

## Prevention strategies for age related cataract: present limitations and future possibilities

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Age related cataract is the leading cause of blindness in the world today,<sup>1</sup> with an estimated 17 million individuals bilaterally blind.<sup>2</sup> Though surgery may be an effective means to reverse cataract blindness, visual outcomes will be poor where experienced surgeons and appropriate postoperative care, including refraction, are not available.<sup>3–4</sup> Moreover, even where high quality surgery is readily accessible, it may be expensive—cataract extraction is currently the most frequently performed surgical procedure among Medicare beneficiaries in the United States, at an annual cost of over \$3 billion.<sup>5</sup>

It has been estimated that a delay in cataract onset of only 10 years could reduce the need for cataract surgery by as much as half.<sup>6</sup> At present, no proved methods exist to effect such a result. This article will review existing and possible future strategies to prevent or delay age related cataract.

An association between nuclear cataract and smoking is one of the most robust findings in cataract epidemiology.<sup>7–11</sup> There is also evidence that smoking cessation can reduce the likelihood of cataract,<sup>12–13</sup> and studies of attributable risk have proposed “quit smoking” campaigns as a major cataract prevention strategy.<sup>10</sup> However, it is not clear whether damage to the lens resulting from smoking is indeed reversible, or whether individuals who quit smoking are simply subjected to a lower cumulative risk than those who persist.<sup>12</sup>

Evidence for an effect of ultraviolet-B (UV-B) light on cataractogenesis in animal models, presumably on the basis of increased oxidative damage, is comparatively plentiful.<sup>14–16</sup> Early evidence on chronic exposure from human studies has been from ecological investigations examining some proxy for ultraviolet exposure such as latitude.<sup>17–18</sup> Another ecological association which has been studied is that between location and severity of cortical opacities in the lens, with the suggestion being that higher exposure to solar energy in the inferonasal quadrant may explain the greater prevalence and severity of cortical opacities in that region.<sup>19–20</sup>

Recently, methodologies have been developed to directly measure individual ultraviolet exposure using validated techniques in human populations. These studies have consistently

found that exposure to UV-B light is a risk factor for cortical and perhaps posterior subcapsular (PSC) cataract.<sup>21–23</sup> Studies of attributable risk suggest that ocular UV-B exposure may explain approximately 10% of the cortical cataract in a population.<sup>10</sup>

Reduction of sun exposure is in many ways an attractive means of preventing cataract related visual disability: the evidence suggesting a causal relation is strong and scientifically plausible, and strategies are potentially inexpensive and essentially risk free. Unfortunately, the proportion of risk attributable to sunlight exposure is small, and the type of lens opacity most consistently associated with UV-B is cortical opacity, a form which has generally been shown to be less visually disabling and less likely to require surgery than nuclear or PSC cataract.<sup>24</sup> Furthermore, studies showing high rates of loss of aphakic spectacles,<sup>25–26</sup> which, as opposed to sunglasses, presumably tend to improve vision significantly and thus encourage use, cast doubt on the practicality of strategies to reduce ocular sun exposure in a developing world setting.

There has recently been much interest in the impact of nutrition on the development of lens opacity, particularly with regard to those nutrients with antioxidant potential. In vitro and animal research has suggested that antioxidant substances present in the diet,<sup>27</sup> in particular vitamins A, C,<sup>28</sup> and E,<sup>29</sup> may have a protective role in preventing damage to lens proteins, membranes, and enzymes from activated oxygen species. Epidemiological evidence for the antioxidant hypothesis among human subjects, however, has been conflicting.<sup>30–33</sup>

The uncontrolled nature of the majority of studies evaluating the link between lens opacity and antioxidant intake has made it difficult to establish a clear protective role for any particular agent. This is due to the large number of different antioxidants that have been examined, levels for many of which are likely to be highly colinear across individuals. The prospective randomised clinical trial design offers several advantages in testing the antioxidant hypothesis. The randomisation process will tend to eliminate potential confounders such as socioeconomic status and exposure to sunlight. Prospective follow up after a specific intervention allows the role of different nutritional factors to be distinguished more readily.

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The Linxian cataract trial identified a limited protective role against nuclear cataract among older people receiving riboflavin and niacin, among four different vitamin/mineral combinations tested.<sup>34</sup> Additional trials which may be expected to offer insight into this question include the Age-Related Eye Disease Study (AREDS),<sup>35</sup> which is examining the effect of pharmacological doses of vitamins A, C, and E on lens opacity, and three additional large randomised trials of antioxidants in the prevention of cancer and/or cardiovascular disease which will also evaluate impact on progression of cataract. These ongoing trials include the Women's Antioxidant Cardiovascular Study (WACS),<sup>36</sup> the Women's Health Study,<sup>37</sup> and the Physicians' Health Study II.<sup>30</sup> Until one or more of these trials provides strong evidence in favour of a protective role for antioxidants against age related cataract, there remains no clear nutritional strategy for the prevention of lens opacity.

A set of potentially interrelated personal factors—diabetes, hypertension, and body mass index—has been implicated as increasing risk for various forms of lens opacity. Body mass index (BMI) has been identified as an independent risk factor for PSC and nuclear cataract,<sup>38, 39</sup> and also cortical opacity,<sup>40</sup> when controlling for diabetes, age, and smoking. Diabetes has also been associated significantly with cortical cataract, as has hypertension.<sup>41</sup> While all of these factors are potentially remediable, suggesting possible avenues for cataract prevention, the effectiveness of such strategies remains to be proved. Although there is some evidence that better diabetic control (demonstrated by lower haemoglobin A<sub>1c</sub> levels) may reduce the risk of lens opacity,<sup>42</sup> no controlled, prospective data yet exist to demonstrate that improved treatment of diabetes or hypertension will in fact prevent or delay lens opacity. An added difficulty of intervening on BMI to prevent cataract is that the directionality of the association (for example, whether elevated or reduced BMI, or both, contribute to lens opacity) has not been definitively established.

An alternative strategy to risk factor reduction in the prevention of cataract would be pharmacological intervention. Compounds receiving attention as potential anticataract agents include aldose reductase inhibitors,<sup>43</sup> pantethine,<sup>44, 45</sup> and aspirin-like drugs such as ibuprofen.<sup>46-48</sup> Population studies have also revealed a decreased risk of nuclear sclerosis among current users of oestrogen replacement therapy.<sup>49-51</sup> However, none of these agents has demonstrated efficacy in the prevention of human lens opacity in a trial setting, and the weight of evidence would not appear to be in favour of undertaking such trials with any currently known drug. A number of new drugs and pharmacological strategies remain under investigation.<sup>52-54</sup> It is clear, however, that challenges to development of a practical anticataract agent for wide human distribution will be substantial: such an agent would need to be sufficiently safe for (presumably) long term use, and sufficiently inexpensive to compete with increasingly cheap cataract surgery. It

appears very unlikely that a pill or eye drops requiring regular, long term use would be practical or sufficiently inexpensive. However, the tremendous public health success stories of fluoridated water<sup>55</sup> and iodised salt<sup>56</sup> provide exemplary models of what might be achieved in the pharmacological prevention of cataract if an appropriate agent could be identified.

In summary, it must be said that those cataract prevention strategies for which adequate evidence exists—namely, smoking cessation and avoidance of ocular sun exposure, are not likely to result in large reductions in visual disability. Other strategies which have been considered, involving nutritional, pharmacological, and specific medical interventions (against diabetes, for example), remain of unproved benefit. Where will researchers look to generate new hypotheses regarding the development of lens opacity and, eventually, new strategies for its prevention? It seems likely that at least one fruitful avenue of investigation will be the genetics of age related cataract, an area which has as yet been little studied.

Population based epidemiological studies in Melbourne<sup>57</sup> and Framingham<sup>58</sup> have reported a twofold to threefold elevation in cataract prevalence among subjects with affected siblings for cortical and nuclear/subcapsular cataract respectively. Studies involving 564 sibships in the Beaver Dam population have estimated the contribution of genetics as 35% of the total variability in nuclear cataract,<sup>59</sup> and up to 75% for cortical cataract among men.<sup>60</sup>

While these population studies have not been designed to distinguish between familial aggregation of cataract due to shared genes and that resulting from a common environment, more direct evidence for a genetic effect has recently been provided by classic twin studies on nuclear<sup>61</sup> and cortical<sup>62</sup> cataract. Both subjective grading at the slit lamp and computerised image analysis were used to assess lens opacity among 506 female white twin pairs (226 monozygotic, 280 dizygotic). The genetic effect reported for nuclear cataract (heritability of 48%) exceeded that of both age and environment, while the heritability for cortical opacity was higher still at 59%.

Less direct evidence for a genetic effect on the distribution of age related cataract lies in the very great differences in prevalence between racial groups. The age adjusted prevalence of cataract among Indians<sup>63</sup> has been reported to be some three times higher than for Americans in the Framingham Eye Study,<sup>64</sup> with a stricter visual criterion having been used in the India study. Lens opacity was also found to develop on average 12 years earlier among the Indian subjects. When standardised cataract grading systems (LOCS III)<sup>65</sup> were used, rates for significant nuclear opacity in the Indian population aged 30 years and above were 45%,<sup>66</sup> significantly higher than for this age group in Italy<sup>67</sup> and Barbados.<sup>68</sup> The prevalence of previous cataract surgery among Indian people 40 years and above in Hyderabad, India, was 13.7%,<sup>69, 70</sup> as opposed to 3.79% for the same age group in Melbourne.<sup>71</sup> It has previously been reported that fewer than

half of visually impaired subjects in the Hyderabad study had sought eyecare services,<sup>72</sup> suggesting that the disparity in the true cataract burden may have been even more marked.

These observed differences could be due to environmental factors rather than genetic, and in fact a number of such factors have been postulated which might differ sufficiently between India and the West to explain the observed disparity in cataract prevalence. These include differences in nutrition,<sup>73</sup> exposure to ultraviolet light,<sup>74 75</sup> and rates of dehydrating episodes of diarrhoea.<sup>76 77</sup> However, migrant studies of Indians living in Great Britain, where environmental differences with the local dwelling population might be expected to be reduced over time, have continued to demonstrate elevated rates of lens opacity and cataract surgery among people of subcontinental descent. Thompson surveyed outpatient clinics in Leicester and reported an age adjusted demand incidence for cataract surgery among Indians aged 45 years and above which was five times that of the local British population.<sup>78</sup> Das *et al*, also working in Leicester, examined random samples from the lists of registered eye patients. Reported rates of cataract among Indians below 60 years of age were 30%, compared with 3% for indigenous British residents of the area.<sup>79</sup> Other studies not making a direct comparison between Indian and indigenous subjects have reported rates of cataract for Indians or south Asians living in England which are significantly higher than those reported elsewhere for the British population as a whole.<sup>80 81</sup> While these studies do not exclude the possibility that persistent cultural and environmental differences between migrant and local populations underlie the apparent disparities in cataract prevalence, the data in favour of a hereditary tendency for cataract among Indians are suggestive.

Although evidence of a genetic effect on the development and progression of lens opacity is growing, to date no genes have yet been identified which are clearly associated with any form of isolated, adult onset cataract. Moreover, age related cataract is a complex trait, and it is likely that multiple loci will be involved. Among strategies currently being employed are the "candidate gene" approach, which seeks to identify mutations or sequence variants in well characterised genes thought likely to be associated with age related cataract. These have generally been genes implicated in congenital cataract. The goal is to establish statistically significant associations between these variants and the presence of lens opacity. Candidate genes of current interest include those affecting crystallins,<sup>82-86</sup> structural proteins,<sup>87</sup> gap junction proteins,<sup>88 89</sup> and aquaporins.<sup>90</sup>

An approach which does not rely on a priori knowledge of specific candidate genes is the sibling pair design. This method requires that genetic material be obtained from two or more siblings with lens opacity (the affected sib pair design), or even sib pairs who do not necessarily have cataract at all (the general sib pair design, in which lens opacity is treated as a

continuous variable, and information can be gained even from subjects with clear lenses). Sib pair methods are used to test for excess sharing of marker alleles between siblings throughout the genome, as a way to establish linkage between the observed markers and an unobserved susceptibility locus.<sup>91</sup> In this way, "hot spots" on various chromosomes likely to be associated with lens opacity may be identified. These techniques can be used to identify multiple genes associated with complex traits,<sup>92 93</sup> and thus are potentially powerful tools in the search for genes controlling age related cataract.

Assuming that these methods will be effective in identifying genes associated with the various types of lens opacity, what are the chances that practical cataract prevention strategies will result? Several possibilities exist. Genetic studies might identify people at greater risk for cataract, who could then be encouraged to modify behaviours (smoking, sun exposure) known to contribute to lens opacity. Given the present knowledge of modifiable risk factors, the potential benefit for the majority of people, non-smokers with moderate sun exposure, would probably be minimal. Alternatively, specific abnormalities at critical loci could be identified and repaired via transfection or other techniques. This approach would depend upon much progress in the area of genetic technology in order to be remotely practical or cost efficient. A third possibility is that identifying the genes controlling age related cataract will lead to a better understanding of lens pathophysiology, which in turn will result in the discovery of specific anticataract agents which are broadly effective and sufficiently safe to be included as supplements in staple foods or added to the water supply. This is certainly the most difficult strategy to carry out, but also the one most likely to bring practical results. Without a deeper understanding of the aetiology of age related cataract at the protein level which genetic studies may bring, development of such anticataract drugs can only proceed by luck and guesswork.

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