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

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Abstract

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

Design—Randomized, double-masked, placebo-controlled trial.

Participants—Eleven thousand five hundred forty-five apparently healthy US male physicians aged 50 years or older who were without a diagnosis of cataract at baseline.

Intervention—Participants 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.

Results—After 8 years of treatment and follow-up, a total of 1,174 incident cataracts were confirmed. There were 579 cataracts in the vitamin E treated group and 595 in the vitamin E placebo group (hazard ratio [HR], 0.99; 95 percent confidence interval [CI], 0.88 to 1.11). For vitamin C, there were 593 cataracts in the treated group and 581 in the placebo group (HR, 1.02; CI, 0.91 to 1.14).

Conclusions—In a large-scale randomized trial of US male physicians, long-term alternate day use of 400 IU of vitamin E and/or daily use of 500 mg of vitamin C had no significant beneficial or harmful effect on the risk of cataract.

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

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Dr. Christen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

An estimated 20.5 million persons aged 40 years and older in the U.S. 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). Clearly, 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.

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 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 (17-30). However, the results of completed randomized trials to date have been disappointing. Vitamin E, either alone or in combination with other vitamin supplements, has been tested in six trials and results indicate little benefit for treatment durations as long as 6.5 years in men, and 10 years in women (31-36). Vitamin C in combination with other antioxidants has been tested in three trials and results indicate little benefit for treatment durations up to 6.5 years (32-34). Currently, there are no data for vitamin E treatment durations greater 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 II (PHS II). PHS II is a randomized, double-blind, 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. The data reported here with respect to 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-blind, placebo-controlled, 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), vitamin C (500 mg synthetic ascorbic acid or its placebo daily; BASF Corporation), and a multivitamin (Centrum Silver or its placebo daily; Wyeth Pharmaceuticals) on occurrence of cancer and CVD among 14,641 male physicians aged 50 years and older (37). A fourth randomized component, β -carotene (50 mg Lurotin or placebo on alternate days; BASF Corporation), was terminated in March, 2003. Incident cataract was a prespecified secondary endpoint of the trial (37). The final results for the vitamin E and vitamin C component 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 PHS II occurred in two phases (Figure 1). In phase I, which began in 1997, 7,641 willing and eligible participants from PHS I (40-43) retained their original β -carotene treatment assignment and were newly randomized to

vitamin C, vitamin E, and a multivitamin. In phase II, which began 1999, 7,000 new physician participants identified from a list provided by the American Medical Association were randomized to beta-carotene, vitamin C, vitamin E, and a multivitamin. Informed consent was obtained from all men, and the research protocol was reviewed and approved by the institutional review board at Brigham and Women's Hospital in Boston. This trial is registered at clinicaltrials.gov (NCT00270647).

Participants completed annual questionnaires supplying information about compliance with pill taking and the occurrence of new endpoints, including cataract. 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. Morbidity and mortality follow-up were extremely high, at 95.3% and 97.7%, respectively.

Compliance with pill taking was based on self-report and was defined as taking at least two thirds of the study agents. For the active vitamin E and its placebo, compliance at 4 years was 78% and 77%, respectively ($P=0.12$), and at the end of follow-up (mean of 8 years), 72% and 70% ($P=0.004$). For the active vitamin C and its placebo, compliance at 4 years was 78% and 78%, respectively ($P=0.99$), and at the end of follow-up, 71% and 71% ($P=0.54$).

Ascertainment and Confirmation of Cataract

Participants with a diagnosis of cataract at baseline ($n=3,096$) were excluded. Following 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 requested 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 sclerosis, cortical, posterior subcapsular [PSC]) and origin (including age-related, traumatic, congenital, inflammatory, or surgery- or steroid-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, steroids, intraocular inflammation, or surgery were excluded), with best-corrected visual acuity of 20/30 or worse and with no alternate ocular disease to explain the visual acuity loss. In the presence of alternate ocular disease, a lens opacity was considered a cataract if in the judgement 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 who were without a diagnosis of cataract at baseline are included in this analysis. Of these, 5,771 were in the vitamin E group and 5,774 were in the vitamin E placebo group; 5,799 were in the vitamin C group and 5,746 were in the vitamin C placebo group.

Statistical Analysis

Estimated power of the trial for incident cataract was based on historical event rates observed in Physicians Health Study I (PHS I). 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, Π^2 tests for proportions, and tests for trend for ordinal categories. We used Kaplan-Meier curves to estimate cumulative incidence over 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 among those in the vitamin E group compared to placebo, and the vitamin C group compared to placebo, after adjustment for age (years) at baseline, PHS cohort (original PHS I participant, 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 dosage 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 within three age groups; 50-59, 60-69, $\geq$ 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 1 to 3 corresponding to the three age groups) in a proportional hazards model. Interaction terms tested for additivity of the two 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 endpoint, the proportionality assumption was not violated for treatment with vitamin E ($P = 0.68$) or vitamin C ($P = 0.37$). For each HR, the 95% confidence interval (CI) and two-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 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 two eyes had the same date of diagnosis, we designated the eye with the worse visual acuity at the most recent eye exam as the worse eye. When the worse eye was excluded because of visual acuity loss attributed to other ocular abnormalities or a cause which was not age-related, the fellow eye was considered for classification.

Results

The distribution of baseline characteristics in the active and placebo groups for vitamin E and vitamin C are presented in Table 1. As expected in this large randomized trial, the characteristics were distributed equally between the active and placebo groups for both vitamins E and C. A total of 1,174 cataracts and 801 cataract extractions were confirmed during a mean follow-up of 8 years. Figure 2 shows subtypes for 1,160 (98.8%) participants with diagnosed cataract.

Vitamin E

There were 579 cataracts in the vitamin E group and 595 in the placebo group (HR, 0.99; CI, 0.88-1.11) (Table 2). Analyses of cataract subtypes indicated no significant effects of vitamin E on incidence of nuclear (HR, 0.99; CI, 0.88-1.11), cortical (HR, 0.96; CI, 0.80-1.15), or PSC cataract (HR, 0.95; CI, 0.77-1.18) (Table 2). Similar non-significant 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 active vitamin E 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 the year of follow-up are shown in Figure 3. There was no apparent benefit of vitamin E at any point during the trial.

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

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 incidence of nuclear (HR, 1.01; CI, 0.89-1.14), cortical (HR, 1.10; CI, 0.92-1.31), or PSC cataract (HR, 0.94; CI, 0.76-1.17) (Table 2). For both cataract and subtypes, HRs did not vary significantly over the three age groups. Similar non-significant findings were observed for extraction of cataract and subtypes (Table 3).

Figure 3 presents cumulative incidence rates of cataract according to the 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-significant, trend toward increased risk among those with a reported history of CVD (data for cataract shown in Table 4). HRs did not differ significantly according to treatment assignment for the other randomized interventions in PHS II (Table 4 and Figure 4).

Discussion

These randomized trial data from a large population of middle-aged and older, generally well-nourished men clearly exclude any large effect of long-term dietary supplementation with vitamin E and vitamin 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. HRs did tend to be lower in younger men assigned vitamin E, 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

Our finding that long term vitamin E supplementation has no overall effect on cataract occurrence is consistent with the results of previous clinical trials, and in particular with three trials designed to estimate the individual effect of vitamin E supplementation. In the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Trial, 29,133 Finnish male smokers, aged 50 to 69 years, were randomly assigned in a 2 × 2 factorial design to vitamin E (50 mg daily) or placebo, and beta carotene (20 mg daily) or placebo (31). Analyses based on 425 cataract extractions documented during a median of 5.7 years of treatment and follow-up indicated that men assigned to vitamin E had a non-significant 9% reduced risk of extraction (HR, 0.91; 95% CI, 0.74-1.11) (31). In the Vitamin E, Cataract, and Age-Related Macular Degeneration (VECAT) Study, 1193 men and women aged 55-80 years with early or no cataract were randomly assigned to 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 group in cataract incidence (HR, 1.0; 95% CI, 0.8-1.4) or progression (HR, 1.0; 95% CI, 0.7-1.3), nor was there any overall benefit of daily vitamin E on any cataract subtype (35). In the Women's Health Study (WHS), 39,876 apparently healthy female health professionals aged

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 an average follow-up of 9.7 years and 2,376 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 current findings in 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, 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 tested vitamin C as a component of an antioxidant cocktail, and thus were unable to estimate its individual effect on cataract (32-34). In the Linxian Cataract Study, comprised of 2,141 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 among persons aged 65 to 74 years (OR, 0.57; 95% CI, 0.36-0.90), but not among younger persons aged 45 to 64 years (OR, 1.28; 95% CI, 0.76-2.14) (32). In the Roche European American Cataract Trial (REACT), 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 three 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 ($p=0.048$) as quantified by image analysis (34). Finally, in the Age-Related Eye Disease Study (AREDS), conducted among 4,629 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 (HR of any lens event, 1.00; 95% CI, 0.87-1.15) (33). Our findings in PHS II for vitamin C are most consistent with the null findings for the high-dose antioxidant combination in AREDS, 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 have described an interaction between vitamin E and vitamin C *in vitro* and *in vivo*, and have noted the ability of vitamin C to regenerate oxidized vitamin E (44-47). However, when we examined the combination of vitamin E and vitamin 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 PHS II, we found no evidence for any modification of the lack of effect of vitamin E or C on cataract among individuals with an increased oxidative burden such as smokers, or persons with hypertension or diabetes. In fact, risks of cataract and extraction appeared higher in persons who reported a history of CVD and were assigned 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 daily) tested in 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 vitamin E and vitamin C would be required for a beneficial effect on cataract to emerge. Adherence to treatment also seems unlikely to explain the null findings as adherence remained consistent after a mean follow-up of 8.0

years, with no difference between the treated and placebo groups. The form of vitamin E used in PHS should also be considered. We used synthetic vitamin E (all-rac-alpha-tocopheryl acetate) which may not be the form most closely associated with cataract. However, similar null results for cataract were observed in WHS which tested natural source vitamin E (*d*-alpha-tocopheryl acetate) (36). Still, others have suggested that gamma-tocopherol, which may be suppressed in the presence of alpha-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 eight years of treatment and follow-up, this was the longest trial of antioxidant supplementation and cataract in men. Nonetheless, cataracts develop slowly over many years and may require even longer periods of treatment, and perhaps treatment at earlier ages. It should be noted that 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 impact on rates of cataract. In PHS II, we 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 impact 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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Figure 1. Flow diagram of the Vitamin E and Vitamin C components of the Physicians' Health Study II. A total of 3,096 participants who had a diagnosis of cataract at baseline were excluded.

Figure 2.

Venn diagram showing subtypes for 1,160 participants with diagnosed cataract in Physicians' Health Study II. Excludes 14 participants with missing subtype information. NS, nuclear sclerosis; PSC, posterior subcapsular.

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

Figure 4.

Hazard ratios and 95% confidence intervals of cataract and subtypes comparing vitamin E alone, vitamin C alone, and vitamin E plus C groups with placebo (combined vitamin E and C placebo groups) in the Physicians' Health Study II. Adjusted for age, PHS cohort, and beta-carotene and multivitamin treatment assignment. NS, nuclear sclerosis; PSC, posterior subcapsular. ^a With or without other subtypes; ^b Test of the null hypothesis of no difference in treatment effect across treatment combinations.

Table 1Baseline Characteristics by Randomized Groups in Physicians' Health Study II.^a

	Total No. Of Participants	Vitamin E		Vitamin C	
		Active (n=5,771)	Placebo (n=5,774)	Active (n=5,799)	Placebo (n=5,746)
Age (mean $\pm$ SD, y)		62.0 (7.9)	62.0 (7.9)	62.0 (7.9)	62.0 (7.9)
Age, y					
50-59 years	5,614	48.4	48.9	48.7	48.6
60-69 years	3,931	34.2	33.9	33.8	34.3
$\geq$ 70 years	2,000	17.4	17.3	17.5	17.2
Cigarette smoking					
Never	6,848	58.8	59.9	59.3	59.4
Former	4,285	38.0	36.3	37.0	37.3
Current	403	3.2	3.7	3.7	3.3
Alcohol use					
Rarely/never	2,117	18.4	18.5	18.4	18.5
$\geq$ 1 drink/month	9,356	81.6	81.5	81.6	81.5
Body mass index (kg/m ²)					
(mean $\pm$ SD)		26.0 (3.4)	26.0 (3.4)	26.1 (3.4)	26.0 (3.4)
<25	4,739	41.6	40.6	40.8	41.4
25 to <30	5,549	47.5	48.7	48.2	48.0
$\geq$ 30	1,245	10.9	10.7	11.0	10.6
History of hypertension ^b					
Yes	4,449	38.6	38.9	38.2	39.4
No	7,023	61.4	61.1	61.8	60.6
History of high cholesterol ^c					
Yes	4,000	35.8	36.3	36.1	35.9
No	7,102	64.2	63.7	63.9	64.1

	Total No. Of Participants	Vitamin E		Vitamin C	
		Active (n=5,771)	Placebo (n=5,774)	Active (n=5,799)	Placebo (n=5,746)
History of diabetes					
Yes	551	5.0	4.5	4.6	5.0
No	10,984	95.0	95.5	95.4	95.0
Exercise E1 time/wk					
Yes	7,051	62.8	62.4	62.4	62.7
No	4,214	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

^aData are given as percentage of participants unless otherwise noted. Numbers of subjects for some characteristics do not sum to 11,545 because of missing values.

^bHistory of hypertension was defined as self-reported systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or past or current treatment for hypertension.

^cHistory of high cholesterol was defined as self-reported total cholesterol ≥ 240 mg/dL, or past or current treatment for high cholesterol.

^dHistory of CVD included nonfatal myocardial infarction or nonfatal stroke.

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

	Vitamin E						Vitamin C					
	Active (n= 5,771)	Placebo (n= 5,774)	HR ^b	95% CI	P Value	P Trend ^d	Active (n=5,799)	Placebo (n=5,746)	HR ^c	95% CI	P Value	P Trend ^d
<u>Total cataract</u>												
50-59 years	99	126	0.79	0.61-1.03	0.09	0.46	107	118	0.89	0.69-1.16	0.40	0.87
60-69 years	268	246	1.09	0.92-1.29	0.33		273	241	1.17	0.99-1.40	0.07	
≥70 years	212	223	0.95	0.79-1.15	0.61		213	222	0.94	0.77-1.13	0.49	
Total	579	595	0.99	0.88-1.11	0.82		593	581	1.02	0.91-1.14	0.77	
<u>NS^a</u>												
50-59 years	84	103	0.82	0.62-1.10	0.19	0.75	87	100	0.86	0.64-1.14	0.30	0.98
60-69 years	249	231	1.08	0.90-1.29	0.41		253	227	1.16	0.97-1.38	0.11	
≥70 years	202	217	0.93	0.77-1.13	0.47		206	213	0.94	0.78-1.14	0.54	
Total	535	551	0.99	0.88-1.11	0.81		546	540	1.01	0.89-1.14	0.90	
<u>Cortical^a</u>												
50-59 years	32	50	0.65	0.41-1.01	0.054	0.34	38	44	0.85	0.55-1.32	0.48	0.67
60-69 years	105	94	1.12	0.85-1.48	0.44		110	89	1.28	0.97-1.70	0.08	
≥70 years	93	99	0.94	0.71-1.25	0.69		100	92	1.06	0.80-1.41	0.69	
Total	230	243	0.96	0.80-1.15	0.68		248	225	1.10	0.92-1.31	0.31	
<u>PSC^a</u>												
50-59 years	32	57	0.57	0.37-0.88	0.01	0.20	43	46	0.92	0.61-1.40	0.70	0.97
60-69 years	83	60	1.38	0.99-1.93	0.056		70	73	0.99	0.72-1.38	0.97	
≥70 years	47	54	0.86	0.58-1.28	0.46		49	52	0.92	0.62-1.36	0.67	
Total	162	171	0.95	0.77-1.18	0.67		162	171	0.94	0.76-1.17	0.60	

Abbreviations: HR, hazard ratio; CI, confidence interval; NS, nuclear sclerosis; PSC, posterior subcapsular.

^aWith or without other subtypes.

^bAdjusted for age, PHS cohort, and vitamin C, β-carotene, and multivitamin treatment assignment.

^c Adjusted for age, PHS cohort, and vitamin E, β -carotene, and multivitamin treatment assignment.

^d Test for trend of the effect of age on the association between randomized treatment assignment and cataract.

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

	Vitamin E						Vitamin C					
	Active (n= 5,771)	Placebo (n= 5,774)	HR ^b	95% CI	P Value	P Trend ^d	Active (n=5,799)	Placebo (n=5,746)	HR ^c	95% CI	P Value	P Trend ^d
<u>Total extraction</u>												
50-59 years	65	91	0.72	0.52-0.99	0.04	0.40	70	86	0.80	0.59-1.10	0.17	0.87
60-69 years	180	164	1.10	0.89-1.35	0.40		182	162	1.15	0.93-1.43	0.18	
≥70 years	145	156	0.92	0.74-1.16	0.49		145	156	0.90	0.72-1.13	0.37	
Total	390	411	0.96	0.83-1.10	0.53		397	404	0.97	0.85-1.12	0.71	
<u>NS^a</u>												
50-59 years	55	75	0.74	0.52-1.05	0.09	0.71	58	72	0.79	0.56-1.12	0.19	0.84
60-69 years	169	153	1.10	0.89-1.37	0.38		170	152	1.15	0.92-1.43	0.21	
≥70 years	135	151	0.89	0.70-1.12	0.32		139	147	0.92	0.73-1.16	0.46	
Total	359	379	0.96	0.83-1.10	0.54		367	371	0.98	0.85-1.13	0.79	
<u>Cortical^a</u>												
50-59 years	22	37	0.60	0.35-1.02	0.06	0.28	25	34	0.73	0.43-1.22	0.22	0.49
60-69 years	70	64	1.09	0.78-1.54	0.60		81	53	1.57	1.11-2.22	0.01	
≥70 years	63	66	0.96	0.68-1.35	0.80		68	61	1.09	0.77-1.54	0.64	
Total	155	167	0.94	0.76-1.17	0.58		174	148	1.16	0.94-1.45	0.17	
<u>PSC^a</u>												
50-59 years	23	47	0.49	0.30-0.81	0.005	0.11	34	36	0.93	0.58-1.49	0.76	0.97
60-69 years	64	49	1.31	0.90-1.89	0.16		56	57	1.01	0.70-1.46	0.97	
≥70 years	40	44	0.89	0.58-1.37	0.61		41	43	0.93	0.60-1.42	0.73	
Total	127	140	0.91	0.72-1.16	0.45		131	136	0.96	0.75-1.21	0.71	

Abbreviations: HR, hazard ratio; CI, confidence interval; NS, nuclear sclerosis; PSC, posterior subcapsular.

^aWith or without other subtypes.

^bAdjusted for age, PHS cohort, and vitamin C, β-carotene, and multivitamin treatment assignment.

^c Adjusted for age, PHS cohort, and vitamin E, β -carotene, and multivitamins treatment assignment.

^d Test for trend of the effect of age on the association between randomized treatment assignment and cataract extraction.

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

	Vitamin E				Vitamin C			
	No. of cataracts/Total ^d				No. of cataracts/Total ^d			
	Active	Placebo	HR (95% CI) ^b	P Interaction ^e	Active	Placebo	HR (95% CI) ^c	P Interaction ^e
Cigarette smoking								
Never	292/3391	315/3457	0.97 (0.83-1.14)	0.94	298/3437	309/3411	0.98 (0.83-1.15)	0.49
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)	0.71	109/1059	119/1058	0.96 (0.74-1.24)	0.57
≥1 drink/month	426/4677	477/4679	0.98 (0.86-1.12)		481/4073	458/4653	1.04 (0.91-1.18)	
Body mass index (kg/m ²)								
<25	261/2397	242/2342	1.05 (0.88-1.26)	0.25	248/2364	255/2375	0.99 (0.83-1.18)	0.87
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)	0.91	312/3563	303/3460	0.99 (0.84-1.16)	0.59
Yes	271/2215	285/2234	0.98 (0.83-1.15)		280/2201	276/2248	1.05 (0.89-1.24)	
History of high cholesterol								
No	355/3568	346/3534	1.01 (0.87-1.17)	0.58	344/3583	357/3519	0.95 (0.82-1.10)	0.10
Yes	215/1987	241/2013	0.94 (0.78-1.13)		243/2026	213/1974	1.15 (0.96-1.38)	
History of diabetes								
No	536/5479	561/5505	0.97 (0.86-1.10)	0.41	559/5530	538/5454	1.03 (0.91-1.16)	0.49
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)	0.97	258/2130	239/2084	1.07 (0.90-1.28)	0.40

	Vitamin E					Vitamin C				
	No.of cataracts/Total ^d		No.of cataracts/Total ^d		P Interaction ^e	No.of cataracts/Total ^d		No.of cataracts/Total ^d		P Interaction ^e
	Active	Placebo	Active	Placebo		Active	Placebo	Active	Placebo	
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)		0.55	556/5564	556/5526	0.99 (0.88-1.11)		0.055
Yes	33/226	29/229	1.16 (0.70-1.92)			37/235	25/220	1.56 (0.94-2.60)		
Randomized to vitamin C or E										
No	286/2886	295/2860	0.95 (0.81-1.12)		0.51	300/2914	295/2860	0.98 (0.84-1.15)		0.51
Yes	293/2885	300/2914	1.02 (0.87-1.20)			293/2885	286/2886	1.06 (0.90-1.25)		
Randomized to E-carotene										
No	305/2881	310/2879	0.99 (0.85-1.16)		0.91	311/2896	304/2864	1.03 (0.88-1.21)		0.83
Yes	274/2890	285/2895	0.98 (0.83-1.15)			282/2903	277/2882	1.00 (0.85-1.19)		

Abbreviations: HR, hazard ratio; CI, confidence interval; CVD cardiovascular disease;

^aBaseline factors are defined as in Table 1.

^bAdjusted for age, PHS cohort, and vitamin C, E-carotene, and multivitamin treatment assignment.

^cAdjusted for age, PHS cohort, and vitamin E, E-carotene, and multivitamin treatment assignment.

^dTotal number of cataracts may not equal 1174 because of missing covariate information for some participants.

^eTest of the null hypothesis of no difference in treatment effect across risk factor subgroups.