The Use of Vitamin Supplements and the Risk of Cataract among US Male Physicians

Johanna M. Seddon, MD, William G. Christen, DSc, JoAnn E. Manson, MD, Fran S. LaMotte, BS, Robert J. Glynn, DSc, Julie E. Buring, DSc, and Charles H. Hennekens, MD

A B S T R A C T

Objectives. The purpose of this study was to examine prospectively the association between reported use of vitamin supplements and risk of cataract and cataract extraction.

Methods. The study population consisted of 17 744 participants in the Physicians' Health Study, a randomized trial of aspirin therapy and beta-carotene among US male physicians 40 to 84 years of age in 1982 who did not report cataract at baseline and provided complete information about vitamin supplementation and other risk factors for cataract. Self-reports of cataract and cataract extraction were confirmed by medical record review.

Results. During 60 months of follow-up, there were 370 incident cataracts and 109 cataract extractions. In comparison with physicians who did not use any supplements, those who took only multivitamins had a relative risk of cataract of 0.73 after adjustment for other risk factors. For cataract extraction, the corresponding relative risk was 0.79. Use of vitamin C and/or E supplements alone was not associated with a reduced risk of cataract, but the size of this subgroup was small.

Conclusions. These data suggest that men who took multivitamin supplements tended to experience a decreased risk of cataract and support the need for rigorous testing of this hypothesis in large-scale randomized trials in men and women. (*Am J Public Health.* 1994;84:788–792)

Introduction

Cataract is the leading cause of blindness and visual impairment in the world.[1] In the growing US elderly population, cataract is a leading cause of functional impairment and morbidity,[2] and cataract surgery has become the most common procedure performed among people more than 65 years of age.[2] Modifiable preventive factors such as diet (including vitamin supplementation) are receiving increased attention and merit careful evaluation.

Nutritional factors, particularly vitamins with antioxidant properties, may affect cataract development, possibly by protecting against free radical oxidative damage that results from many normal metabolic processes as well as exposure to ultraviolet light.[3,4] At present, data concerning the possible associations between vitamins and cataract are sparse and inconsistent.[5–14] We therefore sought to determine whether vitamin supplementation affected risk of cataract in a large prospective cohort of male physicians participating in the Physicians' Health Study.[15]

Methods

Study Population

The subjects and methods of the Physicians' Health Study have been described previously.[15] Briefly, the study is a randomized, double-masked, placebo-controlled trial that has tested (in a 2 × 2 factorial design) the effect of low-dose aspirin therapy (325 mg every other day) on the risks of cardiovascular disease and is continuing to evaluate beta-carotene (50 mg on alternate days) in the prevention of cancer and cardiovascular disease. The study involves 22 071 US male physicians who were 40 to 84 years of age in 1982. On January 25, 1988, the randomized aspirin component of the study was terminated early, principally as a result of the emergence of a statistically extreme 44% reduction in risk of a first myocardial infarction among those assigned to aspirin.

Supplement and Risk Factor Data

At baseline, participants completed questionnaires that requested information about dietary supplements. Questions included whether multiple vitamins had been taken regularly (never, past only, or current) and the number of years taken (if current). Questions were also asked about whether participants had ever regularly taken capsules containing only vitamin A, only vitamin C, and only vitamin E (never, past only, or current). For each vitamin currently used, partici-

Johanna M. Seddon and William G. Christen are with the Department of Ophthalmology, Harvard Medical School, Boston, Mass; Johanna M. Seddon is also with the Department of Epidemiology, Harvard School of Public Health. William G. Christen was and JoAnn E. Manson, Fran S. LaMotte, Robert J. Glynn, Julie E. Buring, and Charles H. Hennekens are with the Division of Preventive Medicine, Harvard Medical School and Brigham and Women's Hospital. Julie E. Buring and Charles H. Hennekens are also with the Department of Ambulatory Care and Prevention, Harvard Medical School.

Requests for reprints should be sent to Charles H. Hennekens, MD, Brigham and Women's Hospital, 900 Commonwealth Ave E, Boston, MA 02215-1204.

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pants reported the number of years taken. In these analyses, subjects who reported current use of supplements were classified as supplement users. Since beta-carotene was an assigned treatment, those who reported vitamin A use were ineligible for enrollment in the Physicians' Health Study and were excluded. Although a complete dietary questionnaire was not administered, information was provided on a number of baseline characteristics, including cigarette smoking, alcohol use, history of diabetes mellitus, history of hypertension, history of high cholesterol, height, weight, physical activity, and parental history of myocardial infarction. This report includes 17 744 participants who provided complete information about vitamin supplements and other risk factors and reported that they did not have cataract at baseline.

Cataract Diagnoses

Follow-up questionnaires were sent at 6-month intervals during the first year and annually thereafter; these questionnaires requested information about compliance and occurrence of incident diseases, including cataracts. After report of a cataract diagnosis or extraction, a written consent requesting the name and address of the treating ophthalmologist was obtained. Ophthalmologists were contacted by mail and completed a cataract questionnaire that asked about the presence of lens opacities, visual acuity loss, cataract extraction, other ocular abnormalities that could explain visual acuity loss, cataract type, and primary cause (including age related, traumatic, congenital, inflammatory, or surgery or steroid induced). Alternatively, the ophthalmologists could supply photocopies of the relevant medical records.

The endpoints for this analysis were incident cataract and cataract extraction. Cataract was defined as follows: self-report, confirmed by medical record review, initially diagnosed after randomization, age related in origin, with best corrected visual acuity of 20/30 or worse and no alternate ocular pathology to explain the visual acuity loss. In the presence of alternate ocular pathology, a lens opacity was considered a cataract if, in the judgment of the ophthalmologist, 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. For the present report, we followed the 17 744 eligible participants from randomization until January 25, 1988, the date the randomized aspirin component of the trial was terminated. The average length of follow-up was 60.2 months.

Data Analysis

Incidence rates of cataract and cataract extraction were obtained by dividing the number of incident cases by person-years of follow-up in each category of supplement use. Categories of vitamin use were vitamin C and/or E only, multivitamins only, multivitamins plus vitamin C and/or E, and no supplement intake. Relative risks (RRs) were computed as the rate of cataract in a specific category of supplement use divided by the corresponding rate among nonusers.

Data were analyzed separately for cataract diagnoses and extractions. Crude relative risk estimates controlled for age as well as randomized aspirin and beta-carotene assignment. In proportional hazard models used to control for multiple potential confounders, indicator terms were added for smoking (never, past, current), history of diabetes, history of hypertension (systolic blood pressure of 160 mm Hg or greater, diastolic blood pressure of 95 mm Hg or greater, or history of treatment for high blood pressure), history of high cholesterol (reported history of treatment for high cholesterol or reported blood cholesterol of 260 mg/dL or greater), obesity (body mass index of 27.8 kg/m^2 or greater), alcohol use (reported daily or weekly use), physical activity (reported vigorous exercise once per week or more), and parental history of myocardial infarction. Stratified analyses were performed to evaluate any possible modification of the effect of vitamin supplement use on cataract by category of smoking (never, past, current). Those not using supplements were the referent within each category of smoking.

For each relative risk, two-sided P values and 95% confidence intervals (CIs) were calculated.[16] 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. When the worse eye was excluded because of loss of visual acuity attributed to other ocular abnormalities or a cause that was not age related, the other eye was used for classification.

Results

There were 370 incident cataracts and 109 cataract extractions during follow-up. At baseline, 12.5% of the participants reported multivitamin use only, 7.5% used multivitamin supplements plus C and/or E, and 4.1% reported vitamin C and/or E supplementation. The distribution of baseline characteristics that are possible risk factors for cataract are presented according to supplement status in Table 1. Vitamin supplement users tended to be older and reported more physical activity, more hypertension, and less obesity.

As seen in Table 2, in analyses adjusted for age and randomized treatment assignment, multivitamin-only users had a marginally significant decreased risk of incident cataract relative to nonsupplementers (RR = 0.75, 95% CI = 0.55, 1.01). After adjustment for other potential cataract risk factors, the relative risk was 0.73 (95% CI = 0.54, 0.99). Users of vitamin C and/or E alone, however, did not appear to have a reduced risk of cataract, but the numbers were small. Multivitamin users who also used supplements containing only vitamin C and/or E had a risk of incident cataract similar to users of multivitamins only. The relative risk of cataract decreased with increasing duration of any use of multivitamins, an apparent trend of borderline statistical significance (P = .06) (Table 3).

The adjusted relative risk for cataract extraction among multivitamin users only (0.79, 95% CI = 0.46, 1.35) was similar to that for cataract diagnosis. Risk of cataract extraction was not reduced among participants taking vitamin C and/or E alone. However, as with cataract diagnosis, the number of cataract extractions in this subgroup was small.

The association between any multivitamin use and risk of cataract within categories of cigarette smoking was also assessed. Among those who never smoked, the relative risk was 1.10 (95% CI = 0.76, 1.60) after adjustment for other risk factors. However, among past and current smokers, the risk of cataract was reduced among multivitamin users relative to nonusers (RR = 0.61, 95% CI = 0.42, 0.90, and RR = 0.38, 95% CI = 0.16, 0.92, respectively). This trend for a reduction in risk among multivitamin users who smoked was statistically significant (P = .008). Numbers were too small to evaluate smoking among users of vitamins C and/or E only or the endpoint cataract extraction.

TABLE 1—Differences in Sample's Baseline Characteristics That Are Known or Potential Risk Factors for Cataract, by Supplement Status

	Vitamin C and/or E Only	Multivitamin Only	Multivitamin and C and/or E	No Vitamins
Total n	729	2222	1331	13 462
Mean age, y	54.0	55.4	54.5	52.2
Diabetes, %	0.8	3.7	3.2	2.1
Physical activity, %[a]	76.0	74.0	78.0	71.6
History of high cholesterol, %[b]	5.9	7.7	8.3	6.5
History of parental myocardial infarction, %	10.7	12.7	12.5	13.7
Hypertension, %[c]	16.3	17.6	14.5	13.2
Obesity, %[d]	10.0	12.4	11.3	14.0
Smoking, %				
Never	53.5	45.4	49.6	51.6
Past	39.9	42.2	40.7	38.1
Current	6.6	12.3	9.7	10.3
Alcohol, %				
Daily	24.3	28.9	27.1	23.4
Weekly	49.9	42.8	44.6	50.5

[a]Defined as reported vigorous exercise once per week or more.
[b]Defined as reported high cholesterol or reported blood cholesterol of 260 mg/dL or greater.
[c]Defined as reported systolic blood pressure of 160 mm Hg or greater, diastolic blood pressure of 95 mm Hg or greater, or history of treatment for high blood pressure.
[d]Defined as body mass index of 27.8 kg/m^2 or greater.

TABLE 2—Association between Vitamin Supplement Use and Risk of Cataract Diagnosis, by Supplement Status

	Vitamin C and/or E Only	Multivitamin Only	Multivitamin and C and/or E	No Vitamins
No. of cataracts	22	51	29	268
Total person-years of observation	3598	10 983	6584	67 010
Short model[a]				
Relative risk	1.26	0.75	0.77	1.0
95% confidence interval	0.81, 1.94	0.55, 1.01	0.52, 1.13	. . .
P	.30	.06	.18	. . .
Full model[b]				
Relative risk	1.32	0.73	0.77	1.0
95% confidence interval	0.85, 2.04	0.54, 0.99	0.53, 1.14	. . .
P	.21	.04	.19	. . .

[a]Adjusted for age and randomized treatment assignment.
[b]Adjusted for age, randomized treatment assignment, history of diabetes mellitus, history of hypertension (systolic blood pressure of 160 mm Hg or greater, diastolic blood pressure of 95 mm Hg or greater, or history of treatment of high blood pressure), obesity (body mass index of 27.8 kg/m^2 or greater), alcohol (reported daily or weekly use), physical activity (reported vigorous exercise once per week or more), parental history of myocardial infarction, high cholesterol (reported treatment for high cholesterol or reported blood cholesterol of 260 mg/dL or greater), and smoking status (never, past, or current).

Discussion

These prospective data are compatible with the possibility that vitamin users may have a lower risk of cataract and cataract extraction. If real, even modest decreases in risk such as those suggested in this study are potentially important, given the high prevalence of cataract, the enormous costs associated with cataract extraction, and the feasibility of dietary changes or micronutrient supplementation.

The prospective design of this study precludes the possibility of bias in reporting supplementation use based on disease outcome, since vitamin supplement use was reported at baseline prior to questions regarding the cataract outcomes and only incident cataracts diagnosed after this baseline period were included in the analyses. Because of the mail questionnaire design, the diagnoses of cataract and cataract extraction were based on medical record confirmation. There were essentially no false-positive cases of cataract extraction and, because we required medical record documentation, probably very few if any false-positive incident cataracts. Although there may have been cases that were not ascertained (false negatives), such underascertainment should not bias the relative risks in a cohort study if not associated with exposure.[17,18] Differential misclassification of cataract based on supplement use was extremely unlikely, since medical records were reviewed without knowledge of the participants' exposure data and treating ophthalmologists would have been generally unaware of the participants' dietary habits or the vitamin–cataract hypothesis, which has only been reported recently.

It is possible that multivitamin supplement users may be more health conscious and may, therefore, have more (or less) medical contacts, which would increase (or decrease) the likelihood of having a cataract diagnosed. However, all participants in this study are physicians, so their overall level of medical care is likely to be reasonably uniform, with no large differences between users and nonusers of supplements. Misclassification of vitamin intake is unlikely, since use of supplements is usually accurately recalled.[19] Such misclassification, if present, would probably be random and would tend to bias associations toward the null. Incomplete follow-up is not an issue in this study. Morbidity follow-up was 99.3% complete as of January 25, 1988, and ocular medical records were obtained for more than 90% of both users and nonusers of supplements.

Several known or potential risk factors for cataract, such as diabetes and smoking status, were controlled in the analyses. Of course, the effects of unmeasured or unknown factors cannot be controlled in an observational study. It is possible that users of multivitamins differed from nonusers in ways that were not measured and therefore, could not be adjusted for in these analyses. For example, we were unable to control accurately for the effects of sun exposure. It is unlikely that there are large differences in

sun exposure, however, among this homogeneous group of male physicians, with most having no occupational exposure to sunlight. This possibility is supported by the lack of an association between geographic region and cataract when this variable was included in the multivariate models.

Foods rich in vitamins with antioxidant properties are now considered to have the potential to prevent many chronic diseases, including coronary heart disease and cancer.[20] A similar role has been hypothesized in the formation and progression of cataract[21] that centers on the protective action of certain micronutrients against free radical oxidative damage.[22,23] Experimental studies have demonstrated that both vitamin C[22] and vitamin E[23] prevent lipid peroxidation in response to photo-oxidative assault and limit lens damage after oxidative insult in animals fed these vitamins.[24,25] A few epidemiologic studies have also evaluated the association between antioxidant nutrient status and cataract.[5-14] Some of these cross-sectional or retrospective studies have found an inverse association between cataract and plasma[5] or dietary[7,8] vitamin C, plasma[14] or dietary[7,8] vitamin E, and use of multivitamins.[8] In contrast, others have not shown an inverse association with vitamins C, E, or beta-carotene[9,10,14] or with use of multivitamins.[7] Data from two studies that used prospectively identified cases have also been conflicting. Inverse associations with cataract or cataract extraction were reported for dietary carotenoids,[12] long-term vitamin C supplementation,[12] and plasma levels of vitamin E and beta-carotene.[13] On the other hand, no associations were observed between the cataract endpoint and dietary vitamins C or E.[12]

Our prospective data, combined with evidence from previous studies, are compatible with the possibility that multivitamin supplements are related to cataract. Although the numbers are small, our findings regarding separate supplementation with vitamins C and E, which both have antioxidant properties, do not suggest a protective effect for these vitamins used either alone or in addition to multivitamins. The antioxidant properties of multivitamins, which contain vitamins C and E, represent a plausible mechanism by which risk of cataract may be reduced. However, there may be other components of multivitamins separate from antioxidants that offer protection. Further laboratory and clinical research is needed to elucidate mechanisms to understand how multivitamin supplementation may affect risk of cataract.

TABLE 3—Association between Duration of Multivitamin Supplement Use and Risk of Cataract

	Duration of Use, y[a]			
	<5	5–10	>10	*P* for Trend
No. of cataracts	32	11	18	...
No. of person-years	7847	2598	3229	...
Short model[b]				
Relative risk	0.88	0.75	0.69	.07
95% confidence interval	0.61, 1.27	0.41, 1.36	0.43, 1.11	...
Full model[c]				
Relative risk	0.88	0.74	0.68	.06
95% confidence interval	0.61, 1.27	0.40, 1.35	0.42, 1.10	...

[a]n = 3553 (2222 multivitamin users and 1331 multivitamin plus C and/or E users).
[b]Adjusted for age and randomized treatment assignment.
[c]Adjusted for age, randomized treatment assignment, history of diabetes mellitus, history of hypertension (systolic blood pressure of 160 mm Hg or greater, diastolic blood pressure of 95 mm Hg or greater, or history of treatment of high blood pressure), obesity (body mass index of 27.8 kg/m^2 or greater), alcohol (reported daily or weekly use), physical activity (reported vigorous exercise once per week or more), parental history of myocardial infarction, high cholesterol (reported high cholesterol or reported blood cholesterol of 260 mg/dL or greater), and smoking status (never, past, or current).

Results of our analyses also raise the possibility of a benefit of multivitamin supplementation on risk of cataract, primarily among the subgroups of past and current smokers. Although it is plausible that supplementation might help particularly those with reduced levels of nutrients related to oxidative stress, as may occur among smokers, our subgroup findings are speculative, based on small numbers, and require further study.

As is the case with detection of small to moderate benefits, observational studies have amounts of uncontrolled or uncontrollable confounding that may be as large as the effects being postulated. Thus, the only reliable means to determine whether antioxidant vitamins decrease cataract is through large-scale randomized trials.[17,26] In this regard, the National Eye Institute's Age-Related Eye Disease Study[26] is testing vitamins C, E, and beta-carotene, as well as zinc; the Physicians' Health Study[27] is evaluating beta-carotene; and the Women's Health Study[28] is testing beta-carotene and vitamin E. All of these data will provide relevant and complementary information to a body of evidence on which reliable clinical decision making and public policy can safely be based.

In summary, these prospective data from the Physicians' Health Study suggest that multivitamin supplementation may be associated with a modest decrease in the risk of cataract. Results were marginally significant and were derived from an observational study design. Findings support the need for large-scale randomized trials in men and women to evaluate definitively the possibility that micronutrient supplementation may reduce the worldwide burden of blindness due to cataract. □

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