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Contribution of epidemiology to understanding relations of diet to age-related cataract[1,2]

Julie A Mares-Perlman

Epidemiology is an increasingly important research tool in nutrition science as the research agenda shifts toward establishing the role of diet components in optimizing health and longevity. Because of the long-term and multifactorial nature of chronic and degenerative conditions of aging, it is difficult to predict the influence of nutrients on these processes from short-term experiments alone. Animal experimentation provides evidence of the biological plausibility and specific mechanisms of nutrient actions. However, appropriate animal models for slowly developing age-related lesions are often unavailable. Furthermore, the environmental and lifestyle factors that may modify the influence of nutrient actions on the development of degenerative conditions cannot be sufficiently modeled in animal experiments.

An epidemiologic study published in this issue addresses the potential relation of vitamin C supplements to the development of age-related cataracts (1). The hypothesized protective role of vitamin C supplements against cataract is based on concentrations in the lens that greatly exceed those in human plasma (2) and on evidence that ascorbic acid protects against experimentally induced oxidative damage (3) and cataracts (4) in animal lenses. There are no animal models of senile cataract in species that require vitamin C (as humans do). Epidemiologic studies can provide evidence that these relations can be generalized to senile cataract in humans. They can also provide evidence of the importance of vitamin C intake relative to other risk and protective factors.

The observations made by Jacques et al (1) suggest the possibility that higher long-term intakes of vitamin C may protect against age-related opacification of the lens nucleus. Furthermore, the low risk ratios for cataract among women who had used supplements for long durations indicate that these relations could be quite strong. These investigators used strategies that are unique to epidemiologic investigations in this area. For example, they used data regarding vitamin C intake that were collected over a relatively long time period and a sampling scheme that excluded women who were likely to have substantially changed their intake of vitamin C over the period of time assessed. These approaches minimized the chance that potentially important associations were masked by dietary assessment errors, which can occur when diet changes over time but is measured at only one time point.

Because results of single observational studies are subject to confounding and design biases that statistical procedures cannot always fully account for, the strength of epidemiologic evidence must be drawn from a large body of evidence from separate study populations. The possibility that vitamin C protects against the development of age-related cataract is supported now by a small and inconsistent body of evidence that was reviewed recently (5).

What specific types of evidence are needed to develop stronger conclusions regarding the potential for vitamin C supplements to protect against age-related cataract? Data from additional populations are needed to better understand the strength of the association between the use of vitamin C supplements and cataract development in the general population. The strength of this association could not be reliably determined in the study by Jacques et al (1) because there were a limited number of women with cataract who had used supplements for a long period of time. Moreover, the strength of the association needs to be evaluated in populations representing the diverse health and lifestyle characteristics of the American population. The temporal nature of this relation is also unknown. The rate of new cataract development needs to be compared in people with low and high intakes of vitamin C in prospective studies.

The body of evidence needs to adequately address the possibility that differences in lifestyle or medical attributes may explain differences in the prevalence of cataract among people with low compared with high durations of vitamin supplement use. Although the investigators of this study adjusted for other risk factors for cataracts in the statistical modeling (smoking, sun exposure, body mass index, and age), confounding bias may remain if these variables were measured with error or were classified into broad categories. In addition, there may be other unknown and unmeasured factors that protect against cataracts that are more common among people who use vitamin C supplements. Strong and consistent observations across study populations, despite varied distributions of these confounding factors, are needed to address the possibility of bias.

Jacques et al (1) minimized the possibility that these relations reflect other aspects of diet or supplement use that are related to the long-term use of vitamin C supplements by

[1] From the Department of Ophthalmology and Visual Sciences, University of Wisconsin–Madison Medical School.

[2] Address reprint requests to JA Mares-Perlman, Department of Ophthalmology and Visual Sciences, University of Wisconsin–Madison, 610 North Walnut Street, 405 WARF, Madison, WI 53705-2397. E-mail: maresp@epi.ophth.wisc.edu.

adjusting the associations observed for other nutritional exposures that are suspected of being related to cataract (vitamin E and carotenoid intake and multivitamin use). However, the effectiveness of the statistical adjustment for diet and supplement factors, in accounting for the associations observed, depends on the accuracy of measurement of these exposures. Imperfect dietary estimates of the carotenoids present in lenses (lutein and zeaxanthin; 6) can be expected because values that are currently available for foods are based on few samples and, in some cases, are quite variable (7). Furthermore, we have observed that people who use supplements have diets that are dense in a wide variety of nutrients (B Lyle, unpublished observations, 1997). Consequently, adjustment for single nutrients may not sufficiently account for high intakes of many nutrients that protect against cataract development. Additional evidence to support a protective role of vitamin C, specifically, could be provided in large observational studies in which the association between long-term use of vitamin C and cataract development remains among people with both high and low amounts of these other components in the diet. Clinical trials, in which vitamin C supplementation is the sole treatment, can also provide evidence that vitamin C itself slows cataract development.

More data on the potentially adverse effects of vitamin C on the lens and other aspects of health must be gathered before we can confidently recommend the use of vitamin C supplements to prevent cataract. Some data suggest potential adverse effects on the lens. For example, the possibility that ascorbic acid contributes to glycosylation of lens proteins is suggested by the observation of an ascorbate oxidation product cross-linked to human lens proteins and by the fact that the concentration of these products correlates with lens pigmentation (8). Cataracts were more frequent among people with higher blood concentrations of vitamin C in two previous studies (9, 10) although the relations were not always statistically significant (10).

In summary, epidemiologic studies are essential to further explore the role of diet in the development of chronic and degenerative aging conditions because they evaluate issues that cannot be addressed solely by other means of scientific inquiry. Results of this single epidemiologic study (1) contribute to a larger body of evidence from other limited populations and animal experiments that is, now, inconsistent. Because of the large effect that reducing cataract would have on lowering health care costs and increasing quality of life of the growing population of older Americans, continued research in this area is crucial.

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