Too soon for lutein supplements

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Cataracts are common in older adults, affecting ≈55–85% of people > 75 y of age (1, 2), so that the identification of dietary strategies to delay their onset could have tremendous influence on the health of older people and on health care costs. Two reports in this issue of the Journal (3, 4) provide evidence to support a possible protective effect of the xanthophyll carotenoid lutein on the development of lens opacities by showing associations with incident cataract extraction. Cataracts are likely to develop over long periods of time and to be influenced by a variety of lifestyle and personal attributes that cannot be duplicated in experimental settings in animals or humans. Therefore, these types of scientific observations in large cohorts of people over time contribute unique and important insights.

There is no doubt that such findings will double the supply of lutein supplements on pharmacy shelves, despite yet unproven benefits. Indeed, our scientific enthusiasm for possible protective influences of dietary lutein is boosted by these studies. However, let us learn a lesson from β-carotene. A high level of optimism existed about its ability to reduce the risk of cancer and cardiovascular disease until randomised trials showed no benefits (5–8) and the possibility of increased risk with supplementation (5, 6). Observational studies had indicated associations of these health outcomes with diets that were rich in β-carotene (rather than β-carotene itself). Large, prospective studies had not yet evaluated other diet attributes that might explain these associations and had not yet fully explored associations in population subgroups before β-carotene was added to supplements and clinical trials began. This recent scenario serves as a reminder to temper the temptation to encourage lutein supplements and launch clinical trials of the benefits of lutein supplementation before adequate information is available for each. Accordingly, the authors limit the discussion of the implications of their findings to the possible benefit of eating foods that are rich in these carotenoids, rather than to the notion that these carotenoids should be taken separately.

Overall, there is still not a strong body of scientific evidence to support a protective role of lutein in the prevention of this or other age-related eye diseases. Providing such causal relations requires a large body of evidence to establish their likely existence “beyond a reasonable doubt.” Some of the criteria established by Hill (9) in the 1960s as requirements for showing causal relations with epidemiologic data can be used as a guideline. Of the 9 criteria he suggested, the most relevant to evaluating relations of dietary xanthophylls to cataract are 1) biological plausibility, 2) consistency of the relation across populations, 3) time sequence, 4) the strength of the relation, and 5) specificity.

At this time, there is inadequate evidence to confirm biological plausibility. Although lutein, and its structural isomer zeaxanthin, have been identified in human lenses (10, 11), experiments that show a mechanism by which these compounds specifically protect the lens against cataractogenesis have not been done. That these carotenoids can be antioxidants (12) and also absorb light (13) offers 2 possible mechanisms that can be further investigated in animal experiments.

The consistency of associations between dietary xanthophylls and cataract across populations is growing. Data from the 2 investigations reported in this issue (3, 4) add to the previous evidence of lower incidence of nuclear cataracts in Beaver Dam Eye Study participants who reported diets high compared with low in lutein and zeaxanthin (14) and of relations between amounts of these xanthophylls in the diet and severity of nuclear cataracts in women in this same population (15). Further evidence of relations between the concentrations of these xanthophylls in the retina and the density of the lens (16) is supportive as well. Although the observation of consistency in 4 separate study populations (3, 4, 14–16) provides promise, additional evidence in population groups that are different, with respect to the distribution of potential confounders (in other cultures, for example), would strengthen the evidence.

Evidence from prospective studies of a time sequence in which dietary intake is documented before the photographic documentation of lens changes strengthens the case for a causal relation. This evidence is available in 1 of the 4 populations in which this relation has been studied (14). Thus, this evidence of time sequence indicates that dietary lutein may be an antecedent factor rather than a consequence of having cataracts or related conditions. However, this evidence needs confirmation in additional prospective studies.

The evidence from observational studies would also be strengthened if strong relations were observed. This would reduce the possibility that other lifestyle or dietary factors that are associated with high xanthophyll intake might be explain-
ing the associations observed. In the 2 studies reported in this issue (3, 4), weak relations are reported such that only about a 20% decline in risk of cataract extraction was observed in people with high, compared with low, intakes. Although even a 20% reduction in true risk could have important public health significance because of the large magnitude of the problem, the weak association makes it more likely that other factors that were unmeasured and associated with eating lutein-rich foods could explain the relations that were observed. However, one explanation for the rather weak associations in the 2 investigations presented here could be that people who have cataracts extracted are more likely than those with cataracts who do not seek extraction to have health-conscious behaviors that include eating more vegetables. This would tend to reduce the magnitude of the association one could observe. This possibility is supported by results of a separate study in which photographic evidence of cataract was obtained (14). A stronger reduction in risk for nuclear cataract was observed (50% lower risk over 5 y in people with diets in the high compared with the low quintiles) than in the studies of cataract extraction reported in the Journal (3, 4). Additional data about the strength of relations in which long-term xanthophyll intake is estimated, together with the assessment of cataracts from lens photographs, would provide better precision to estimate the strength of relations in additional populations.

There is insufficient evidence to support the specificity of this association with dietary lutein. It is possible that other attributes of fruit- and vegetable-rich diets that provide large amounts of lutein could explain the association that was attributed to lutein. The authors of these reports in the Journal have attempted to show independence of this relation from other lifestyle and dietary factors that could be related to high lutein intake. They have measured and adjusted for several other dietary and lifestyle attributes that might explain the associations with lutein that were observed. However, unknown and unmeasured confounders may not be accounted for. Also having an ability to measure some potential confounders and adjust for them in regression models does not ensure that they have been accounted for completely in statistical analyses. When confounders, such as other dietary components, are measured with error (as is inevitable in estimating the intake of specific food components), then there is the possibility that statistical adjustment may not fully account for the influence of other diet or lifestyle factors on the relations observed (17).

Clinical trials could provide evidence that implicates lutein specifically. However, we have too little information now to design effective trials. Before trials are designed, it would be helpful to have information about the strength of the association in different population subgroups (such as in people with and without other risk factors for cataract) and the time course of the relation. Additional observational studies can provide insights about these factors.

Why should we proceed with caution in view of the possibility that lutein and zeaxanthin may have such important health benefits? First, making recommendations before there is adequate knowledge to support them erodes the credibility of science to the public. Second, lutein supplements may not promote optimal overall health. We know that some carotenoids may influence the absorption of other carotenoids (18) and do not yet know the long-term physiologic consequences.

In summary, the reports of relations of lower incidence of cataract extraction in men (4) and women (3) who have reported high intakes of dietary xanthophyll carotenoids constitute an exciting scientific development that will spur further research into these relations. Further careful exploration of these relations in observational studies will allow us to gain a greater understanding of the consistency of relations in different segments of the population, of the time course, and of other factors that might explain or influence the association. This information is needed before effective clinical trials can be designed and reliable dietary recommendations can be made.

REFERENCES