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Vitamin E and Age-related Macular Degeneration in a Randomized Trial of Women

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Abstract

Objective—To test whether alternate day vitamin E affects incidence of age-related macular degeneration (AMD) in a large-scale randomized trial of women.

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

Participants—Thirty-nine thousand eight hundred seventy-six apparently healthy female health professionals aged 45 years or older.

Intervention—Participants were randomly assigned to receive either 600 IU of natural-source vitamin E on alternate days or placebo.

Main Outcome Measure—Incident AMD 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 10 years of treatment and follow-up, there were 117 cases of AMD in the vitamin E group and 128 cases in the placebo group (relative risk [RR], 0.93; 95 percent confidence interval [CI], 0.72 to 1.19).

Conclusions—In a large-scale randomized trial of female health professionals, long-term alternate day use of 600 IU of natural-source vitamin E had no large beneficial or harmful effect on risk of AMD.

Introduction

Age-related macular degeneration (AMD) is a chronic condition of the eye that involves pathological changes in the central region of the retina responsible for high-resolution visual acuity. It is the leading cause of severe irreversible visual impairment in the United States (1). Most of the vision loss in AMD is due to the advanced form of the disease, either geographic atrophy or neovascular AMD, which affects an estimated 1.7 million older Americans (1). An

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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.

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additional 7.3 million persons have early AMD which is usually associated with little or no vision loss (2,3), but does increase the risk of developing advanced AMD (4,5). Treatment options include laser photocoagulation, photodynamic therapy, and anti-vascular endothelial growth factor therapy, but these options are expensive and are limited to a minority of persons with late-stage, neovascular AMD (6–12). For these reasons, identification of means to prevent AMD onset and progression is of particular clinical and public health importance.

Basic research studies indicate a possible role for oxidative mechanisms in the pathophysiology of AMD (13), and data from observational studies generally support a link between nutritional factors, particularly those with antioxidant capabilities, and risks of AMD (14,15). Among specific nutrients, data for vitamin E have been mixed with some studies reporting lower risks of AMD or signs (eg. drusen) in those with higher intake (16–18) while others report no association (19–22). Data from clinical trials are limited. The Age-related Eye Disease Study (AREDS) demonstrated that supplementation with high-dose antioxidant supplements (vitamin C, vitamin E, and beta carotene) and zinc for an average of 6.3 years could reduce the risk of progression to advanced AMD in persons with intermediate AMD or advanced AMD in one eye (23). However, AREDS could not determine whether the zinc and antioxidant combination could delay progression of early stage AMD, or prevent the onset of AMD in persons at usual risk. Results of three other trials, comprised primarily of persons at usual risk, found little evidence that supplementation with vitamin E for 4 to 6 years, or beta carotene for 10 years, could materially reduce risks of AMD (24–27). Thus, at present, there are no identified means to prevent the development or progression of early stage AMD, other than avoidance of cigarette smoking (28–30).

In this report we present the results for AMD from the vitamin E component of the recently-completed Women's Health Study (WHS), a large-scale trial of vitamin E and low-dose aspirin among 39,876 apparently healthy women followed for a mean of 10 years.

Methods

Study Design

The WHS was a randomized, double-blind, placebo-controlled, 2×2 factorial trial designed to test whether vitamin E (600 IU α -tocopherol [Natural Source Vitamin E Association, Washington, DC] every other day) and low-dose aspirin (Bayer Healthcare, Leverkusen, Germany) (100 mg every other day) could reduce rates of cardiovascular disease and cancer among 39,876 apparently-healthy female health professionals aged 45 years or older (31–33). Final results for vitamin E indicated no overall benefit for major cardiovascular events, cancer, or total mortality, but a significant decrease for cardiovascular mortality and venous thromboembolism (31,34). A third component, beta carotene, was terminated early in January 1996 after a median treatment duration of 2.1 years (35,36). Women completed baseline questionnaires providing information on height, weight, history of cigarette smoking, history of alcohol use, blood pressure level, cholesterol level, history of diabetes mellitus, history of multivitamin use, parental history of myocardial infarction, postmenopausal hormone use, and history of an eye exam in the last 2 years. They also provided information about a personal history of AMD. A total of 39,421 women did not report a diagnosis of AMD at baseline and are included in these analyses: 19,697 were in the vitamin E group and 19,724 were in the placebo group (Figure 1). Informed consent was obtained from all women, 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 (NCT00000161).

The women also completed annual questionnaires on which they provided information on their compliance with pill-taking and the occurrence of any relevant events including AMD. Pill-taking and end point ascertainment were continued in blinded fashion through the scheduled

end of the trial on March 31, 2004. Morbidity and mortality follow-up were 97.2% and 99.4% complete, respectively. Compliance (defined as taking at least two thirds of the study capsules) was 78.9% at 5 years, 71.6% at 10 years, and averaged 75.8% throughout the trial.

Ascertainment and definition of endpoints

Women who reported a prior diagnosis of AMD at baseline were excluded. On annual questionnaires, women were asked about new diagnoses in the past year including “macular degeneration right eye” and “macular degeneration left eye”. Women who responded affirmatively were asked to provide the month and year of the diagnosis and to complete a consent form granting permission to examine medical records pertaining to the diagnosis. Eye doctors were contacted by mail and asked to complete an AMD questionnaire which requested information on the date of initial diagnosis, the best-corrected visual acuity at the time of diagnosis, and the date when best-corrected visual acuity reached 20/30 or worse (if different from the date of initial diagnosis). The questionnaire also asked about signs of AMD observed (drusen, retinal pigment epithelium [RPE] hypo/hyperpigmentation, geographic atrophy, RPE detachment, subretinal neovascular membrane, or disciform scar) when visual acuity was first noted to be 20/30 or worse, and the date when exudative neovascular disease, if present, was first noted (defined by presence of RPE detachment, subretinal neovascular membrane, or disciform scar). If ocular abnormalities were noted that could explain or contribute to vision loss, the eye doctor was asked to indicate whether the AMD, by itself, was significant enough to cause the best-corrected visual acuity to be reduced to 20/30 or worse. Eye doctors could also provide the requested information by supplying photocopies of the relevant medical records. Medical record data were obtained for 85.2% of participants reporting AMD.

The primary study endpoint was visually-significant AMD defined as a self-report confirmed by medical record evidence of an initial diagnosis made after randomization but before March 31, 2004, and with best-corrected visual acuity reduced to 20/30 or worse attributable to AMD. Two secondary endpoints were also defined: advanced AMD, comprised of those cases of exudative neovascular AMD plus cases of geographic atrophy; and AMD with or without vision loss, comprised of all incident cases confirmed in medical record review.

Data analysis

We used Cox proportional hazards regression models to estimate the relative risks (RRs) and 95% confidence intervals (95% CIs) of AMD among those assigned to receive vitamin E compared with those assigned to receive placebo after adjustment for age (years) at baseline and randomized aspirin and beta carotene assignments (37). Statistical significance was set at $P < .05$ using 2-sided tests. Models were also fit separately within three predefined age groups; 45–54, 55–64, 65+ years. The proportionality assumption was tested by including an interaction term of vitamin E with the logarithm of time in the Cox models. The proportionality assumption was not violated for the primary endpoint of visually-significant AMD ($P = 0.70$), or for either of the secondary endpoints (advanced AMD, $P = 0.53$; AMD with or without vision loss, $P = 0.56$).

We conducted subgroup analyses by categories of baseline variables that are possible risk factors for AMD. We explored possible effect modification by using interaction terms between subgroup indicators and vitamin E 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, and participants were classified according to the status of the worse eye as defined by disease severity. When the worse eye was excluded because of visual acuity loss attributed to other ocular abnormalities, the fellow eye was considered for classification.

Results

The distribution of baseline characteristics in the vitamin E and placebo groups is shown in Table 1. As expected in this large randomized trial, baseline characteristics were equally distributed between the two treatment groups.

During an average of 10 years of treatment and follow-up, a total of 245 cases of visually-significant AMD were confirmed. For most of these cases, the retinal signs observed when visual acuity was first noted to be 20/30 or worse consisted of some combination of drusen and RPE changes indicating an early stage of AMD development. Fifty-five visually-significant cases developed signs of advanced AMD during follow-up.

Comparing women in the vitamin E group to women in the placebo group, there was a statistically non-significant 7% reduced risk of the primary endpoint of visually-significant AMD (117 cases in the vitamin E group vs 128 cases in the placebo group; relative risk [RR], 0.93; 95% confidence interval [CI], 0.72–1.19) (Table 2). For advanced AMD, there was a statistically non-significant 13% increased risk for those assigned vitamin E (29 cases in the vitamin E group vs 26 cases in the placebo group; RR, 1.13; CI, 0.67–1.92). When we considered all cases of AMD with or without vision loss, 280 cases were documented in the vitamin E group and 313 in the placebo group (RR, 0.90, CI, 0.77 to 1.06).

Cumulative incidence rates of visually significant AMD according to the year of follow-up are shown in Figure 2. There was no apparent benefit of vitamin E on visually-significant AMD at any point during follow-up.

There was no evidence for any modification of the lack of effect of vitamin E on AMD by baseline categories of possible risk factors for AMD, although RRs tended to be lower in younger women.

Discussion

In this large randomized trial, women assigned to alternate-day treatment with 600 IU of natural-source vitamin E and followed for an average of 10 years had a non-significant 7% reduced risk of the primary study endpoint of visually-significant AMD. The 95% CIs excluded with reasonable certainty reductions of 28% or greater, and harmful effects of 20% or greater. Vitamin E treatment had no significant effect on the secondary endpoints of advanced AMD and total AMD with or without vision loss.

The WHS is the longest randomized trial of vitamin E supplementation in AMD to date. Three other trials have examined vitamin E in AMD, but only two were able to evaluate the separate effects of vitamin E supplementation. The Alpha-Tocopherol Beta-Carotene (ATBC) Study was a 2 × 2 factorial trial of vitamin E (50 mg daily) and beta carotene (20 mg daily) conducted among more than 29,000 Finnish male smokers aged 50 to 69 years. Median treatment duration was 6.1 years (24). End-of-trial eye examinations for a small sub-sample of 941 participants aged 65 years and older identified 269 (29%) participants who showed signs of AMD based on evaluation of fundus photographs. The majority of cases (239/269 [89%]) were classified as dry maculopathy with hard drusen and/or pigmentary changes. There was no beneficial effect of vitamin E (RR, 1.13; 95% CI, 0.81–1.59) on the prevalence of AMD in that trial. In the Vitamin E, Cataract and Age-Related Maculopathy Trial (VECAT), comprised of 1193 participants aged 55 to 80 years, there was no overall benefit of 4 years of treatment with daily vitamin E (500 IU) on incidence of early (RR, 1.05; 95% CI, 0.69–1.61; n=69 cases) or late AMD (RR, 1.36; 95% CI, 0.67–2.77; n=7 cases), although the number of cases was small (25). Our findings in WHS are broadly consistent with the findings for early AMD in ATBC and VECAT. Furthermore, with a treatment duration of 10 years, our findings extend these

earlier findings by showing that very long-term supplementation with vitamin E alone is unlikely to have an important effect on AMD occurrence.

Comparison of our findings with the findings in AREDS is limited by differences in the study populations and primary endpoints, and by the absence of specific information on the effect of vitamin E in the AREDS formulation. AREDS tested a higher-risk population and the primary study endpoint was progression to advanced AMD (choroidal neovascularization or central geographic atrophy). Our primary endpoint was visually-significant AMD which represents, on average, a less severe stage of disease development than cases meeting the criteria for advanced AMD in AREDS. When we examined the more advanced cases of AMD in our population (defined as the occurrence of exudative neovascular disease or geographic atrophy), we found no evidence that vitamin E supplementation reduced the risk of advanced AMD. However, the number of advanced cases was small and the 95% confidence interval was compatible with the risk reduction observed in AREDS for combined treatment with antioxidants and zinc. Of course, it is possible that the benefit observed for the antioxidant combination in AREDS reflects the actions of other antioxidants tested (i.e. vitamin C, beta carotene) and that vitamin E has little effect on AMD at any stage.

There are several possible limitations of our study that warrant consideration, particularly in view of the absence of any statistically significant effects. The dose of vitamin E tested in this trial (600 IU taken every other day) was slightly lower than the dose tested in AREDS (400 IU daily), but was considerably greater than doses associated with a possible benefit in AMD in observational studies (38). Thus, an inadequate dose of vitamin E seems unlikely to explain the observed lack of benefit. Compliance with study medication in WHS decreased over time (78.9% reported taking at least two thirds of the study capsules at 5 years), but was similar to that reported in AREDS (71% reported taking at least three fourths of the study capsules at 5 years). Inadequate duration of treatment also seems an unlikely explanation. The WHS was several years longer than AREDS which observed a benefit during an average of 6.3 years of treatment and follow-up. Several aspects of our methodology also deserve consideration. Identification of AMD cases was based on participant reports, and thus some degree of underascertainment of AMD is plausible. Such underascertainment would likely reduce study power (and limit the comparison of incidence rates between this and other populations), but is not associated with bias in randomized comparisons. Random misclassification of reported AMD, which would tend to shift the relative risk estimate toward the null, was reduced by the use of medical records to confirm the participant reports. Non-random or differential misclassification was unlikely since medical records were reviewed by an investigator (WGC) masked to treatment assignment, and study participants and treating ophthalmologists and optometrists were similarly unaware of treatment assignment. Finally, the equal distribution of baseline characteristics between the vitamin E and placebo groups in this large randomized trial indicates that confounding by measured factors is unlikely, and provides reassurance that other potential confounders, which were either unmeasured or unknown, were also likely to be evenly distributed between the two treatment groups.

In summary, these randomized trial data from a large population of healthy women indicate that 10 years of alternate-day treatment with 600 IU of natural source vitamin E alone has no material beneficial or harmful effect on AMD occurrence. Whether vitamin E as a component of an antioxidant combination can help to reduce risks of AMD, as suggested by the findings in AREDS, warrants continued investigation.

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Figure 1.

Flow diagram illustrating the vitamin E component of the Women's Health Study (WHS). A total of 455 participants who had a diagnosis of age-related macular degeneration at baseline were excluded.

Visually Significant AMD

Figure 2.
Cumulative incidence rates of visually-significant age-related macular degeneration (AMD) in the Women's Health Study.

Table 1

Baseline Characteristics in Randomized Vitamin E and Placebo Treatment Groups in the Women's Health Study.*

Characteristics	Vitamin E (n=19,697)	Placebo (n=19,724)
Mean age, y	54.5	54.5
45–54	60.7	60.6
55–64	29.5	29.4
65+	9.8	10.0
Cigarette smoking		
Current	13.1	13.3
Past/Never	86.9	86.7
Alcohol use		
<1/wk	58.5	58.0
≥1/wk	41.5	42.0
Body-mass index [†]		
Mean	26.0	26.0
<25.0	50.6	51.0
25.0–29.9	31.1	30.8
≥30.0	18.3	18.2
Hypertension [‡]		
Yes	25.4	26.0
No	74.6	74.0
Hyperlipidemia [§]		
Yes	29.1	29.5
No	70.9	70.5
Diabetes mellitus		
Yes	2.5	2.5
No	97.5	97.5
Menopausal status and use of HT		
Premenopausal	27.6	27.9
Uncertain	18.0	18.1
Postmenopausal and current HT	30.1	29.9
Postmenopausal and no HT	24.3	24.1
Parental history of MI before 60 yrs of age		
Yes	13.0	12.9
No	87.0	87.1

<u>Characteristics</u>	<u>Vitamin E</u> (n=19,697)	<u>Placebo</u> (n=19,724)
Multivitamin use		
Current	37.0	36.4
Past/Never	63.0	63.6
Eye exam in past 2 yrs		
Yes	82.6	82.8
No	17.4	17.2

Abbreviations: HT, hormone therapy; MI, myocardial infarction.

* Data are given as the percentage of participants, unless otherwise indicated. Percentages may not total 100 because of rounding.

[†] Body-mass index is the weight in kilograms divided by the square of the height in meters.

[‡] Hypertension was defined as a systolic blood pressure of at least 140 mm Hg, a diastolic blood pressure of at least 90 mm Hg, or self-reported physician-diagnosed hypertension.

[§] Hyperlipidemia was defined as a total cholesterol of at least 240 mg per deciliter or self-reported physician-diagnosed high cholesterol levels.

Table 2

Confirmed Cases of Age-related Macular Degeneration.

Endpoint	Vitamin E (N=19,697)	Placebo (N=19,724)	RR [*]	(95% CI)	P-value
Visually significant AMD	117	128	0.93	0.72–1.19	0.54
Advanced AMD	29	26	1.13	0.67–1.92	0.65
AMD with or without vision loss	280	313	0.90	0.77–1.06	0.20

Abbreviations: AMD, age-related macular degeneration; RR, relative risk; CI, confidence interval

^{*} Adjusted for age and aspirin and beta carotene treatment assignment

Table 3
Effect of Randomized Vitamin E Assignment on Visually Significant Age-related Macular Degeneration by Subgroups.

	No. of AMD/Total					
	Vitamin E	Placebo	RR *	95% CI	P-value	P(test of interaction)
Age, y						0.09
45–54	9/11,949	20/11,958	0.45	0.21–1.00	0.049	
55–64	38/5,807	40/5,800	0.95	0.61–1.48	0.81	
≥65	70/1,941	68/1,966	1.05	0.75–1.46	0.78	
Smoke Cigarettes						0.89
Current	19/2,569	22/2,622	0.91	0.49–1.68	0.76	
Past/Never	97/17,110	106/17,085	0.92	0.70–1.22	0.57	
Alcohol Use						0.99
<1/wk	74/11,517	81/11,431	0.91	0.66–1.24	0.55	
≥1/wk	43/8,173	47/8,290	0.96	0.64–1.46	0.85	
Body-mass index						0.13
<25.0	64/9,763	56/9,866	1.18	0.82–1.69	0.37	
25.0–29.9	30/5,999	38/5,953	0.77	0.48–1.24	0.28	
≥30.0	23/3,519	30/3,520	0.78	0.45–1.34	0.37	
Hypertension						0.40
Yes	51/4,995	50/5,130	1.05	0.71–1.54	0.83	
No	66/14,700	78/14,587	0.84	0.61–1.17	0.31	
Hyperlipidemia						0.20
Yes	49/5,736	44/5,819	1.17	0.78–1.76	0.45	
No	68/13,955	84/13,895	0.81	0.59–1.11	0.18	
Diabetes						0.35
Yes	3/497	6/494	0.45	0.11–1.80	0.26	
No	114/19,191	122/19,215	0.95	0.73–1.22	0.67	

	No. of AMD/Total		RR [*]	95% CI	P-value	P(test of interaction)
	Vitamin E	Placebo				
Menopausal status and use of HT						0.38
Premenopausal	4/5,431	6/5,490	0.70	0.20–2.50	0.59	
Uncertain	4/3,532	11/3,556	0.37	0.12–1.15	0.09	
Postmenopausal and current HT	39/5,907	38/5,892	1.05	0.67–1.64	0.83	
Postmenopausal and no HT	70/4,777	73/4,736	0.96	0.69–1.33	0.80	
Parental history of MI before 60 yrs of age						0.82
Yes	10/2,301	12/2,284	0.83	0.36–1.92	0.66	
No	90/15,384	104/15,455	0.88	0.66–1.16	0.35	
Multivitamin Use						0.52
Current	43/7,185	53/7,080	0.81	0.54–1.21	0.30	
Past/Never	73/12,233	75/12,369	0.99	0.72–1.37	0.95	
Eye exam in past 2 yrs						0.65
Yes	98/16,262	111/16,321	0.90	0.69–1.18	0.46	
No	19/3,431	17/3,400	1.07	0.55–2.05	0.85	

Abbreviations: AMD, age-related macular degeneration; CI, confidence interval; HT, hormone therapy; MI, myocardial infarction.

* Adjusted for age and aspirin and beta carotene treatment assignment