A Randomized Trial of Beta Carotene and Age-Related Cataract in US Physicians

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Objective: To examine the development of age-related cataract in a trial of beta carotene supplementation in men.

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

Methods: Male US physicians aged 40 to 84 years (n=22071) were randomly assigned to receive either beta carotene (50 mg on alternate days) or placebo for 12 years.

Main Outcome Measures: Age-related cataract and extraction of age-related cataract, defined as an incident, age-related lens opacity, responsible for a reduction in best-corrected visual acuity to 20/30 or worse, based on self-report confirmed by medical record review.

Results: There was no difference between the beta carotene and placebo groups in the overall incidence of cataract (998 cases vs 1017 cases; relative risk [RR], 1.00; 95% confidence interval [CI], 0.91-1.09) or cataract extraction (584 vs 593; RR, 1.00; 95% CI, 0.89-1.12). In subgroup analyses, the effect of beta carotene supplementation appeared to be modified by smoking status at baseline (P=.02). Among current smokers, there were 108 cases of cataract in the beta carotene group and 133 in the placebo group (RR, 0.74; 95% CI, 0.57-0.95). Among current nonsmokers, there was no significant difference in the number of cases in the 2 treatment groups (884 vs 881; RR, 1.03; 95% CI, 0.94-1.13). The results for cataract extraction appeared to be similarly modified by baseline smoking status (P=.05).

Conclusions: Randomized trial data from a large population of healthy men indicate no overall benefit or harm of 12 years of beta carotene supplementation on cataract or cataract extraction. However, among current smokers at baseline, beta carotene appeared to attenuate their excess risk of cataract by about one fourth.

Arch Ophthalmol. 2002;120:372-378

OXIDATIVE PROCESSES are believed to be an important contributing factor in the development of age-related cataract, a leading cause of visual impairment in the United States.1,2 Thus, there is considerable interest in determining whether vitamins with antioxidant properties lower risks of cataract development and progression. Laboratory studies support this possibility by showing that supplementation with antioxidant vitamins and minerals prevents or delays cataract development in vitro and in animal models.3-7 Observational epidemiologic studies in humans provide further support by showing that persons with higher intakes of fruits and vegetables, or higher plasma levels of various antioxidant nutrients, tend to have lower risks of cataract. The data for individual nutrients, however, including vitamins C and E and the carotenoids, are inconsistent. More important, in these observational studies the amount of uncontrolled and uncontrolable confounding may be as large as the most plausible small to moderate effect sizes, so data from randomized trials are necessary.

Among the carotenoids, beta carotene received considerable early interest as a possible anticataract agent, in part because it was known to be an effective antioxidant at low partial pressures of oxygen,8 conditions found in the lens, but also because it is readily available in fruits and vegetables and was not associated with any harmful effects, even in the very large doses used to treat patients with erythropoietic protoporphyria.9,10 Subsequent investigations, however, have provided only modest support for a beneficial effect of beta carotene against cataract. Thus, while most,11-17 but not all,18,19 observational studies report an inverse association between beta carotene level in the diet or blood and risk of cataract, none attain statistical sig-
nificance. Furthermore, findings from 3 randomized trials, 2 of which tested antioxidant vitamin cocktails and a third that tested beta carotene alone in a population of male heavy smokers in Finland, indicate that supplementation with beta carotene for 5 to 6 years has little effect on the risk of cataract. These trial data, however, are limited in interpretability by the duration of treatment, which may be insufficient to affect cataract development.

In this report, we describe the results for cataract development and extraction during 12 years of randomized beta carotene treatment in Physicians’ Health Study I (PHS I), a randomized trial among 22,071 US male physicians. Because of the possible adverse effect of beta carotene on lung cancer in smokers, and because cigarette smoking is an important risk factor for cataract, we present results for cataract in the overall population, as well as for subgroups according to smoking status at baseline.

STUDY DESIGN

Physicians’ Health Study I was a randomized, double-masked, placebo-controlled, $2 \times 2$ factorial trial designed to evaluate low-dose aspirin and beta carotene in the primary prevention of cardiovascular disease and cancer. The methods of the trial have been described in detail previously. Briefly, 22,071 US male physicians, who had no history of cancer (except nonmelanoma skin cancer), myocardial infarction, stroke, or transient cerebral ischemia, were randomly assigned to aspirin (325 mg on alternate days [Bufferin; provided by Bristol-Myers Products, New York, NY]) or its placebo, plus beta carotene (50 mg on alternate days [Lurotin; provided by BASF Corporation, Mt Olive, NJ]) or its placebo (Figure 1). Baseline information included height, weight, history of cigarette smoking, history of alcohol use, blood pressure level, cholesterol levels, history of diabetes mellitus, and history of multivitamin use. Information on personal history of cataract was also obtained at baseline. A total of 20,968 physicians did not report cataract at baseline and are included in these analyses. Annual questionnaires were sent to all participants to monitor their compliance with assigned treatment and the occurrence of any relevant events, including cataract. Informed consent was obtained from all participants, and the research protocol was reviewed and approved by the institutional review board at Brigham and Women’s Hospital, Boston, Mass.

The aspirin component of PHS I was terminated early, on January 25, 1988, after a mean follow-up of 60.2 months, due primarily to the emergence of a statistically extreme 44% reduced risk of a first myocardial infarction among those taking aspirin. The randomized beta carotene component of the trial continued uninterrupted until the scheduled termination date of December 31, 1995.

By the end of 1995, participants had been taking beta carotene or placebo for a mean of 12 years (range, 11.6–14.2 years). At the end of 11 years of follow-up (the last year completed for all participants), 99.2% were still providing information on morbidity, and follow-up for mortality was 99.9% complete. In both the beta carotene group and the placebo group, 80% of participants were still taking the study pills, with a mean compliance among pill takers of more than 97%. Thus, even after 11 years in the beta carotene group, 78% of the study pills were reported as still being taken. In the placebo group, 6% reported taking supplemental beta carotene or vitamin A.

METHODS

STUDY DESIGN

ASSEMBLING AND DEFINITION OF END POINTS

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 asked to complete cataract questionnaires 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, cataract type, 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 participating ophthalmologists.

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, 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 to be 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.

STATISTICAL ANALYSIS

The Cox proportional-hazards model was used to estimate the relative risk (RR) of cataract among those assigned to beta carotene compared with those assigned placebo after adjustment for age (years) at baseline and randomized aspirin treatment.
As is expected in a large randomized trial, baseline characteristics were equally distributed between the 2 treatment groups (Table 1). In each group, 11% of participants were current smokers at baseline.

During a mean of 12 years of treatment and follow-up, a total of 2015 cataracts and 1177 cataract extractions were confirmed by medical record review. Overall, there was no significant benefit or harm of beta carotene supplementation on risk of cataract (998 cases in the beta carotene group vs 1017 in the placebo group; RR, 1.00; 95% CI, 0.91-1.09) (Table 2). Similarly, there was no effect of beta carotene supplementation on risk of cataract extraction (584 cases in the beta carotene group vs 593 in the placebo group; RR, 1.00; 95% CI, 0.89-1.12) (Table 2). Relative risks decreased slightly with increasing duration of treatment, but the trend was not statistically significant (data not shown).

In subgroup analysis, the effect of beta carotene supplementation on cataract appeared to be modified by smoking status at baseline (P for interaction=.02). Among current smokers, men assigned to the beta carotene group had a statistically significant 26% reduced risk of cataract compared with those in the placebo group (108 cases vs 133 cases; RR, 0.74; 95% CI, 0.57-0.95) (Table 4). There was no apparent effect of beta carotene supplementation in men who were nonsmokers at baseline (884 cases vs 881 cases; RR, 1.03; 95% CI, 0.94-1.13). Similar results were observed for cataract extraction (P for interaction=.05). Among current smokers, men assigned to beta carotene had a 27% reduced risk of extraction compared with men assigned to placebo (68 cases vs 86 cases; RR, 0.73; 95% CI, 0.53-1.00). Among nonsmokers, there was no effect of beta carotene supplementation (512 cases in the beta carotene group vs 505 cases in the placebo group; RR, 1.04; 95% CI, 0.92-1.17). For both cataract and cataract extraction, the reduction in risk among current smokers assigned to beta carotene was apparent during the early years of treatment and follow-up (years 1-5), although the confidence intervals around these RR estimates included the null value of 1.0 because of the smaller number of events (Figure 2).

There was no significant trend toward greater benefit with an increasing duration of treatment for either cataract end point.

Cigarette smoking is a well-established risk factor for cataract. To explore the relative effects of baseline smoking status and beta carotene treatment assignment on risk of cataract, models were fit with current nonsmokers assigned to placebo as the reference group. For current smokers assigned to placebo, there was a statistically significant 65% increased risk of cataract (RR, 1.65; 95% CI, 1.37-1.98) compared with the reference group.
Figure 3). This excess risk associated with being a current smoker was markedly attenuated by assignment to beta carotene treatment (RR, 1.22; 95% CI, 1.00-1.49). The results for cataract extraction were similar.

**COMMENT**

In this large-scale randomized trial among apparently healthy, well-nourished men, there was no statistically significant benefit or harm of 12 years of beta carotene supplementation on overall risk of cataract or cataract extraction. The narrow CIs excluded even a modest effect of beta carotene supplementation (ie, 15%-20% increase or decrease in risk) on cataract. In subgroup analyses, there was a possible beneficial effect of beta carotene in men who were current smokers at baseline. Cigarette smoking is a well-established risk factor for cataract,\textsuperscript{27-30} and beta carotene appeared to attenuate the excess risk.

Several possible limitations of the trial should be considered, particularly in view of the overall finding of no benefit or harm. Inadequate dosage of beta carotene is an unlikely explanation for the findings. The dosage tested in the trial (50 mg on alternate days) placed participants in the top few percentiles of the general population with respect to usual intake. Moreover, bioavailability studies in our population showed that the alternate-day dosage and formulation increased plasma beta carotene concentrations approximately 4-fold.\textsuperscript{32,33} The finding of a possible beneficial effect for beta carotene in the subgroup of men who were current smokers at baseline provides some support for the adequacy of the dosage tested. Poor compliance with assigned treatment is also not a plausible explanation for our overall findings, because there was 85% compliance with beta carotene treatment after 5 years and compliance was still 78% after 12 years. In the placebo group, the use of beta carotene or vitamin A supplements was reported by only 6% of participants, even by the end of the trial. Random misclassification of cataract, which would tend to shift the RR estimate toward the null, was reduced by the use of medical records to confirm the self-reports and by the use of strict diagnostic criteria that included reduction in best-corrected visual acuity to 20/30 or worse owing to cataract. Nonrandom or differential misclassification was unlikely because medical records were reviewed without knowledge of beta carotene treatment assignment, and study participants and treating ophthalmologists and optometrists were unaware of beta carotene treatment assignment.

Randomized trial data regarding the effect of beta carotene supplementation on cataract are limited to 3 trials of 5 to 6 years’ duration. In 2 of these trials, beta carotene was tested as part of an antioxidant mixture. In a poorly nourished population in China, 5 to 6 years of treatment with vitamin and mineral combinations that included beta carotene (15 mg daily) had no effect on end-of-trial prevalence of cataract.\textsuperscript{29} In the recently completed Age-Related Eye Disease Study, there was no apparent effect of an antioxidant combination of vitamin E (400 IU), vitamin C (500 mg), and beta carotene (15 mg) on the development and progression of lens opacities during 6.3 years of treatment and follow-up.\textsuperscript{31} The use of a combined treatment regimen in these 2 trials precludes estimation of the effect of any specific nutrient. In the Alpha-Tocopherol, Beta Carotene Cancer Prevention (ATBC) study,\textsuperscript{22} which was the first large-scale randomized trial to test antioxidant vitamins in a well-nourished population, a total of 29 133 Finnish male smokers aged 50 to 69 years were randomly assigned in a 2 × 2 factorial trial to α-tocopherol (50 mg daily) or placebo and beta carotene (20 mg daily) or placebo. Four hundred twenty-five cataract surgeries were documented during about 6 years of treatment and follow-up. Overall results indicated little effect of beta carotene supplementation on the incidence of cataract surgery (RR, 0.97; 95% CI, 0.79-1.19). Because all participants smoked, effect modification could not be evaluated in that study, but there were no interactions with duration or amount smoked per day. In the PHS I, among current smokers, a subgroup more comparable to the study population in ATBC, we did observe a 25% to 30% reduced risk of cataract and cataract extraction for those assigned to beta carotene. This apparent benefit among current smokers does not appear simply to reflect the longer treatment period in PHS I. Specifically, analyses of data for the first 5 years in PHS I (comparable to the period of treatment in the ATBC study) suggested a beneficial effect on cataract ex-

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**Table 2. Confirmed Cases of Cataract According to Beta Carotene Treatment Assignment**

<table>
<thead>
<tr>
<th>Participants</th>
<th>Beta Carotene (n = 10 475)</th>
<th>Placebo (n = 10 493)</th>
<th>RR† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>78</td>
<td>62</td>
<td>1.26 (0.90-1.76)</td>
</tr>
<tr>
<td>50-59</td>
<td>280</td>
<td>303</td>
<td>0.93 (0.79-1.09)</td>
</tr>
<tr>
<td>60-69</td>
<td>444</td>
<td>450</td>
<td>0.99 (0.87-1.13)</td>
</tr>
<tr>
<td>70-84</td>
<td>196</td>
<td>202</td>
<td>1.01 (0.83-1.22)</td>
</tr>
<tr>
<td>Total</td>
<td>998</td>
<td>1017</td>
<td>1.00 (0.91-1.09)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.
\*Test for trend of the effect of age on the association between beta carotene and cataract, \( P = .85 \).
†Adjusted for aspirin treatment assignment.

**Table 3. Confirmed Cases of Cataract Extraction According to Beta Carotene Treatment Assignment**

<table>
<thead>
<tr>
<th>Participants</th>
<th>Beta Carotene (n = 10 475)</th>
<th>Placebo (n = 10 493)</th>
<th>RR† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>57</td>
<td>48</td>
<td>1.19 (0.81-1.74)</td>
</tr>
<tr>
<td>50-59</td>
<td>176</td>
<td>164</td>
<td>0.96 (0.78-1.18)</td>
</tr>
<tr>
<td>60-69</td>
<td>237</td>
<td>251</td>
<td>0.96 (0.79-1.13)</td>
</tr>
<tr>
<td>70-84</td>
<td>114</td>
<td>110</td>
<td>1.06 (0.81-1.37)</td>
</tr>
<tr>
<td>Total</td>
<td>584</td>
<td>593</td>
<td>1.00 (0.89-1.12)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.
\*Test for trend of the effect of age on the association between beta carotene and cataract extraction, \( P = .88 \).
†Adjusted for aspirin treatment assignment.
traction (RR, 0.57; 95% CI, 0.32-1.03) during the early years of the trial.

These subgroup findings among smokers in PHS I must be interpreted with caution. Although a possible beneficial effect for beta carotene supplementation in smokers was observed for both end points of cataract and cataract extraction, these findings are not independent because participants undergoing extraction are a subset...
of participants with incident cataract. Furthermore, these results in smokers appear to be at odds with randomized trial data from the ATBC study, and evidence from several observational studies provides little support for a beneficial effect of beta carotene supplementation in smokers. Additionally, the subgroup of current smokers in PHS I was small (11% current smokers at baseline), and, thus, the result in smokers could simply be due to chance. However, if real, these findings raise questions about mechanisms by which supplemental beta carotene might exert a beneficial effect on cataract among smokers. Beta carotene has not been detected in the normal or cataractous human lens, nor has it been detected in the human lens following extensive dietary supplementation. Thus, a direct effect of beta carotene supplementation on lens concentrations seems unlikely. Beta carotene could have an indirect effect by increasing concentrations of other antioxidant nutrients in the lens. Ascorbate, \( \alpha \)-tocopherol, and the xanthophylls lutein and zeaxanthin have been detected in the human lens, and evidence suggests that plasma concentrations of ascorbate and perhaps lutein and zeaxanthin (but probably not \( \alpha \)-tocopherol) are reduced in smokers. There is no evidence, however, that beta carotene supplementation has any effect on plasma levels of \( \alpha \)-tocopherol or ascorbate, and plasma levels of lutein and zeaxanthin may even decrease with beta carotene supplementation. Thus, an indirect effect, mediated by an increase in plasma concentrations of other antioxidant nutrients, also appears unlikely. Alternatively, beta carotene might interact directly with oxidants present in the gas phase of cigarette smoke and thereby decrease oxidative stress in the environment surrounding the lens. Beta carotene may also minimize the deleterious effects of smoking-related oxidants on other antioxidant nutrients. Consistent with this possibility, recent laboratory data have shown that both \( \alpha \)-tocopherol and ascorbate are oxidized more slowly by gas-phase smoke exposure in liposomes containing beta carotene.

In summary, these randomized trial data from a large population of apparently healthy US male physicians indicate no overall benefit or harm of 12 years of beta carotene supplementation on cataract or cataract extraction. The subgroup finding of a possible beneficial effect of beta carotene in current smokers should be interpreted with caution, particularly in view of findings in 2 previous trials of possible adverse effects of beta carotene on lung cancer in smokers. However, if real, this finding could have important scientific implications and needs to be confirmed in other randomized trials in men and women.

Submitted for publication June 7, 2002; final revision received November 1, 2002; accepted November 14, 2002.

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This study was supported by research grants HL 26490, HL 34595, CA 34944, CA 40360, and EY 06633 from the National Institutes of Health, Bethesda.

We thank the entire staff of the PHS, under the leadership of Charlene Belanger, MA, as well as Mary Breen, Vadim Babes, PhD, Jean MacFadyen, BA, Geneva McNair, David Potter, BA, Leslie Power, Harriet Samuelson, MA, Miriam Schwartz, MD, Mickie Sheehy, Joanne Smith, BS, and Phyllis Johnson Wojciechowski, BS, for their crucial contributions. We are also indebted to the 22071 dedicated and committed participants of the PHS.

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