Cataract

The rust on the magic bullet

J Katz

Antioxidants for cataract prevention bite the dust

Cataract is still the leading cause of blindness and low vision in most of the developing world.¹ With the ageing of the population, even large increases in surgery rates will not keep pace with the increasing incidence of cataract. Minor decreases in incidence and progression of cataract could have a large impact on the burden of blindness and low vision. In India, it is estimated that there are 100 million eyes blind (visual acuity <6/60) as a result of cataract.² This issue of the *BJO* (p 847) reports the results of a randomised clinical trial of antioxidant supplementation to prevent the onset and/or progression of cataract in south India.³ The unfortunate news is that antioxidant supplementation had no impact on cataract progression in this population. Although such "negative" trials are often seen as disappointments, and sometimes the authors have difficulty getting the results published, it is important to know whether to bother to spend money and effort to provide supplements. The publication of such results allows us to abandon certain inefficacious interventions and spend our money and time on ones with proved benefit.

Numerous cross sectional and cohort studies have documented strong associations between antioxidants intake (through food and/or supplements) and cataract, amply referenced in the paper by Gritz *et al.*³ However, only one randomised trial has been conducted previously in the developing world.⁴ That study showed a reduction in the prevalence of nuclear cataract with certain micronutrient combinations, suggesting promise for such interventions. Given the high prevalence of cataract blindness, and its large and ageing population, India was an ideal location in which to conduct a randomised, community based clinical trial. This study, a collaboration between the Aravind Eye Hospitals and Proctor Foundation, was different in that it tested a combination of three vitamins with antioxidant properties (A, C, and E) taken three times a week at larger

than a recommended minimum daily allowance dose, but not at megadose levels. Individuals were randomised, treatments masked, and participants followed for 5 years with very high adherence. The design and conduct of this study was one that should produce strong evidence for or against the study hypothesis.

So what is it about observational studies that show strong associations between antioxidant micronutrient intakes and cataract that do not pan out in randomised trials?

What are some of the limitations of this study? As with many micronutrient trials, there is always concern as to whether this combination of vitamins was the right one to produce the level of antioxidant activity that might lead to a reduction in cataract progression. How deficient was the diet of this population and was the slightly larger than one recommended minimum daily allowance's worth of these vitamins adequate, or are megadoses required? Is 5 years of supplementation enough, or is a longer exposure critical for protection? The age range was 35–50 years. Might the impact have been different in an older or younger population? Were there risk factors for cataract progression in this population that were so overwhelming that this level of supplementation could not mitigate them? A recent trial of vitamin E to reduce cataract progression in a well nourished Australian population also found no evidence of benefit for any type of cataract,⁵ supporting the lack of effect in a very different population. In spite of these concerns and issues, the results of this trial present compelling evidence that supplementation with nutrients that have antioxidant activity did not impact progression of any type of cataract over a 5 year period in rural Indians ages 35–50 years.

So what is it about observational studies that show strong associations between antioxidant micronutrient intakes and cataract that do not pan

out in randomised trials? The world of ophthalmology is not alone in this dilemma. Recent results of randomised trials of calcium to prevent osteoporotic fractures, vitamin E to prevent heart disease, and earlier ones of β carotene for reduction of cancer risk have all demonstrated no benefit,^{6–8} in spite of strong and compelling evidence from cohort studies to suggest the potential for enormous benefit. Observational studies do suffer from selection bias that is clearly very strong in the case of diet and supplement use. People with healthier diets, whether through food or nutritional supplements, are different in their disease risk from those who do not have such high intakes. No amount of adjustment for covariates that have been observed and recorded appear to be able to erase this selection bias.

Where do we go now with cataract prevention? Clearly back to the drawing board in terms of strategies to test, hopefully, in well designed and conducted randomised trials. In the interim, we should make sure that we support and advocate resources to improve access to and quality of cataract surgery, our currently most effective strategy for preventing blindness and visual impairment from cataract.

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Correspondence to: Joanne Katz, Johns Hopkins Bloomberg School of Public Health, Department of International Health, 615 N Wolfe Street, Baltimore, MD 21205-2103, USA; jkatz@jhsph.edu

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