High-dose Antioxidant Supplementation and Cataract Risk

In a recent clinical trial, supplementation with high-dose antioxidants lowered the progression of lens opacities. These results differ from those of several other larger trials, in which no benefit to high-dose antioxidant supplementation was observed. Although a large body of observational evidence suggests that supplement use is associated with lower risk for cataract, there is insufficient evidence that high-dose antioxidants slow the progression of cataracts beyond that provided by multivitamins or healthful diets.

Key words: antioxidants, cataract, vitamin supplements

The lens of the eye is a translucent tissue that focuses light rays onto the retina. Lenses age slowly, beginning in the second decade of life and progressing more rapidly in middle and older age. The aging process results in the accumulation of light-scattering opacities that interfere with vision; this occurs during approximately the sixth or seventh decade of life, but may occur earlier or later depending on the individual. By age 75, clinically significant opacities, or cataract, are estimated to affect more than half of Americans.1,2 Whereas the removal of cataracts is a relatively simple procedure, it is expensive, accounting for more than 12% of the Medicare budget during the last evaluation in 1992.3 As the population ages,4 the impact of cataract will be greater. In addition, a recent report cited the association between cataracts and cataract surgery and risk for age-related macular degeneration,5,6 which is the most common cause of blindness in older people.

The possibility that vitamin supplements can lower risk for cataracts presents a relatively easy means of modifying the impact of cataracts on older people and society. The results of a recently published clinical trial,7 the Roche European American Cataract Trial (REACT) study, which was conducted in people in the United States and Great Britain, support the idea that supplements may slow the development of lens opacities. In this randomized, double-masked, placebo-controlled trial, 81 people who consumed a mixture of antioxidant nutrients (containing 18 mg of β-carotene, 750 mg of vitamin C, and 600 IU of vitamin E) for 3 years had lower rates of progression of lens opacities than the 77 people who did not take these supplements.

Although it is generally recognized that oxidative stress contributes to the development of lens opacities, REACT is the only clinical trial, to date, in which high-dose antioxidants have been shown to influence the occurrence of cataract (Table 1). In another large (4629 subjects), double-masked, placebo-controlled trial, the Age-Related Eye Disease Study (AREDS), a similar formulation of high-dose antioxidants did not influence progression of age-related lens opacities.1 In the Alpha-Tocopherol Beta-Carotene (ATBC) Trial in 28,934 male Finnish smokers, supplementation with α-tocopherol and/or β-carotene or placebo did not lower rates of cataract extraction over 5 to 8 years of follow up,8 nor did it lower prevalence of lens opacities observed in a random sub-sample of participants.9 In U.S. physicians taking β-carotene for 12 years, cataract extraction was not lowered.10 A 5-year clinical trial in Linxian, China, assessed the influence of vitamin supplementation on risk of cataract. No supplement combinations of antioxidants, neither vitamin C with molybdenum nor vitamin E with β-carotene and selenium were associated with lower prevalence of cataracts, even though multivitamins were associated with lower prevalence (discussed below).11 Overall, the evidence from clinical trials alone suggests that supplementation with high-dose antioxidants containing β-carotene, vitamin E, and/or vitamin C for 3 to 12 years does not influence the rate of cataract development.

Even though results of only one in five clinical trials of high-dose antioxidant supplements suggest a benefit, evidence from eight observational studies12–19 indicates lower rates of some types of cataract or cataract extraction among people who use multivitamin supplements. Two other observational studies found supplement use was not associated with cataract...
## Table 1. Summary of Clinical Trials of the Effect of Vitamin Supplementation on Lens Opacities or Cataract

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Design</th>
<th>Sample*</th>
<th>Supplement Tested</th>
<th>Lens Endpoint</th>
<th>Treatment Effect on Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>REACT†</td>
<td>3-year double-masked, placebo-controlled, randomized trial</td>
<td>158 people in the United States and Great Britain</td>
<td>18 mg β-carotene, 750 mg vitamin C, 600 IU vitamin E‡</td>
<td>Digitally assessed progression of opacities</td>
<td>Reduced</td>
</tr>
<tr>
<td>AREDS</td>
<td>7-year double-masked, placebo-controlled, randomized trial</td>
<td>4629 people in the United States</td>
<td>15 mg β-carotene, 500 mg vitamin C, 400 IU vitamin E</td>
<td>Photographic evidence of progression of lens opacities</td>
<td>None</td>
</tr>
<tr>
<td>ATBC</td>
<td>5–8-year double-masked, placebo-controlled, randomized trial</td>
<td>28,934 male Finnish smokers, Random subsample of 1828 subjects</td>
<td>20 mg β-carotene, 111 IU vitamin E</td>
<td>Cataract extraction</td>
<td>None</td>
</tr>
<tr>
<td>Physicians Health Study</td>
<td>12-year double-masked, placebo-controlled, randomized trial</td>
<td>22,071 male physicians, 50 mg β-carotene on alternate days</td>
<td>Prevalence of cataract or lens density</td>
<td>Cataract extraction</td>
<td>None</td>
</tr>
<tr>
<td>Linxian Cataract Study</td>
<td>5–6-year randomized trial, Four-way factorial design</td>
<td>2608 subjects, 120 mg vitamin C, 30 mg molybdenum</td>
<td>Prevalence of cataract assessed in eye examinations</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2608 subjects, 15 mg β-carotene, 400 IU vitamin E, 50 mg selenium</td>
<td></td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2141 subjects, Multivitamin containing (among other ingredients) 15 mg β-carotene, 60 IU vitamin E, 180 mg vitamin C</td>
<td></td>
<td>Subjects aged 45 to 64 years: none</td>
<td>Subjects aged 65 to 74 years: reduced prevalence of nuclear cataract</td>
</tr>
</tbody>
</table>
but had limited designs: one used cataract extraction as an outcome, which might be related to factors other than degree of opacity, and one used a sample in which supplement use was not prevalent. In several of these studies, the protection against cataracts was strongest among people who used multivitamin supplements for more than 10 years.

Among observational studies, however, there was little consistent evidence of a dose-dependent relationship between nutrient intake and cataracts. For example, in a sub-sample of the Nurse’s Health Study, the odds ratios for nuclear opacities declined approximately 40 to 50% between the first and third quintiles for vitamin C, vitamin E, and β-carotene, and little more with the higher intakes in the forth and fifth quintiles. In a sub-sample of the Beaver Dam Eye study, odds ratios for incident nuclear cataracts declined from 1.0 to approximately 0.5 from the first to the second tertile for blood levels of total tocopherols but only to 0.4 in the highest tertile.

There are several possible explanations why only one clinical trial found results that correspond with observational studies. The protective qualities of vitamin supplementation may accumulate over many years, such that a benefit can only be observed over longer periods of time or with sensitive methods to detect the progression of lens opacities. This theory is consistent with observations that long-term use of supplements, but not short-term use, is associated with lower risk for cataract. In the REACT study, a digital imaging system was used to evaluate lens opacities that might have been a more sensitive method of detecting differences in lens opacities over a short period of time than lens photographs or differences in rates of cataract surgeries. If so, investigators would have had greater opportunity to observe an impact among subjects given antioxidant supplements than investigators that used photographic evidence of cataract or cataract extraction as the outcome.

A second possible reason for conflicting results between clinical and observational trials is varying levels of blood nutrients among treated and reference subjects, which can result from using different supplement doses, varying bioavailability, or different dietary levels of these nutrients. In the REACT study, blood levels of vitamins C and E in the control groups were lower than those in AREDS (49 vs. 56 μmol/L for vitamin C and 31 vs. 38 μmol/L for vitamin E in the REACT vs. AREDS samples, respectively). AREDS participants were permitted to use multivitamins in addition to the high-dose antioxidant supplement. Once adequate blood levels were attained, therefore, there might have been diminished benefit to higher doses. Results of many observational studies support this possibility with findings of a lower occurrence of cataract among people who take multivitamins but no further reduction among people who take higher doses of antioxidants.

There is also evidence to support the benefit of multivitamin supplements from a clinical trial conducted in the Linxian region of China in which malnutrition is common. In this study, 65- to 74-year-old subjects given multivitamin supplements (containing similar levels of β-carotene [15 mg] as the REACT study but lower levels of α-tocopherol [60 IU] and vitamin C [180 mg]) plus a wide variety of other vitamins and minerals for 5 to 6 years in a double-masked fashion, had lower prevalence of cataract than subjects not given supplements (this was not true among persons 45 to 64 years of age, in whom the rate of cataract development was likely to be slower). The Linxian Study was limited in that cataracts were not assessed before the treatments were initiated. A 9-year, randomized, placebo-controlled clinical trial of the influence of multivitamin supplementation on cataract development and progression is currently underway in Italy in approximately 1000 people. If the results of this study confirm those of the Linxian Study, which are consistent with results of most observational studies, there would be considerable evidence to suggest that multivitamins decrease risk for cataract and little evidence that high-dose antioxidants provide additional benefit.

Results of the REACT study, which were different from other trials, may have reflected some limitations in study design or analysis. For example, the loss of subjects to follow-up may have biased the results of the REACT study; only 53% of the initial 297 persons randomized to receive treatment or placebo remained in the study through the third year. If those who dropped out of the supplemented group had a higher rate of progression of cataract than those who remained in the study, or than those who dropped out of the control group, differential drop-out could explain the lower progression among the group supplemented with high-dose antioxidants. Thirteen percent of those supplemented with high-dose antioxidants died, compared with only 4% in the control group. Those who dropped out of the treated group tended to be older. The rate of progression of lens opacities among older subjects who remained would therefore be expected to be lower. The possibility of this bias is unknown, as the authors have not compared characteristics of the total sample lost to follow-up in each treatment group. Even unmeasured characteristics of subjects who remain and are lost to follow-up could bias the results.
Although clinical trials of antioxidants generally have not supported the benefits of a few select antioxidants given in high doses, collectively they have provided consistent evidence that β-carotene is not likely to protect against cataract. β-Carotene did not reduce risk for cataract over 12 years in the Physicians Health Study (except in a small number of smokers), in which median levels of β-carotene in the serum among controls were high (0.30 μg/dL), or in the ATBC Study, in which blood levels increased tenfold with supplementation. In a clinical trial in Linxian, China, in which malnutrition is common, taking a supplement containing β-carotene (15 mg) and selenium (50 mg) did not reduce the prevalence of cataracts of any type.11 Because β-carotene is not found in the lens,24 this finding is not surprising.

The larger body of current data does not support broad health benefits of high-dose antioxidants, taken individually or in combination, on overall health.25 Whereas some early studies suggested lower rates of heart attacks among people who take vitamin E at levels higher than 100 IU, a level only attainable from supplements,26,27 numerous other clinical trials have shown no or limited benefit of vitamin E in supplements,25 especially in those with high risk for heart disease. Moreover, high-dose antioxidants may pose health risks. Recently, high-dose antioxidants given to people who were also taking high doses of niacin and statin drugs caused an unexpected reduction in high-density lipoprotein cholesterol and an increase in the risk of heart attacks and strokes.28 Similarly, vitamin E supplementation (50 mg/day of all rac-tocopherol acetate) increased risk for hemorrhagic stroke by 50% in the ATBC study.29

Short-term (4 months) vitamin E supplementation with less than 800 IU showed no adverse effects on plasma lipid or lipoprotein profile, white blood cells, platelet numbers, or bleeding time.30 However, high-dose supplementation may warrant concern when taking antithrombotic compounds such as aspirin because of decreased platelet adhesion and increased bleeding.31

Previous studies have shown that high-dose supplemental β-carotene (20 mg or greater) increased the risk of lung cancer.32,33 Supplementation with high-dose β-carotene decreases absorption of lutein and zeaxanthin,34 the only carotenoids that are present in the lens, and24 which might protect the lens against cataract development.35

In summary, although a large body of evidence suggests that multivitamin use and diets rich in fruits and vegetables are associated with lower risk for cataracts, these associations may reflect protection against cataract that is associated with other healthy lifestyle factors. Clinical trials are needed to confirm the benefits of antioxidant supplements, per se, independent of associated healthy lifestyle factors. Evidence to support the benefits of supplements in clinical trials are limited to the most recent trials of high-dose antioxidant supplements and an earlier trial of multivitamin supplements in Linxian, China. A larger body of evidence suggests no benefits of high-dose antioxidants, particularly β-carotene. An ongoing trial of multivitamins will soon provide new evidence about the potential benefit of multivitamins. At this time, however, there is very little evidence that high-dose antioxidants provide benefit beyond that which may be provided by multivitamins or nutrient-rich diets.

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23. CTNS Study Group. The Italian-American Clinical Trial of Nutritional Supplements and Age-Related Cataract (CTNS). Controlled Clinical Trials. 2003. [In press].


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