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Age-Related Cataract in a Randomized Trial of Vitamins E and C in Men

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Objective: To test whether supplementation with alternate-day vitamin E or daily vitamin C affects the incidence of age-related cataract in a large cohort of men.

Methods: In a randomized, double-masked, placebo-controlled trial, 11 545 apparently healthy US male physicians 50 years or older without a diagnosis of cataract at baseline were randomly assigned to receive 400 IU of vitamin E or placebo on alternate days and 500 mg of vitamin C or placebo daily.

Main Outcome Measure: Incident cataract responsible for a reduction in best-corrected visual acuity to 20/30 or worse based on self-report confirmed by medical record review.

Application to Clinical Practice: Long-term use of vitamin E and C supplements has no appreciable effect on cataract.

Results: After 8 years of treatment and follow-up, 1174 incident cataracts were confirmed. There were 579 cataracts in the vitamin E–treated group and 595 in the vitamin E placebo group (hazard ratio, 0.99; 95% confidence interval, 0.88-1.11). For vitamin C, there were 593 cataracts in the treated group and 581 in the placebo group (hazard ratio, 1.02; 95% confidence interval, 0.91-1.14).

Conclusion: Long-term alternate-day use of 400 IU of vitamin E and daily use of 500 mg of vitamin C had no notable beneficial or harmful effect on the risk of cataract.

Trial Registration: clinicaltrials.gov Identifier: NCT00270647.

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An estimated 20.5 million persons 40 years and older in the United States show some evidence of age-related cataract.[1-3] For 50% of these persons, the cataracts are of sufficient severity to impair vision.[3] Treatment in the form of cataract surgery is readily available, but this procedure accounts for a large portion of Medicare expenditures.[4] Prevention of cataract is a preferred strategy, but other than avoidance of cigarette smoking,[5-8] no modifiable risk factors or preventive agents have been identified.

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Nutrition is suspected to be an important factor in cataract development. Because oxidative damage is a prominent feature of cataracts,[9-11] one focus of nutrition research has been the link between dietary intake of nutrients with antioxidant potential, particularly vitamins E and C, and the risk of cataract. Vitamin E is a lipid-soluble antioxidant concentrated in lens fibers and membranes that may inhibit cataract formation by reducing photoperoxidation of lens lipids and stabilizing lens cell membranes.[12-15] Vitamin C is located in aqueous compartments of lens membranes, where it may function as an antioxidant and protect lens proteases from photooxidative destruction.[16]

Data from prospective observational studies[17-30] generally support the antioxidant hypothesis by indicating an inverse association between dietary and supplemental intake of vitamins E and C and other antioxidant nutrients and the risk of cataract. However, the results of completed randomized trials to date have been disappointing. Vitamin E, either alone or combined with other vitamin supplements, has been tested in 6 trials,[31-36] and the results indicate little benefit for treatment durations as long as 6.5 years in men and 10 years in women. Vitamin C combined with other antioxidants has been tested in 3 trials,[32-34] and the results indicate little benefit for treatment durations up to 6.5 years. There are

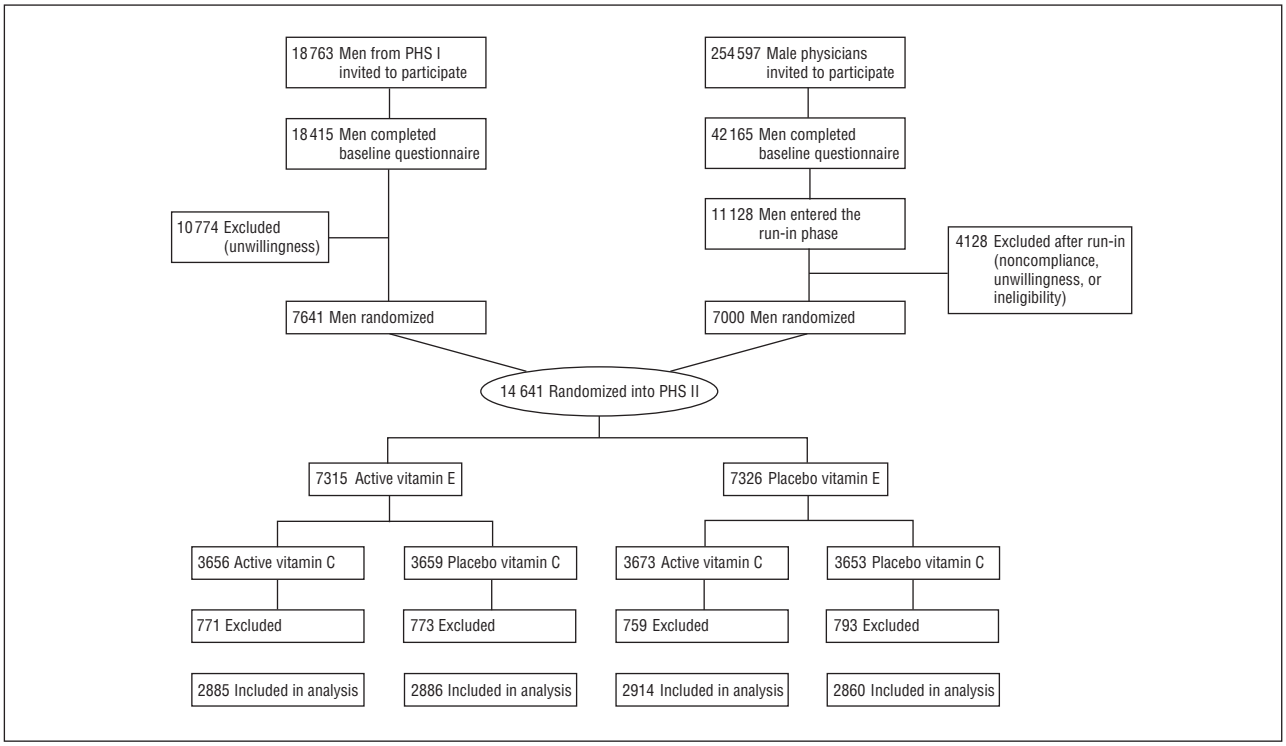

Figure 1. Flow diagram of the vitamin E and vitamin C components of the Physicians' Health Study (PHS) II. A total of 3096 participants who had a diagnosis of cataract at baseline were excluded.

no data for vitamin E treatment durations longer than 6.5 years in men and no data for supplementation with vitamin C alone in men or women.

Herein, we report the final results for cataract from the vitamin E and vitamin C components of the Physicians' Health Study (PHS) II. The PHS II is a randomized, double-masked, placebo-controlled trial designed to examine the effects of vitamin E, vitamin C, and a multivitamin in the prevention of cancer and cardiovascular disease (CVD) in a large population of male physicians. Data reported herein regarding cataract represent the longest treatment duration for vitamin E in men and the first trial data for vitamin C alone.

METHODS

STUDY DESIGN

The PHS II is a randomized, double-masked, placebo-controlled, 2×2×2×2-factorial trial evaluating the balance of risks and benefits of treatment with vitamin E (400 IU of synthetic α-tocopherol or its placebo on alternate days) (BASF Corp, Florham Park, New Jersey), vitamin C (500 mg of synthetic ascorbic acid or its placebo daily) (BASF Corp), and a multivitamin (Centrum Silver or its placebo daily) (Wyeth Pharmaceuticals, Madison, New Jersey) on the occurrence of cancer and CVD in 14 641 male physicians 50 years and older.[37] A fourth randomized component, beta carotene (50 mg of Lurotin or placebo on alternate days) (BASF Corp), was terminated in March 2003. Incident cataract was a prespecified secondary end point of the trial.[37] The final results of the vitamin E and vitamin C components of the trial for cancer and CVD have recently been published.[38,39] The multivitamin component is continuing at the recommendation of the data and safety monitoring committee.

The PHS II study design has previously been described.[37] Briefly, recruitment, enrollment, and randomization of men into the PHS II occurred in 2 phases (**Figure 1**). In phase 1, which began in 1997, 7641 willing and eligible participants from the PHS I[40-43] retained their original beta carotene treatment assignment and were newly randomized to receive vitamin C, vitamin E, and a multivitamin. In phase 2, which began in 1999, 7000 new physician participants identified from a list provided by the American Medical Association were randomized to receive beta carotene, vitamin C, vitamin E, and a multivitamin. Informed consent was obtained from all the men, and the research protocol was reviewed and approved by the institutional review board at Brigham and Women's Hospital.

Participants completed annual questionnaires supplying information about compliance with pill taking and the occurrence of new end points, including cataract. Treatment and follow-up continued in a masked manner through August 31, 2007, the scheduled end of the vitamin E and vitamin C components of the PHS II. Follow-up was 95.3% for morbidity and 97.7% for mortality.

Compliance with pill taking was based on self-report and was defined as taking at least two-thirds of the study agents. For active vitamin E and its placebo, compliance at 4 years was 78% and 77%, respectively ($P=.12$), and at the end of follow-up (mean of 8 years) was 72% and 70% ($P=.004$). For active vitamin C and its placebo, compliance at 4 years was 78% and 78%, respectively ($P=.99$), and at the end of follow-up was 71% and 71% ($P=.54$).

ASCERTAINMENT AND CONFIRMATION OF CATARACT

Participants with a diagnosis of cataract at baseline (n=3096) were excluded. After the report of a cataract diagnosis or extraction, written consent was obtained to contact the treating ophthalmologist or optometrist. Ophthalmologists and optometrists were contacted by mail and were asked to complete a cataract questionnaire supplying information about the presence of lens opacities, date of diagnosis, visual acuity loss, cataract extraction, other ocular abnormalities that could explain visual acuity loss, and cataract type (eg, nuclear, cortical, or posterior subcapsular [PSC])

and origin (including age related, traumatic, congenital, inflammatory, or surgery or corticosteroid induced). Ophthalmologists and optometrists were given the option to provide the requested information by supplying copies of the relevant medical records. Medical records were obtained for more than 92% of participants reporting cataract.

End points included incident cataract and extraction. Cataract was defined as a self-report confirmed by medical record review to be initially diagnosed after randomization but before August 31, 2007, age related in origin (congenital cataracts and those due to trauma, corticosteroid use, intraocular inflammation, or surgery were excluded), with best-corrected visual acuity of 20/30 or worse and no other ocular disease to explain the visual acuity loss. In the presence of another ocular disease, a lens opacity was considered a cataract if in the judgment of the ophthalmologist or optometrist the opacity was of sufficient severity to reduce visual acuity to 20/30 or worse when considered alone. Extraction was defined as the surgical removal of an incident cataract.

A total of 11 545 participants without a diagnosis of cataract at baseline are included in this analysis. Of these, 5771 were in the vitamin E group and 5774 were in the vitamin E placebo group, and 5799 were in the vitamin C group and 5746 were in the vitamin C placebo group.

STATISTICAL ANALYSIS

The estimated power of the trial for incident cataract was based on historical event rates observed in the PHS I. The PHS II had greater than 80% power to detect an 11% reduction in the hazard of cataract.

Baseline characteristics were compared in the vitamin E and vitamin C groups using 2-sample *t* tests, χ^2 tests for proportions, and tests for trend for ordinal categories. We used Kaplan-Meier curves to estimate cumulative incidence across time by randomized group and the log-rank test to compare curves. The Cox proportional hazards model was used to estimate the hazard ratio (HR) of cataract in the vitamin E group compared with placebo and in the vitamin C group compared with placebo after adjustment for age at baseline, PHS cohort (original PHS I participant or new PHS II participant), and randomized beta carotene, vitamin E or vitamin C, and multivitamin assignments. No adjustment was made for vitamin E or vitamin C dose contained in the multivitamin. Analyses were also conducted to examine the effect of age on any association between vitamin E or vitamin C and cataract. Models were fit separately in 3 age groups (50-59, 60-69, and ≥70 years), and tests of trend were calculated by including a term for the interaction of the antioxidant and age (expressed as a continuous variable, with values of 1 to 3 corresponding to the 3 age groups) in a proportional hazards model. Interaction terms were tested for additivity of the 2 antioxidant agents using multiplicative terms in the Cox model. We tested the proportionality assumption by including an interaction term of vitamin E or vitamin C with the logarithm of time in the Cox models. For the cataract end point, the proportionality assumption was not violated for treatment with vitamin E ($P=.68$) or vitamin C ($P=.37$). For each HR, the 95% confidence interval (CI) and 2-sided *P* value were calculated.

We also conducted subgroup analyses by categories of baseline variables that are possible risk factors for cataract. We explored possible effect modification by using interaction terms between subgroup indicators and antioxidant assignment, and we tested for trend when subgroup categories were ordinal.

Individuals, rather than eyes, were the unit of analysis because eyes were not examined independently. Participants were classified according to the status of the worse eye as defined by the occurrence of cataract surgery or, in the absence of cataract surgery, by an earlier date of diagnosis. When the 2 eyes had the same date of diagnosis, we designated the eye with the worse visual acuity at the most recent eye examination as the worse eye. When the worse eye was excluded because of visual acuity loss attributed to other ocular abnormalities or a cause that was not age related, the fellow eye was considered for classification.

Table 1. Baseline Characteristics by Randomized Groups in the Physicians' Health Study II[a]

Characteristic	Participants, Total No. (N=11 545)	Vitamin E Group		Vitamin C Group	
		Active (n=5771)	Placebo (n=5774)	Active (n=5799)	Placebo (n=5746)
Age, mean (SD), y	NA	62.0 (7.9)	62.0 (7.9)	62.0 (7.9)	62.0 (7.9)
Age, y					
50-59	5614	48.4	48.9	48.7	48.6
60-69	3931	34.2	33.9	33.8	34.3
≥70	2000	17.4	17.3	17.5	17.2
Cigarette smoking					
Never	6848	58.8	59.9	59.3	59.4
Former	4285	38.0	36.3	37.0	37.3
Current	403	3.2	3.7	3.7	3.3
Alcohol use					
Rarely/never	2117	18.4	18.5	18.4	18.5
≥1 drink/mo	9356	81.6	81.5	81.6	81.5
BMI					
Mean (SD)	NA	26.0 (3.4)	26.0 (3.4)	26.1 (3.4)	26.0 (3.4)
<25	4739	41.6	40.6	40.8	41.4
25 to <30	5549	47.5	48.7	48.2	48.0
≥30	1245	10.9	10.7	11.0	10.6
History of hypertension[b]					
Yes	4449	38.6	38.9	38.2	39.4
No	7023	61.4	61.1	61.8	60.6
History of high cholesterol[c]					
Yes	4000	35.8	36.3	36.1	35.9
No	7102	64.2	63.7	63.9	64.1
History of diabetes mellitus					
Yes	551	5.0	4.5	4.6	5.0
No	10 984	95.0	95.5	95.4	95.0
Exercise ≥1 time/wk					
Yes	7051	62.8	62.4	62.4	62.7
No	4214	37.2	37.7	37.6	37.3
Self-reported history of CVD[d]					
Yes	455	3.9	4.0	4.1	3.8
No	11 090	96.1	96.0	96.0	96.2

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CVD, cardiovascular disease; NA, not available.

[a] Data are given as percentage of participants unless otherwise noted. Number of participants for some characteristics do not sum to 11 545 because of missing values. Due to rounding, percentages do not total 100.

[b] Defined as a self-reported systolic blood pressure of at least 140 mm Hg, diastolic blood pressure of at least 90 mm Hg, or past or current treatment for hypertension.

[c] Defined as a self-reported total cholesterol level of at least 240 mg/dL (to convert to millilmoles per liter, multiply by 0.0259) or past or current treatment for hypercholesterolemia.

[d] Included nonfatal myocardial infarction and nonfatal stroke.

RESULTS

As expected in this large randomized trial, the baseline characteristics were distributed equally between the active and placebo groups for vitamins E and C (**Table 1**).

A total of 1174 cataracts and 801 cataract extractions were confirmed during mean follow-up of 8 years. **Figure 2** shows subtypes for 1160 participants (98.8%) with diagnosed cataract.

VITAMIN E

There were 579 cataracts in the vitamin E group and 595 in the placebo group (HR, 0.99; 95% CI, 0.88-1.11) (**Table 2**). Analyses of cataract subtypes indicated no significant effects of vitamin E on the incidence of nuclear (HR, 0.99; 95% CI, 0.88-1.11), cortical (0.96; 0.80-1.15), or PSC (0.95; 0.77-1.18) cataract (Table 2). Similar nonsignificant findings were observed for extraction of cataract and subtypes (**Table 3**). In age-stratified analyses, men in the youngest age group (50-59 years) who were assigned to the active vitamin E group tended to have lower risks of cataract and subtypes, although no test of trend attained statistical significance (diagnosis and extraction). Cumulative incidence rates of cataract according to year of follow-up are shown in **Figure 3**A. There was no apparent benefit of vitamin E at any point during the trial.

For cataract and extraction, the effect of vitamin E did not differ markedly within categories of known or possible risk factors (data for cataract are given in **Table 4**) or by treatment assignment for the other randomized interventions in the PHS II (Table 4 and **Figure 4**).

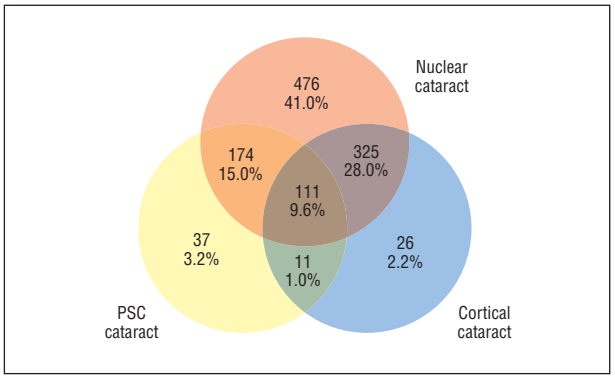

Figure 2. Venn diagram showing subtypes for 1160 participants with diagnosed cataract in the Physicians' Health Study II. Excludes 14 participants with missing subtype information. PSC indicates posterior subcapsular.

VITAMIN C

There were 593 cataracts in the vitamin C group and 581 in the placebo group (HR, 1.02; 95% CI, 0.91-1.14) (Table 2). For subtypes, there were no significant effects of vitamin C on the incidence of nuclear (HR, 1.01; 95% CI, 0.89-1.14), cortical (1.10; 0.92-1.31), or PSC (0.94; 0.76-1.17) cataract (Table 2). For cataract and subtypes, HRs did not vary statistically significantly among the 3 age groups. Similar nonsignificant findings were observed for extraction of cataract and subtypes (Table 3). Figure 3B presents cumulative incidence rates of cataract according to year of follow-up. No apparent benefit of vitamin C was observed at any point during the trial.

The effect of vitamin C on cataract and extraction did not differ appreciably within categories of known or possible risk factors, other than a possible, but statistically non-

Table 2. Cases of Cataract and Cataract Subtypes According to Randomized Treatment Assignment in 3 Age Groups

	Vitamin E Group					Vitamin C Group				
Cataract Type and Participant Age, y	Active, No. (n=5771)	Placebo, No. (n=5774)	HR (95% CI)[a]	*P* Value	*P* Value for Trend[b]	Active, No. (n=5799)	Placebo, No. (n=5746)	HR (95% CI)[c]	*P* Value	*P* Value for Trend[b]
Total cataract										
50-59	99	126	0.79 (0.61-1.03)	.09		107	118	0.89 (0.69-1.16)	.40	
60-69	268	246	1.09 (0.92-1.29)	.33	.46	273	241	1.17 (0.99-1.40)	.07	.87
≥70	212	223	0.95 (0.79-1.15)	.61		213	222	0.94 (0.77-1.13)	.49	
Subtotal	**579**	**595**	0.99 (0.88-1.11)	.82		**593**	**581**	1.02 (0.91-1.14)	.77	
Nuclear[d]										
50-59	84	103	0.82 (0.62-1.10)	.19		87	100	0.86 (0.64-1.14)	.30	
60-69	249	231	1.08 (0.90-1.29)	.41	.75	253	227	1.16 (0.97-1.38)	.11	.98
≥70	202	217	0.93 (0.77-1.13)	.47		206	213	0.94 (0.78-1.14)	.54	
Subtotal	**535**	**551**	0.99 (0.88-1.11)	.81		**546**	**540**	1.01 (0.89-1.14)	.90	
Cortical[d]										
50-59	32	50	0.65 (0.41-1.01)	.054		38	44	0.85 (0.55-1.32)	.48	
60-69	105	94	1.12 (0.85-1.48)	.44	.34	110	89	1.28 (0.97-1.70)	.08	.67
≥70	93	99	0.94 (0.71-1.25)	.69		100	92	1.06 (0.80-1.41)	.69	
Subtotal	**230**	**243**	0.96 (0.80-1.15)	.68		**248**	**225**	1.10 (0.92-1.31)	.31	
PSC[d]										
50-59	32	57	0.57 (0.37-0.88)	.01		43	46	0.92 (0.61-1.40)	.70	
60-69	83	60	1.38 (0.99-1.93)	.056	.20	70	73	0.99 (0.72-1.38)	.97	.97
≥70	47	54	0.86 (0.58-1.28)	.46		49	52	0.92 (0.62-1.36)	.67	
Subtotal	**162**	**171**	0.95 (0.77-1.18)	.67		**162**	**171**	0.94 (0.76-1.17)	.60	

Abbreviations: CI, confidence interval; HR, hazard ratio; PSC, posterior subcapsular.
[a] Adjusted for age, Physicians' Health Study cohort, and vitamin C, beta carotene, and multivitamin treatment assignment.
[b] Test for trend of the effect of age on the association between randomized treatment assignment and cataract.
[c] Adjusted for age, Physicians' Health Study cohort, and vitamin E, beta carotene, and multivitamin treatment assignment.
[d] With or without other subtypes.

Table 3. Cases of Extraction of Cataract and Cataract Subtypes According to Randomized Treatment Assignment in 3 Age Groups

Cataract Type and Participant Age, y	Vitamin E Group					Vitamin C Group				
	Active, No. (n=5771)	Placebo, No. (n=5774)	HR (95% CI)[a]	*P* Value	*P* Value for Trend[b]	Active, No. (n=5799)	Placebo, No. (n=5746)	HR (95% CI)[c]	*P* Value	*P* Value for Trend[b]
Total extraction										
50-59	65	91	0.72 (0.52-0.99)	.04	.40	70	86	0.80 (0.59-1.10)	.17	.87
60-69	180	164	1.10 (0.89-1.35)	.40		182	162	1.15 (0.93-1.43)	.18	
≥70	145	156	0.92 (0.74-1.16)	.49		145	156	0.90 (0.72-1.13)	.37	
Subtotal	**390**	**411**	0.96 (0.83-1.10)	.53		**397**	**404**	0.97 (0.85-1.12)	.71	
Nuclear[d]										
50-59	55	75	0.74 (0.52-1.05)	.09	.71	58	72	0.79 (0.56-1.12)	.19	.84
60-69	169	153	1.10 (0.89-1.37)	.38		170	152	1.15 (0.92-1.43)	.21	
≥70	135	151	0.89 (0.70-1.12)	.32		139	147	0.92 (0.73-1.16)	.46	
Subtotal	**359**	**379**	0.96 (0.83-1.10)	.54		**367**	**371**	0.98 (0.85-1.13)	.79	
Cortical[d]										
50-59	22	37	0.60 (0.35-1.02)	.06	.28	25	34	0.73 (0.43-1.22)	.22	0.49
60-69	70	64	1.09 (0.78-1.54)	.60		81	53	1.57 (1.11-2.22)	.01	
≥70	63	66	0.96 (0.68-1.35)	.80		68	61	1.09 (0.77-1.54)	.64	
Subtotal	**155**	**167**	0.94 (0.76-1.17)	.58		**174**	**148**	1.16 (0.94-1.45)	.17	
PSC[d]										
50-59	23	47	0.49 (0.30-0.81)	.005	.11	34	36	0.93 (0.58-1.49)	.76	.97
60-69	64	49	1.31 (0.90-1.89)	.16		56	57	1.01 (0.70-1.46)	.97	
≥70	40	44	0.89 (0.58-1.37)	.61		41	43	0.93 (0.60-1.42)	.73	
Subtotal	**127**	**140**	0.91 (0.72-1.16)	.45		**131**	**136**	0.96 (0.75-1.21)	.71	

Abbreviations: CI, confidence interval; HR, hazard ratio; PSC, posterior subcapsular.
[a] Adjusted for age, Physicians' Health Study cohort, and vitamin C, beta carotene, and multivitamin treatment assignment.
[b] Test for trend of the effect of age on the association between randomized treatment assignment and cataract extraction.
[c] Adjusted for age, Physicians' Health Study cohort, and vitamin E, beta carotene, and multivitamin treatment assignment.
[d] With or without other subtypes.

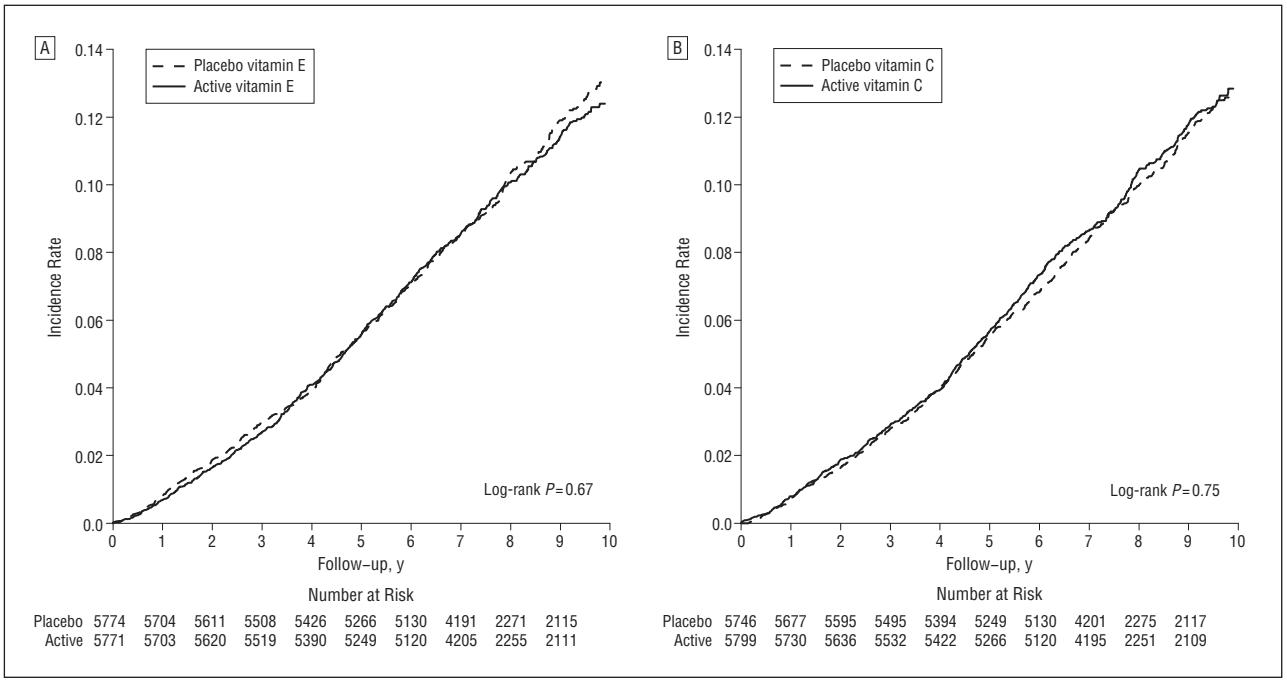

Figure 3. Cumulative incidence rates of cataract in the vitamin E (A) and vitamin C (B) groups in the Physicians' Health Study II.

significant, trend toward increased risk in those with a reported history of CVD (data for cataract are shown in Table 4). The HRs did not differ statistically significantly according to treatment assignment for the other randomized interventions in the PHS II (Table 4 and Figure 4).

COMMENT

These randomized trial data from a large population of middle-aged and older, generally well-nourished men exclude any large effect of long-term dietary supplemen-

Table 4. Cases of Cataract by Randomized Treatment Assignment in Risk Factor Subgroups in the Physicians' Health Study II[a]

Risk Factor	Vitamin E Group				Vitamin C Group			
	Cataracts, No./ Total No.[b]				Cataracts, No./ Total No.[b]			
	Active	Placebo	HR (95% CI)[c]	*P* Value for Interaction[d]	Active	Placebo	HR (95% CI)[e]	*P* Value for Interaction[d]
Cigarette smoking								
Never	292/3391	315/3457	0.97 (0.83-1.14)	.94	298/3437	309/3411	0.98 (0.83-1.15)	.49
Former	263/2190	256/2095	0.99 (0.83-1.17)		265/2143	254/2142	1.03 (0.87-1.22)	
Current	24/187	24/216	1.07 (0.60-1.89)		30/216	18/187	1.36 (0.76-2.45)	
Alcohol use								
Rarely/never	114/1053	114/1064	1.04 (0.80-1.13)	.71	109/1059	119/1058	0.96 (0.74-1.24)	.57
≥1 drink/mo	426/4677	477/4679	0.98 (0.86-1.12)		481/4073	458/4653	1.04 (0.91-1.18)	
BMI								
<25	261/2397	242/2342	1.05 (0.88-1.26)	.25	248/2364	255/2375	0.99 (0.83-1.18)	.87
25 to <30	262/2738	283/2811	0.98 (0.83-1.16)		278/2795	267/2754	1.02 (0.86-1.21)	
≥30	56/631	70/614	0.75 (0.53-1.06)		67/635	59/610	1.12 (0.79-1.59)	
History of hypertension								
No	305/3520	310/3503	0.99 (0.84-1.16)	.91	312/3563	303/3460	0.99 (0.84-1.16)	.59
Yes	271/2215	285/2234	0.98 (0.83-1.15)		280/2201	276/2248	1.05 (0.89-1.24)	
History of hypercholesterolemia								
No	355/3568	346/3534	1.01 (0.87-1.17)	.58	344/3583	357/3519	0.95 (0.82-1.10)	.10
Yes	215/1987	241/2013	0.94 (0.78-1.13)		243/2026	213/1974	1.15 (0.96-1.38)	
History of diabetes mellitus								
No	536/5479	561/5505	0.97 (0.86-1.10)	.41	559/5530	538/5454	1.03 (0.91-1.16)	.49
Yes	43/289	34/262	1.13 (0.72-1.78)		34/265	43/286	0.91 (0.58-1.43)	
Exercise ≥1 time/wk								
No	241/2090	256/2124	0.98 (0.82-1.17)	.97	258/2130	239/2084	1.07 (0.90-1.28)	.40
Yes	332/3533	335/3518	0.99 (0.85-1.15)		329/3542	338/3509	0.97 (0.83-1.13)	
Self-reported history of CVD								
No	546/5545	566/5545	0.98 (0.87-1.10)	.55	556/5564	556/5526	0.99 (0.88-1.11)	.055
Yes	33/226	29/229	1.16 (0.70-1.92)		37/235	25/220	1.56 (0.94-2.60)	
Randomized to receive vitamin C or E								
No	286/2886	295/2860	0.95 (0.81-1.12)	.51	300/2914	295/2860	0.98 (0.84-1.15)	.51
Yes	293/2885	300/2914	1.02 (0.87-1.20)		293/2885	286/2886	1.06 (0.90-1.25)	
Randomized to receive beta carotene								
No	305/2881	310/2879	0.99 (0.85-1.16)	.91	311/2896	304/2864	1.03 (0.88-1.21)	.83
Yes	274/2890	285/2895	0.98 (0.83-1.15)		282/2903	277/2882	1.00 (0.85-1.19)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.

[a] Baseline factors are defined as in Table 1.

[b] The total number of cataracts may not equal 1174 because of missing covariate information for some participants.

[c] Adjusted for age, Physicians' Health Study cohort, and vitamin C, beta carotene, and multivitamin treatment assignment.

[d] Test of the null hypothesis of no difference in treatment effect across risk factor subgroups.

[e] Adjusted for age, Physicians' Health Study cohort, and vitamin E, beta carotene, and multivitamin treatment assignment.

tation with vitamins E and C on diagnosed cataract or extraction. The 95% CIs exclude with reasonable certainty beneficial effects as small as 15% for cataract and 20% for cataract extraction. There was no overall effect of vitamin E or vitamin C on any cataract subtype. The HRs tended to be lower in younger men assigned to the vitamin E group, particularly for the PSC subtype, but this finding should be interpreted with caution, particularly in view of the absence of an overall effect, and may have been due to chance.

VITAMIN E

The finding that long-term vitamin E supplementation has no overall effect on cataract occurrence is consistent with the results of previous clinical trials, in particular with 3 trials designed to estimate the individual effect of vitamin E supplementation. In the Alpha-Tocopherol Beta-Carotene Cancer Prevention Trial,[31] 29 133 Finnish male smokers aged 50 to 69 years were randomly assigned in a 2×2 factorial design to receive vitamin E (50 mg/d) or placebo and beta carotene (20 mg/d) or placebo. Analyses based on 425 cataract extractions documented during a median of 5.7 years of treatment and follow-up indicated that men assigned to the vitamin E group had a nonsignificant 9% reduced risk of extraction (HR, 0.91; 95% CI, 0.74-1.11).[31] In the Vitamin E, Cataract, and Age-Related Maculopathy Study,[35] 1193 men and women aged 55 to 80 years with early or no cataract were randomly assigned to receive daily vitamin E (500 IU) or placebo. After 4 years of treatment and follow-up, during which 142 new cataracts and 168 progressed cataracts were documented, there was no difference between the vitamin E and placebo groups in cataract incidence (HR, 1.0; 95% CI, 0.8-1.4) or progression (1.0; 0.7-1.3), and neither was there any overall benefit of daily vitamin E use on any cataract subtype. In the Women's Health Study, 39 876 apparently healthy fe-

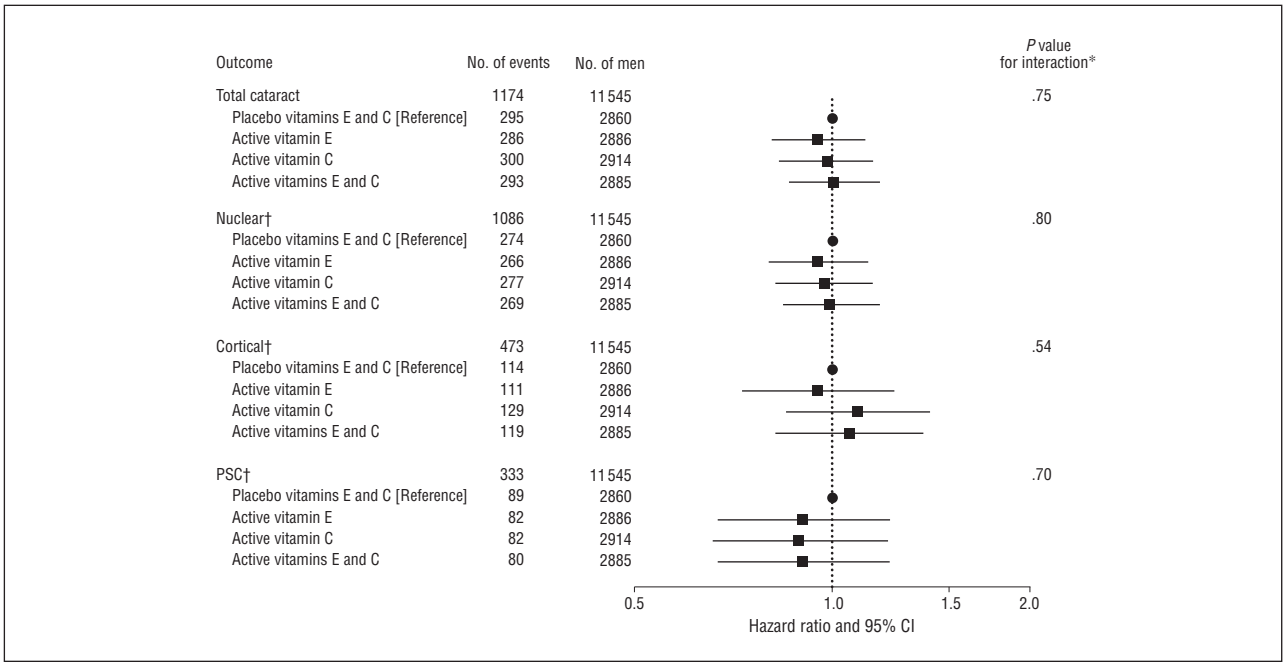

Figure 4. Hazard ratios and 95% confidence intervals (CIs) of cataract and subtypes comparing the vitamin E alone, vitamin C alone, and vitamin E plus vitamin C groups with placebo (combined vitamin E and vitamin C placebo groups) in the Physicians' Health Study II adjusted for age, Physicians' Health Study cohort, and beta carotene and multivitamin treatment assignment. PSC indicates posterior subcapsular. *Test of the null hypothesis of no difference in treatment effect across treatment combinations. †With or without other subtypes. Dotted vertical line indicates the 1.0 hazard ratio.

male health professionals 45 years or older were randomly assigned in a 2×2 factorial design to alternate-day vitamin E (600 IU) or placebo and alternate-day low-dose aspirin (100 mg) or placebo. Results based on average follow-up of 9.7 years and 2376 documented cataracts indicated no benefit of vitamin E supplementation on cataract (HR, 0.96; 95% CI, 0.88-1.04) or on any cataract subtype.[36] The present findings in the PHS II represent the longest treatment duration for vitamin E in men and, together with the results of previous trials, indicate that long-term supplementation with high-dose vitamin E alone is unlikely to have any major effect on cataract development or progression in men or women.

VITAMIN C

To our knowledge, the PHS II is the first randomized trial to report on the individual effect of vitamin C supplementation in the prevention of cataract. Three previous trials[32-34] tested vitamin C as a component of an antioxidant cocktail and, thus, could not estimate its individual effect on cataract. In the Linxian cataract studies,[32] composed of 2141 residents from an undernourished population in China, eye examinations given at the conclusion of 5 to 6 years of treatment with a daily combination of 26 vitamins and minerals, including vitamin C (180 mg) and vitamin E (60 IU), indicated a reduced prevalence of nuclear cataract in persons aged 65 to 74 years (odds ratio, 0.57; 95% CI, 0.36-0.90) but not in younger persons aged 45 to 64 years (1.28; 0.76-2.14). In the Roche European American Cataract Trial,[34] a small trial of 297 American and English outpatients (mean age, 67.6 years) with early age-related cataract, analyses restricted to a subset of participants who completed 3 years of follow-up (n=158) indicated that daily treatment with an antioxidant combination of vitamin C (750 mg), vitamin E (600 mg), and beta carotene (18 mg) slightly reduced progression of cataract ($P=.048$) as quantified by image analysis. Finally, in the Age-Related Eye Disease Study,[33] conducted in 4629 participants aged 55 years and older, an antioxidant combination of vitamin C (500 mg), vitamin E (400 IU), and beta carotene (15 mg) taken daily had no effect on the development and progression of lens opacities during 6.3 years of treatment and follow-up (any lens event: HR, 1.00; 95% CI, 0.87-1.15). The present findings in the PHS II for vitamin C are most consistent with the null findings for the high-dose antioxidant combination in the Age-Related Eye Disease Study and are the first to suggest that long-term supplementation with high-dose vitamin C alone has no appreciable effect on the incidence of cataract or subtypes.

Previous studies[44-47] have described an interaction between vitamins E and C in vitro and in vivo and have noted the ability of vitamin C to regenerate oxidized vitamin E. However, when we examined the combination of vitamins E and C, we found no evidence of a significant interaction on risks of cataract or cataract extraction. It has also been suggested that the benefits of antioxidant supplements may be largely confined to individuals with higher levels of oxidative stress.[48] In the PHS II, we found no evidence of modification of the lack of effect of vitamin E or C on cataract in individuals with an increased oxidative burden, such as smokers, or persons with hypertension or diabetes. In fact, risks of cataract and extraction seemed higher in persons who reported a history of CVD and were assigned to receive active vitamin C, although this may have been a chance observation because of the large number of comparisons.

It is important to consider several aspects of the PHS II design in interpreting these null results. The PHS II population is generally well nourished, and, thus, these findings may not apply to less well-nourished populations. The doses of vitamin E (400 IU every other day) and vitamin C (500 mg/d) tested in the PHS II were far greater than usual dietary levels and generally exceeded doses associated with benefit in observational studies of cataract.[49,50] Thus, it seems unlikely that even higher doses of vitamins E and C would be required for a beneficial effect on cataract to emerge. Adherence to treatment also seems unlikely to explain the null findings because adherence remained consistent after mean follow-up of 8.0 years, with no difference between the treated and placebo groups. The form of vitamin E used in the PHS should also be considered. We used synthetic vitamin E (all-rac-α-tocopheryl acetate), which may not be the form most closely associated with cataract. However, similar null results for cataract were observed in the Women's Health Study,[36] which tested natural source vitamin E (*d*-α-tocopheryl acetate). Still others have suggested that γ-tocopherol, which may be suppressed in the presence of α-tocopherol,[51] may be a more powerful antioxidant and, thus, could be more effective at reducing photoperoxidation of lens lipids.[52] The duration and timing of a large-scale trial is also an issue of concern. With 8 years of treatment and follow-up, this was the longest trial of antioxidant supplementation and cataract in men. Nevertheless, cataracts develop slowly over many years and may require even longer periods of treatment and perhaps treatment at earlier ages. Most previous trials of antioxidant supplements and cataract included participants with prevalent lens opacities at baseline, raising the possibility that the intervention in those trials may have occurred too late in the disease process to have a material effect on rates of cataract. The PHS II excluded participants with a known cataract at baseline. Moreover, analyses that excluded cataracts diagnosed during the first 2 years and the first 5 years of follow-up (cataracts more likely to be present at baseline but not yet detected) (data not shown) showed HRs near the null value of 1.0, suggesting that supplementation with vitamin E or vitamin C had little effect on earlier stages of disease development.

In summary, these randomized trial data from a large population of middle-aged and older, generally well-nourished men indicate that long-term supplementation with high-dose vitamin E and vitamin C, either alone or in combination, has little effect on rates of cataract diagnosis and extraction.

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The filtering cicatrix in glaucoma. BASSO (Genoa) concludes that the formation of a large conjunctival flap tends to delay healing of the sclera section. This is the explanation of the filtering scar in Lagrange's operation, which should be performed with a Graefe knife. The advantages of the conjunctival flap are the facility of regulating circulation, the formation of a fistulous cicatrix completely covered by conjunctiva, which prevents the formation of a cystoid, irregular, or but partly fistulous cicatrix.

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