men were ineligible if they reported a history of cirrhosis or active liver disease, were receiving anticoagulants, or reported a serious illness that might preclude participation. Men with a history of cancer as well as myocardial infarction or stroke were eligible to enroll in PHS II. Participants also must have been willing to forgo during the course of PHS II any current use of multivitamins or individual supplements containing more than 100% of the recommended daily allowance of vitamin E, vitamin C, beta carotene, or vitamin A. A total of 7641 willing participants (41%) from PHS I were randomized into PHS II and retained their original beta carotene treatment assignment.

In 1999, invitational letters and baseline questionnaires were mailed to 254 597 US male physicians 50 years or older identified from a list provided by the American Medical Association, excluding PHS I participants. Between July 1999 and July 2001, 42 165 men completed a baseline questionnaire. Of these, 11 128 were willing and eligible following the same eligibility criteria as PHS I participants. A 12-week placebo run-in period excluded men who were nonadherent, an attribute that typically emerges during the first several months of participation.[21,23] Of 11 128 physicians who entered the run-in phase, 7000 willing and eligible men (63%) took at least two-thirds of their pills and were randomized into PHS II.

Thus, 14 641 men (7641 from PHS I and 7000 new physicians) were randomized into PHS II in blocks of 16 and stratified by age; prior diagnosis of cancer; prior diagnosis of cardiovascular disease; and, for the 7641 PHS I participants, their original beta carotene treatment assignment. Men were randomly assigned to receive vitamin E or its placebo, to receive vitamin C or its placebo, and to receive active or placebo beta carotene and multivitamin. With respect to vitamins E and C, randomization yielded 4 nearly equal-sized groups receiving active vitamin E alone, active vitamin C alone, both active agents, or both placebos. There were 1307 men (8.9%) with a history of cancer (excluding nonmelanoma skin cancer) prior to randomization into PHS II. All participants provided written informed consent, and the institutional review board at Brigham and Women's Hospital approved the research protocol.

Study Treatment, Follow-up, and Adherence

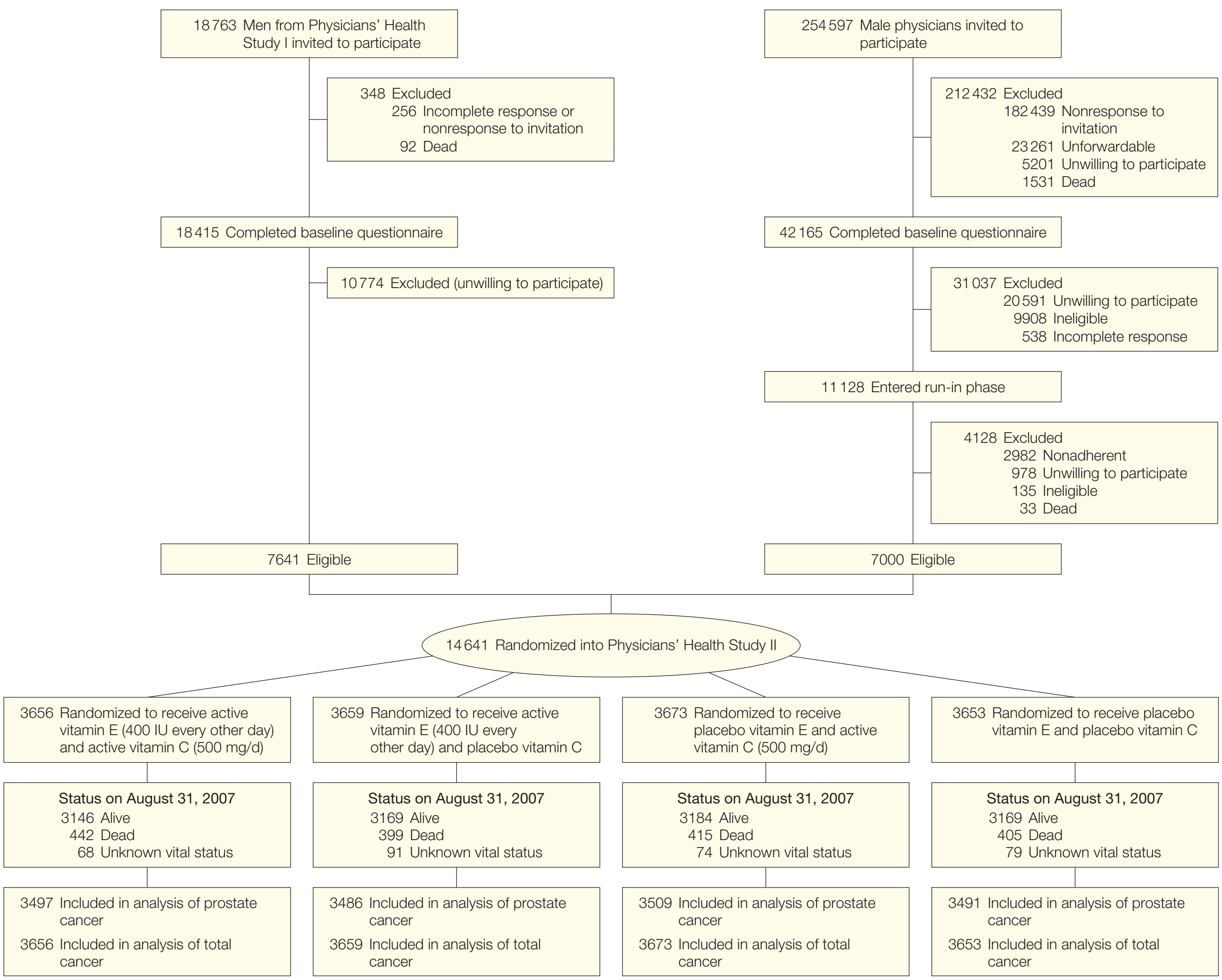
Participants were sent monthly calendar packs containing vitamin E or placebo (taken every other day) and vitamin C or placebo (taken daily) every 6 months for the first year and annually thereafter. Participants were also sent annual questionnaires asking about adherence, potential adverse events, the occurrence of new end points, and updated risk factors. Treatment and follow-up continued in blinded fashion through August 31, 2007, the scheduled end of the vitamin E and C components of PHS II. Analyses include follow-up and validation through September 2008 of reported end points that occurred through the end of August 2007. Morbidity and mortality follow-up rates were extremely high, at 95.3% and 97.7%, respectively. Morbidity and mortality follow-up as a percentage of person-time each exceeded 99.9%, with only 1055 and 289 person-years of potential morbidity and mortality follow-up lost through August 31, 2007.

Adherence was defined from participant self-reports as taking at least two-thirds of the study agents. For active vitamin E and its placebo, adherence at 4 years was 78% and 77%, respectively (P=.12), and at the end of follow-up (mean, 8.0 years), 72% and 70% (P=.004). For active vitamin C and its placebo, adherence at 4 years was 78% and 78%, respectively (P=.99), and at the end of follow-up, 71% and 71% (P=.54). There were no differences between groups in average rates of individual nontrial vitamin E (3.2% active, 3.1% placebo) or vitamin C supplement use (3.8% active, 4.4% placebo) for 31 or more days per year (drop-ins) at the end of the trial (each $P>.05$).

Confirmation of End Points

For the vitamin E component, the primary cancer end point was total prostate cancer; total cancer (excluding nonmelanoma skin cancer) was the primary end point for the vitamin C component and a prespecified secondary end point for vitamin E. Incident colorectal cancer was another prespecified secondary end point for the vitamin E component. Other individual sites of cancer were assessed and validated, as well as total mortality and cancer mortality. For each end point reported by partici-

Figure 1. Flow Diagram of Participants From Screening to Completion of the Vitamin E and Vitamin C Components of the Physicians' Health Study II



Those classified as "unforwardable" were not able to be contacted by mail. For the primary end point of prostate cancer, primary analyses were restricted to 13983 men without prostate cancer at baseline. The primary analysis of total cancer included all 14641 men.

pants by follow-up questionnaire, letter, telephone call, and other correspondence, we requested permission from the participant to examine relevant medical records. Once consent was obtained, records were requested from the hospital or attending physician and reviewed by an end-points committee of physicians blinded to randomized treatment assignment.

The vast majority of cancers were confirmed with pathology or cytology reports. Rarely, the committee confirmed a reported case of cancer based on strong clinical and radiological or laboratory marker evidence when pathology or cytology review was not conducted. Total mortality was confirmed by the end-points committee or by obtaining a death certificate. A National Death Index search was performed for any participants with unknown vital status. Only confirmed end points are included in this report.

Statistical Analyses

All primary analyses classified study participants based on the intention-to-treat principle, in which randomized participants were classified according to their randomized vitamin E or vitamin C treatment assignments and were followed up until the occurrence of a disease end point, death, loss to follow-up, or the end of the vitamin E and vitamin C components of PHS II on August 31, 2007, whichever came first. SAS version 9.1 (SAS Institute Inc, Cary, North Carolina) was used, with statistical significance set at $P<.05$ using 2-sided tests.

The PHS II was designed to have greater-than-80% power to detect a 13% reduction in the hazard of total cancer (excluding nonmelanoma skin cancer) and a 19% reduction in the hazard of prostate cancer. Estimates of study power relied on historical event rates observed in PHS physicians that predicted the trial would accrue 418 incident prostate cancer cases and 877 total cancer cases in the half of participants randomized to a placebo treatment. The actual number of cases of prostate cancer and total cancer accrued in the vitamin E placebo group exceeded the numbers predicted for power calculations by 23% and 9%, respectively.

We first compared baseline characteristics by vitamin E or C treatment assignment to evaluate whether randomization equally distributed baseline characteristics. Cox proportional hazards models were used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) comparing event rates in the vitamin E and placebo groups and the vitamin C and placebo groups. For each prespecified end point, models were stratified on the presence of cancer at randomization and adjusted for study design variables: age; PHS cohort (original PHS I participant, new PHS II participant); and randomized beta carotene, vitamin E or vitamin C, and multivitamin assignments. For total cancer analyses, all new cancers were included, regardless of whether the participant had a baseline history of cancer. For each site-specific cancer analysis, participants were excluded if they had a baseline history of cancer of the same site. Thus, these analyses included 13 983 men initially free of prostate cancer, 14 520 initially free of colorectal cancer, and 14 610 initially free of lung cancer.

For analyses of the secondary end points of total mortality, any cancer mortality, and site-specific cancer deaths, we included all participants. The association between vitamin E and prostate cancer mortality was also examined separately among the 13 334 men without and 1307 with a baseline history of cancer. We tested the proportional hazards assumption by modeling interaction terms separately for vitamin E or C with the logarithm of time, and these assumptions were not violated ($P>.05$). We then investigated whether vitamin E or C adherence affected our primary results through sensitivity analyses that censored follow-up when a participant reported taking less than two-thirds of either vitamin E or vitamin C over the previous year. To explore a possible late benefit associated with vitamin E or C, we analyzed separately the person-time and outcomes in the first 4 years of treatment and then after 4 years. Additional exploratory analyses considered estimated treatment effects within 2-year time intervals and also whether an effect was present if only events and person-time after 6 years of treatment were considered. Finally, we conducted subgroup analyses stratified by major cancer risk factors as well as previous cancer history and assessed effect modification by using interaction terms between subgroup indicators and either vitamin E or C assignment.

RESULTS

The PHS II randomized 14 641 men with a mean (SD) age of 64.3 (9.2) years. Randomization equally distributed all baseline characteristics between vitamin E or vitamin C and their placebo groups (all $P>.05$) (TABLE 1). During a mean follow-up of 8.0 years (median, 7.6 years; interquartile range, 7.1-9.6 years; maximum, 10.0 years), total follow-up was 117 711 person-years. There were 1943 confirmed total cancer cases and 1008 prostate cancer cases, with some men experiencing multiple events. A total of 1661 men died during follow-up.

Vitamin E and Cancer

The overall rates of prostate cancer were 9.1 and 9.5 per 1000 person-years in the active and placebo vitamin E groups, respectively. There was no effect of vitamin E on prostate cancer incidence (HR, 0.97; 95% CI, 0.85-1.09; $P=.58$) (TABLE 2). The cumulative incidence curves indicate that this lack of effect did not vary for up to 10 years of treatment and follow-up (log-rank $P=.53$) (FIGURE 2). For total cancer, the overall rates were 17.8 and 17.3 per 1000 person-years in the active and placebo vitamin E groups, respectively.

Compared with placebo, vitamin E also did not reduce the incidence of total cancer (HR, 1.04; 95% CI, 0.95-1.13; $P=.41$). We found no effect for any site-specific cancers, including colorectal (HR, 0.88; 95% CI, 0.64-1.19; $P=.40$), lung (HR, 0.89; 95% CI, 0.60-1.31;

P=.55), bladder (HR, 1.21; 95% CI, 0.76-1.94; *P*=.43), and pancreatic (HR, 1.14; 95% CI, 0.67-1.93; *P*=.63). In addition, there was no significant effect of vitamin E on total mortality (HR, 1.08; 95% CI, 0.98-1.19; *P*=.13) or cancer mortality (HR, 1.13; 95% CI, 0.95-1.34; *P*=.16). Censoring participants at the time of vitamin E nonadherence did not impact the results for prostate cancer (HR, 0.95; 95% CI, 0.84-1.07; *P*=.38) or total cancer (HR, 1.02; 95% CI, 0.93-1.11; *P*=.68).

We next evaluated whether baseline history of cancer, risk factors, and other randomized interventions from PHS II modified the effect of vitamin E on prostate cancer or total cancer (TABLE 3). Among 13 334 men without a baseline history of cancer, vitamin E had no effect on the prevention of total cancer, nor was there any substantial effect of vitamin E on newly diagnosed cancer among 1307 men with cancer at baseline or on prostate cancer among men with another cancer at baseline. In addition, we found no other significant effect modification by baseline risk factors on prostate cancer. In addition, there was no effect modification by randomized beta carotene or vitamin C or the ongoing multivitamin treatment assignment. Analyses focused on the possibility that a number of years of treatment were required before emergence of an effect found no apparent relationship of vitamin E with either prostate or total cancer in data restricted to person-time and events after 4 years of treatment. Further restriction to events and time after 6 years of treatment similarly found no apparent relationships.

Vitamin C and Cancer

The overall rates of total cancer for the active and placebo vitamin C groups were 17.6 and 17.5 per 1000 person-years, respectively. There was no effect of vitamin C on the primary end point of total cancer (HR, 1.01; 95% CI, 0.92-1.10; *P*=.86) (Table 2). The cumulative incidence curves showed no difference between groups in the HRs over time (log-rank *P*=.92) (Figure 2). The rates of prostate cancer were 9.4 cases per 1000 person-years for the active vitamin C group and 9.2 cases per 1000 person-years for the placebo group (HR, 1.02; 95% CI, 0.90-1.15; *P*=.80). Vitamin C also had no effect on other site-specific cancers, including colorectal (HR, 0.86; 95% CI, 0.63-1.17; *P*=.35), lung (HR, 0.95; 95% CI, 0.64-1.39; *P*=.78), bladder (HR, 0.85; 95% CI, 0.53-1.36; *P*=.49), and pancreatic (HR, 0.97; 95% CI, 0.57-1.64; *P*=.91). In addition, no effect was found between vitamin C and either total mortality (HR, 1.07; 95% CI, 0.97-1.18; *P*=.17) or cancer mortality (HR, 1.06; 95% CI, 0.89-1.25; *P*=.53). Censoring for nonadherence with vitamin C did not ap-

Table 1. Baseline Characteristics According to Vitamin E and Vitamin C Treatment Assignment in 14 641 Men From the Physicians' Health Study II

	Men, No. (%)[a]			
	Vitamin E[b]		Vitamin C[b]	
Self-reported Baseline Characteristics	Active (n = 7315)	Placebo (n = 7326)	Active (n = 7329)	Placebo (n = 7312)
Age, mean (SD), y	64.2 (9.1)	64.3 (9.2)	64.3 (9.2)	64.3 (9.1)
Age, y				
50-59	2940 (40.2)	2951 (40.3)	2953 (40.3)	2938 (40.2)
60-69	2349 (32.1)	2347 (32.0)	2348 (32.0)	2348 (32.1)
≥70	2026 (27.7)	2028 (27.7)	2028 (27.7)	2026 (27.7)
Body mass index, mean (SD)[c]	26.0 (3.6)	26.0 (3.7)	26.0 (3.6)	26.0 (3.7)
Cigarette smoking				
Never	4104 (56.1)	4148 (56.7)	4135 (56.5)	4117 (56.4)
Former	2967 (40.6)	2885 (39.4)	2908 (39.7)	2944 (40.3)
Current	239 (3.3)	285 (3.9)	280 (3.8)	244 (3.3)
Exercise ≥1 time/wk				
No	2739 (38.4)	2766 (38.7)	2759 (38.5)	2746 (38.6)
Yes	4389 (61.6)	4383 (61.3)	4408 (61.5)	4364 (61.4)
Alcohol consumption				
Rarely/never	1372 (18.9)	1358 (18.7)	1364 (18.7)	1366 (18.8)
≥1 drink/mo	5893 (81.1)	5923 (81.4)	5920 (81.3)	5896 (81.2)
Current aspirin use				
No	1627 (22.6)	1634 (22.6)	1638 (22.6)	1623 (22.6)
Yes	5578 (77.4)	5589 (77.4)	5605 (77.4)	5562 (77.4)
Parental history of cancer[d]				
No	2906 (46.5)	2931 (46.5)	2927 (46.5)	2910 (46.5)
Yes	3344 (53.5)	3377 (53.5)	3371 (53.5)	3350 (53.5)
Paternal history of prostate cancer[d]				
No	5713 (89.6)	5792 (89.8)	5755 (89.5)	5750 (89.9)
Yes	663 (10.4)	661 (10.2)	678 (10.5)	646 (10.1)
Parental history of colorectal cancer[d]				
No	5492 (88.0)	5552 (88.5)	5535 (88.5)	5509 (88.1)
Yes	748 (12.0)	719 (11.5)	721 (11.5)	746 (11.9)
Self-reported history of cancer				
No	6657 (91.0)	6677 (91.1)	6675 (91.1)	6659 (91.1)
Yes	658 (9.0)	649 (8.9)	654 (8.9)	653 (8.9)
Self-reported history of prostate cancer				
No	6983 (95.5)	7000 (95.6)	7006 (95.6)	6977 (95.4)
Yes	332 (4.5)	326 (4.4)	323 (4.4)	335 (4.6)
Self-reported history of colorectal cancer				
No	7253 (99.2)	7267 (99.2)	7270 (99.2)	7250 (99.2)
Yes	62 (0.8)	59 (0.8)	59 (0.8)	62 (0.8)

[a] Unless otherwise indicated. The numbers do not always sum to group totals because of missing information for some variables.
[b] $P>.05$ for all comparisons between active and placebo groups of vitamin E and vitamin C.
[c] Calculated as weight in kilograms divided by height in meters squared.
[d] Excludes 2083, 1812, and 2130 men with missing information on parental history of cancer, prostate cancer, and colorectal cancer, respectively.

preciably affect our findings for total cancer (HR, 1.00; 95% CI, 0.92-1.09; *P*=.98).

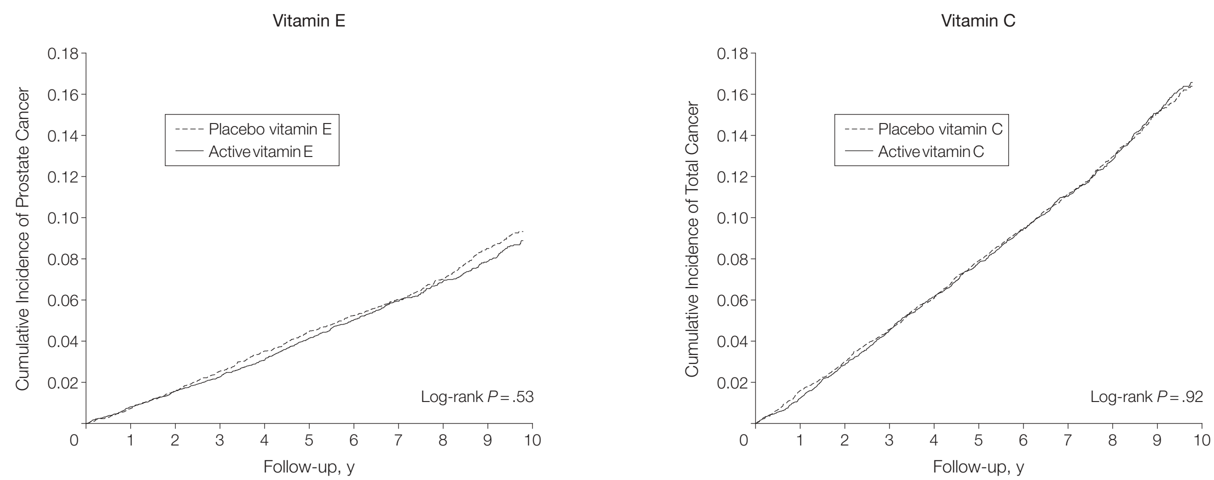
We then evaluated whether baseline history of cancer, risk factors, and other randomized interventions from PHS II or follow-up time modified the effect of vitamin C on the primary end point total cancer (TABLE 4). There was

Table 2. Association Between Randomized Vitamin E and Vitamin C Assignment and the Risk of Total Cancer, Site-Specific Cancer, and Mortality in the Physicians' Health Study II[a]

		Vitamin E			Vitamin C		
		Events, No.			Events, No.		
Outcome	Men in Analysis, No.[b]	Active	Placebo	Adjusted HR (95% CI)[c]	Active	Placebo	Adjusted HR (95% CI)[c]
Total cancer	14 641	984	959	1.04 (0.95-1.13)	973	970	1.01 (0.92-1.10)
Total epithelial cell cancer	14 641	876	877	1.01 (0.92-1.11)	873	880	1.00 (0.91-1.09)
Prostate cancer	13 983	493	515	0.97 (0.85-1.09)	508	500	1.02 (0.90-1.15)
Prostate cancer death	14 641	37	39	1.01 (0.64-1.58)	45	31	1.46 (0.92-2.31)
Colorectal cancer	14 520	75	87	0.88 (0.64-1.19)	75	87	0.86 (0.63-1.17)
Colorectal cancer death	14 641	21	32	0.68 (0.39-1.18)	27	26	1.04 (0.61-1.78)
Lung cancer	14 610	48	55	0.89 (0.60-1.31)	50	53	0.95 (0.64-1.39)
Lung cancer death	14 641	44	43	1.05 (0.69-1.60)	39	48	0.82 (0.53-1.25)
Bladder cancer	14 570	38	32	1.21 (0.76-1.94)	32	38	0.85 (0.53-1.36)
Bladder cancer death	14 641	9	12	0.79 (0.33-1.88)	10	11	0.92 (0.39-2.17)
Pancreatic cancer	14 638	29	26	1.14 (0.67-1.93)	27	28	0.97 (0.57-1.64)
Pancreatic cancer death	14 641	27	23	1.20 (0.69-2.09)	23	27	0.86 (0.49-1.49)
Lymphoma	14 595	73	60	1.23 (0.88-1.74)	69	64	1.08 (0.77-1.52)
Lymphoma death	14 641	25	21	1.24 (0.69-2.21)	21	25	0.84 (0.47-1.50)
Leukemia	14 613	46	34	1.38 (0.88-2.15)	44	36	1.23 (0.79-1.91)
Leukemia death	14 641	20	12	1.71 (0.83-3.49)	18	14	1.30 (0.65-2.62)
Melanoma	14 486	74	63	1.18 (0.85-1.66)	63	74	0.86 (0.61-1.20)
Melanoma death	14 641	6	5	1.25 (0.38-4.09)	7	4	1.75 (0.51-5.98)
Total mortality	14 641	841	820	1.08 (0.98-1.19)	857	804	1.07 (0.97-1.18)
Cancer mortality	14 641	273	250	1.13 (0.95-1.34)	268	255	1.06 (0.89-1.25)

Abbreviations: CI, confidence interval; HR, hazard ratio; PHS, Physicians' Health Study.
[a] Mean follow-up of 8.0 years for all 14 641 men through August 31, 2007.
[b] For total cancer, site-specific mortality, total mortality, and cancer mortality, analyses included all 14 641 participants. For the incidence of site-specific cancers, analyses were restricted to men without that site-specific cancer at baseline.
[c] Adjusted for age, PHS cohort (original PHS I participant, new PHS participant), and randomized treatment assignment (beta carotene, multivitamin, and either vitamin E or vitamin C) and stratified on baseline cancer.

Figure 2. Cumulative Incidence Rates of Total Prostate Cancer by Randomized Vitamin E Assignment or Total Cancer by Randomized Vitamin C Assignment in the Physicians' Health Study II



Vitamin E — No. at Risk

Placebo	7000	6913	6799	6673	6539	6382	6251	5194	2965	2758
Active	6983	6871	6770	6650	6517	6357	6230	5204	2921	2750

Vitamin C — No. at Risk

Placebo	7312	7150	6997	6835	6674	6468	6301	5214	2958	2744
Active	7329	7197	7033	6848	6663	6461	6287	5195	2925	2709

no effect modification by any cancer risk factor on the effect of vitamin C on total cancer, including stratifying by previous history of cancer. In addition, there was no effect modification by randomized treatment assignments, including beta carotene, vitamin E, or the ongoing multivitamin component. To evaluate the effect of the latency period, the effect of vitamin C treatment assignment was examined by years of follow-up in 2-year increments. Further, analyses restricted to events and times after 4 years of treatment, or after 6 years, found no association of vitamin C with total cancer.

When we examined the 2-way interaction between randomized vitamin E and vitamin C assignments, we found no significant interactions for either total cancer (*P* for interaction=.87), prostate cancer (*P* for interaction=.55), colorectal cancer (*P* for interaction=.59), or lung cancer (*P* for interaction=.44) (FIGURE 3).

Adverse Effects

As previously published,[20] we assessed a number of potential adverse effects of vitamins E and C, and there were no significant effects of either agent on minor bleeding (including hematuria, easy bruising, and epistaxis) or gastrointestinal tract symptoms (peptic ulcer, constipation, diarrhea, gastritis, and nausea), fatigue, drowsiness, skin discoloration or rashes, or migraine. A greater number of hemorrhagic strokes was observed among those assigned to vitamin E compared with placebo (39 vs 23 events; HR, 1.74; 95% CI, 1.04-2.91), a finding that was observed in the ATBC Cancer Prevention Trial[9] but not observed in other trials of vitamin E.

Table 3. Association Between Randomized Vitamin E and the Risks of Prostate Cancer and Total Cancer According to Baseline Characteristics, Treatment Assignment, and Follow-up Time in the Physicians' Health Study II[a]

Group	Prostate Cancer Events, No.		Adjusted HR (95% CI)[b]	*P* for Interaction	Total Cancer Events, No.		Adjusted HR (95% CI)[b]	*P* for Interaction
	Active	Placebo			Active	Placebo		
Age, y								
50-59	118	120	0.99 (0.77-1.27)		212	205	1.04 (0.86-1.26)	
60-69	209	237	0.88 (0.73-1.06)	.37	382	381	1.01 (0.87-1.16)	.84
≥70	166	158	1.06 (0.86-1.32)		390	373	1.06 (0.92-1.22)	
Body mass index[c]								
<25	215	211	1.01 (0.84-1.23)		420	396	1.05 (0.92-1.21)	
25-29	231	252	0.95 (0.79-1.13)	.79	449	470	0.99 (0.87-1.13)	.44
≥30	47	51	0.89 (0.60-1.33)		114	92	1.20 (0.91-1.58)	
Smoking status								
Never	269	282	0.98 (0.83-1.16)		491	491	1.04 (0.91-1.17)	
Former	207	218	0.92 (0.76-1.12)	.47	451	424	1.03 (0.90-1.17)	.82
Current	17	14	1.50 (0.74-3.04)		42	43	1.23 (0.80-1.88)	
Exercise ≥1 time/wk								
No	194	198	0.98 (0.81-1.20)	.99	401	374	1.10 (0.95-1.26)	.44
Yes	298	306	0.99 (0.84-1.16)		569	562	1.02 (0.91-1.15)	
Alcohol consumption								
Rarely/never	74	85	0.87 (0.64-1.19)	.43	173	163	1.07 (0.86-1.32)	.80
≥1 drink/mo	415	424	0.99 (0.87-1.14)		806	790	1.03 (0.94-1.14)	
Current aspirin use								
No	97	99	1.00 (0.76-1.33)	.88	218	198	1.14 (0.94-1.39)	.31
Yes	395	411	0.97 (0.85-1.11)		758	749	1.02 (0.92-1.13)	
Parental history of cancer[d]								
No	182	194	0.93 (0.76-1.14)	.73	357	347	1.04 (0.90-1.21)	.88
Yes	249	257	0.98 (0.83-1.17)		473	463	1.03 (0.91-1.17)	
History of cancer								
No	474	498	0.96 (0.85-1.09)	.57	895	882	1.03 (0.94-1.13)	.42
Yes	19	17	1.10 (0.57-2.13)		89	77	1.14 (0.84-1.55)	
Randomized to vitamin C								
Placebo	255	245	1.05 (0.88-1.25)	.19	491	479	1.03 (0.91-1.17)	.89
Active	238	270	0.89 (0.75-1.06)		493	480	1.05 (0.92-1.19)	
Period of follow-up, y								
<4	211	242	0.95 (0.79-1.15)	.39	437	444	1.01 (0.89-1.16)	.53
≥4	282	273	1.04 (0.88-1.23)		547	515	1.08 (0.95-1.21)	

Abbreviations: CI, confidence interval; HR, hazard ratio; PHS, Physicians' Health Study.
[a] For prostate cancer, analyses were restricted to 13 983 men without prostate cancer at baseline. For total cancer, analyses included all 14 641 participants.
[b] Adjusted for age, PHS cohort (original PHS I participant, new PHS participant), and randomized treatment assignment (beta carotene, multivitamin, and vitamin C).
[c] Calculated as weight in kilograms divided by height in meters squared.
[d] Excludes 2083 men with missing information on parental history of cancer.

COMMENT

In this large-scale, randomized controlled trial among middle-aged and older men, neither long-term vitamin E nor vitamin C supplementation reduced the risk of prostate or total cancer. Neither vitamin reduced the risk of cancer death; major site-specific cancers, including colorectal, lung, bladder, pancreatic, lymphoma, leukemia, or melanoma; or total mortality. There was no suggestion of a latent effect for either vitamin.

Vitamin E and Cancer

The most compelling data suggesting that vitamin E may reduce the risk of prostate cancer come from the Finnish ATBC Cancer Prevention Trial. The ATBC trial was a randomized, double-blind, placebo-controlled trial of α-tocopherol (50 mg daily) and beta carotene (20 mg daily) among 29 133 male smokers. Among those assigned to 50 mg of α-tocopherol supplementation daily, there was no overall reduction in cancer risk; however, there was a 34% reduction in prostate cancer incidence during a median follow-up period of 6.1 years.[9]

This effect attenuated after several years of posttrial follow-up. The effect of vitamin E appeared to be stronger on more advanced tumors. A 41% reduction in prostate cancer mortality was also observed. Since prostate cancer was not a prespecified end point, it remains possible that this finding was due to chance. Other completed trials of vitamin E, including several among individuals at high risk for cardiovascular disease, were not powered to address the possible benefit of vitamin E on prostate cancer. The HOPE-TOO prostate cancer results demonstrated no clear harm or benefit of 400 IU daily of vitamin E.[16]

In response to the ATBC finding, we launched the PHS II trial to specifically test the hypothesis that vitamin E might prevent prostate cancer in middle-aged or older men. Because the effect in the ATBC trial appeared to be stronger in later-stage cancers, we chose not to screen for prostate cancer and even included a small number of participants with previously diagnosed cancers. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) was also designed to assess the role of vitamin E in the prevention of incident prostate cancer.[24] In contrast to PHS II, SELECT enrolled men initially free of prostate cancer based on baseline prostate-specific antigen values and digital rectal examinations. Using a factorial design, SELECT also tested selenium in the prevention of prostate cancer.

One notable difference between the PHS II and ATBC trials was the prevalence of smoking in ATBC and the very low levels of smoking in PHS II. If the effect of vitamin E was confined to smokers, PHS II would likely miss this effect. Another notable difference between the 2 trials was the lower dose of vitamin E in ATBC (50 mg daily), compared with 400 IU on alternate days in PHS II. Alternatively, the results of PHS II suggest that the observed beneficial findings of vitamin E on the development of prostate cancer from the ATBC trial may have been due to the

Table 4. Association Between Randomized Vitamin C and the Risk of Total Cancer According to Baseline Characteristics, Treatment Assignment, and Follow-up Time in the Physicians' Health Study II[a]

Group	Total Cancer Events, No. Active	Total Cancer Events, No. Placebo	Adjusted HR (95% CI)[b]	*P* for Interaction
Age, y				
50-59	205	212	0.96 (0.79-1.16)	.77
60-69	388	375	1.05 (0.91-1.21)	
≥70	380	383	1.00 (0.87-1.16)	
Body mass index[c]				
<25	402	414	0.98 (0.86-1.13)	.56
25-29	460	459	0.99 (0.87-1.13)	
≥30	110	96	1.16 (0.88-1.52)	
Smoking status				
Never	506	476	1.08 (0.95-1.23)	.15
Former	426	449	0.95 (0.83-1.08)	
Current	40	45	0.76 (0.49-1.16)	
Exercise ≥1 time/wk				
No	403	372	1.09 (0.94-1.25)	.15
Yes	551	580	0.95 (0.84-1.07)	
Alcohol consumption				
Rarely/never	168	168	1.00 (0.81-1.24)	.99
≥1 drink/mo	801	795	1.01 (0.92-1.11)	
Current aspirin use				
No	205	211	0.97 (0.80-1.18)	.70
Yes	761	746	1.02 (0.92-1.13)	
Parental history of cancer[d]				
No	339	365	0.94 (0.81-1.09)	.20
Yes	483	453	1.06 (0.93-1.21)	
History of cancer				
No	898	879	1.03 (0.94-1.13)	.17
Yes	75	91	0.82 (0.61-1.12)	
Randomized to vitamin E				
Placebo	480	479	1.00 (0.88-1.14)	.89
Active	493	491	1.01 (0.89-1.15)	
Period of follow-up, y				
<4	443	438	0.96 (0.84-1.10)	.43
≥4	530	532	1.01 (0.89-1.13)	

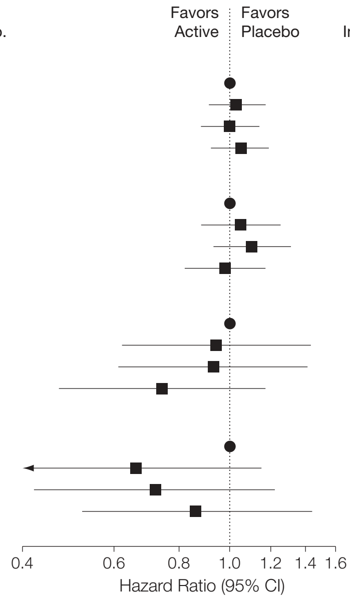
Abbreviations: CI, confidence interval; HR, hazard ratio; PHS, Physicians' Health Study.
[a] For total cancer, analyses included all 14 641 participants.
[b] Adjusted for age, PHS cohort (original PHS I participant, new PHS participant), and randomized treatment assignment (beta carotene, multivitamin, and vitamin E).
[c] Calculated as weight in kilograms divided by height in meters squared.
[d] Excludes 2083 men with missing information on parental history of cancer.

play of chance. This illustrates the importance of cautious interpretation of findings on secondary end points.

Mixed results have been obtained from trials of vitamin E supplementation and total cancer. In the ATBC trial, there was no reduction in risk of total cancer among those randomized to α-tocopherol (50 mg daily) and/or beta carotene (20 mg daily), and vitamin E alone had no effect on the primary end points of lung or total cancer.[25] In the Chinese Cancer Prevention Trial, conducted among 29 584 poorly nourished residents of Linxian, China, those assigned to a combined daily treatment of vitamin E (30 mg), beta carotene (15 mg), and selenium (50 µg) experienced statistically significant reductions of 9% in total mortality, 13% in cancer mortality, and 21% in gastric cancer mortality after nearly 6 years of treatment and follow-up.[5] However, these results may not be generalizable to well-nourished populations. Moreover, because 3 agents were tested in combination, the specific benefit of vitamin E, beta carotene, or selenium cannot be determined. In the ATBC trial, those assigned to vitamin E had a nonsignificant 22% reduction (HR, 0.78; 95% CI, 0.55-1.09) in colorectal cancer incidence.[9,17] In the Women's Health Study, there was no reduction in the risk of colorectal cancer among middle-aged and older women (HR, 1.00; 95% CI, 0.77-1.31).[15] Our findings do not support a role of vitamin E in the prevention of total cancer, colorectal cancer, or other common cancers.

Figure 3. Hazard Ratios of Total Cancer, Prostate Cancer, Colorectal Cancer, and Lung Cancer Comparing Combinations of Active Vitamin E and Active Vitamin C Groups With the Placebo Vitamin E and Placebo Vitamin C Groups in the Physicians' Health Study II

Outcome	Events, No.	Men, No.	P for Interaction
Total cancer	1943	14641	
Placebo vitamin E and C [reference]	479	3653	.87
Active vitamin E	491	3659	
Active vitamin C	480	3673	
Active vitamin E and C	493	3656	
Prostate cancer	1008	13983	
Placebo vitamin E and C [reference]	245	3491	.55
Active vitamin E	255	3486	
Active vitamin C	270	3509	
Active vitamin E and C	238	3497	
Colorectal cancer	162	14520	
Placebo vitamin E and C [reference]	45	3624	.59
Active vitamin E	42	3626	
Active vitamin C	42	3643	
Active vitamin E and C	33	3627	
Lung cancer	103	14610	
Placebo vitamin E and C [reference]	32	3644	.44
Active vitamin E	21	3651	
Active vitamin C	23	3667	
Active vitamin E and C	27	3648	



CI indicates confidence interval; HR, hazard ratio. Error bars indicate 95% CIs.

Vitamin C and Cancer

In contrast to vitamin E, which is available in a limited number of foods, vitamin C is derived from many fruit and vegetable sources. In a review of data from more than 90 epidemiologic studies of dietary intake of vitamin C (or foods that supply vitamin C) and total cancer, Block[26] found that almost all showed a protective relationship, with a median 2-fold increased relative risk for low compared with high intake. The effects were statistically significant in three-fourths of the studies. Both dietary intake[27-29] and blood-based studies have shown inverse relationships. Epidemiologic evidence suggests an inverse association between dietary intake of vitamin C and risk of a variety of specific cancers.[26] Published reports show significant protective effects of vitamin C on breast, oral, gastric, esophageal, pancreatic, lung, cervical, and rectal cancer, while none have reported elevated risk with increasing intake.[26,30,31]

A major gap in the evidence regarding a possible role of vitamin C in the prevention of cancer is lack of data from large-scale primary prevention trials. Secondary prevention trials focusing on vitamin C for the recurrence of colon cancer or polyps have also yielded mixed results, ranging from a nonsignificant reduction (relative risk, 0.86; 95% CI, 0.51-1.45) among individuals with colon polyps assigned to a combination of vitamin E and C, compared with placebo,[32] to no evidence that either combined vitamins E and C or beta carotene alone reduced the incidence of subsequent colorectal adenomas among patients with previous adenoma.[33]

The PHS II attempted to fill the gap in the vitamin C literature with a long-term trial of individual vitamin C supplements at a commonly used dose in a large group of men. Our findings of no reduction in risk of total cancer and no clear evidence of a reduction in site-specific cancers do not support the use of vitamin C supplementation in the prevention of cancer. It remains possible that vitamin C intake is a marker of other nutrients that are consumed with vitamin C in the diet.

Strengths and Limitations

Major strengths of this study were the high levels of adherence to the study agents over a long period of time and the high quality of reporting of health information. Further, the conduct of this trial entirely by mail greatly increased the efficiency and reduced the cost of this study. Recruitment costs were about $200 per participant and annual follow-up costs were about $100 per participant, a fraction of the cost of similar studies that require establishment of many study sites with dedicated research personnel.

The study was conducted in a well-nourished population, and thus, these results may not preclude potential benefits in less well-nourished populations. One concern is the choice of dose used. It is not feasible to test multiple doses in these large-scale trials. The doses of vitamin E and C in the PHS were chosen because they were in the range of those commonly in use, because they did not have known major adverse effects that would impact adherence, and because their safety data were sound—a critical issue when conducting a trial by mail. The form of vitamin E chosen for our study was synthetic α-tocopherol, the most abundant component of natural vitamin E. However, in nature, vitamin E is composed of both α- and γ-tocopherol. γ-Tocopherol has been postulated to possibly play a more important role in prostate cancer protection.[34]

The duration of a large-scale trial is also an issue of concern. We had to balance the desire to extend treatment and follow-up as long as possible considering issues of cost and adherence; however, it remains possible that chemoprevention may require even longer durations of treatment and follow-up than is feasible in randomized trials. We will continue to follow the PHS II cohort for emergent latent effects. Adherence remains an issue of concern in any long-term study, but levels of adherence in the PHS II remained good after a mean follow-up of 8.0 years. It remains possible that these agents have a role in chemoprevention only when taken in the context of other micronutrients, a hypothesis we are testing in the continuation of the multivitamin component of PHS II.

CONCLUSION

In this long-term, large-scale, low-cost trial, after a mean of 8.0 years of treatment and follow-up in 14 641 men, neither vitamin E nor vitamin C supplementation reduced the risk of prostate or total cancer. There was also no clear effect of either agent on other site-specific cancers. It is reassuring that there was not a clear signal of harm for either agent. These data provide no support for the use of these supplements in the prevention of cancer in middle-aged and older men. Results of the multivitamin arm of the PHS II will be forthcoming in several years.

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