Epidemiology of age-related cataract

HUGH R. TAYLOR

ARTICLE

Abstract

To investigate the aetiology of cataract, it is necessary to measure both the type and severity of lens opacities, as well as the dose and duration of exposure to the putative risk factor. Great advances have been made in recent years in our ability to measure cataract and some putative risk factors. Our current understanding of the aetiology of cataract shows that by far the greatest effect is seen with increasing 'age'. However, exposure to ultraviolet-B (UV-B) radiation, use of dietary antioxidant vitamins and the presence of diabetes, the occurrence of dehydration and severe diarrhoea and the use of therapeutic drugs such as steroids, and recreational drugs such as nicotine and alcohol, may be important risk factors. Until the results of the current studies of the effectiveness of antioxidant vitamin supplements become available, the only effective protective interventions to reduce the risk of cataract seem to be to reduce ocular exposure to UV-B radiation and to stop smoking.

Key words Cataract, Epidemiology, Intervention, Risk factors

The first rule of epidemiology if you want to measure the association between two things is that you have to be able to measure each of them. Previous studies of various putative risk factors for cataract have often overlooked this basic rule. They have either not measured cataract particularly well or they have not measured the exposure to the particular risk factor. This has led to many confusing observations and has delayed the development of our understanding of this important disease.

Once appropriate data on the presence, type and severity of cataract and the detailed personal exposure to various risk factors have been well established, it is essential that appropriate statistical analyses are performed. Analyses must fully evaluate the likely associations. They must also explore possible confounding factors and examine for possible interaction between various factors. The ability to perform appropriate data analysis has been greatly enhanced in recent years with the advent of powerful statistical packages now commercially available, even for use on personal computers. However, appropriate statistical expertise and an understanding of the biology of the disease are both essential for the intelligent analysis of risk factors.

Even when an association is seen between a disease and a risk factor, it is important to remember that epidemiological studies usually cannot establish the actual causes of disease – all they can do is point to the association. There are a number of rules that are used to assess the strength of this association and the likelihood of there being a causative effect.[1] These rules include the presence of a temporal relationship – whether the cause precedes the effect; the biological plausibility – whether the association is consistent with other knowledge such as biochemical or animal studies; the strength of the association or the magnitude of its effect – often given as the relative risk; the presence of a dose-response – whether the relationship shows an increased risk with increased exposure; and the consistency of the relationship – whether a similar result been found in other studies in different settings or with different methods. In addition, each study needs to be assessed in terms of the adequacy of its study design, the specificity of its measurement and the potential effect of inadvertent confounding or other biases.

Measuring cataract

One of the major breakthroughs in our understanding of the epidemiology and the risk factors for age-related cataract was the recognition that cataract was not a single disease.[2,3] Even though it was recognised that congenital cataract and secondary cataract had multiple specific aetiologies, 'senile cataract' had been treated as a single entity. However, it is now quite evident that there are three quite specific and different conditions: cortical cataract, nuclear cataract and posterior subcapsular cataract. Each has a different pathology, they occur in anatomically separate areas of the lens, they have a different age of onset, and they also appear to have different risk factors. Each type of opacity may occur singly or in combination with one or both of the other types. The failure to differentiate the three types of age-related cataract would be analogous to trying to study chronic cough or lung disease without distinguishing between tuberculosis, bronchitis and carcinoma.

Hugh R. Taylor, MD, FRACO
Centre for Eye Research Australia
The University of Melbourne
32 Gisborne Street
East Melbourne
Victoria 3002
Australia
Tel: +61 3 9929 8360
Fax: +61 3 9662 3859
e-mail: htaylor@cera.unimelb.edu.au

Over the last 10 to 15 years a number of systems have been developed to specifically grade age-related cataract by type and severity.[4–11] These systems are commonly used for clinical grading but can also be used for the grading of appropriate photographs. A fine optical section created by an angled slit-beam is used to grade nuclear opacity. The observed nuclear opacity is compared with a set of standard photographs. Cortical and posterior subcapsular opacities are assessed in retroillumination and their extent either directly estimated or compared with standard photographs.

These systems have been widely used in a variety of epidemiological studies and clinical trials and have received a general acceptance. Also, they have formed the conceptual basis for a number of computer-based systems that use a digital analysis of images of the lens to more 'objectively' measure cataract.[12–15]

Assessment of exposure to a risk factor

The assessment of exposure to some putative risk factors, for example age or gender, is relatively straightforward. For other factors, such as smoking or alcohol intake, well-developed methodologies are available that have been used extensively in the epidemiological study of other diseases.[16,17] Furthermore, these habits tend to be relatively stable over long periods of a person's life, and can probably be documented retrospectively with reasonable precision.

As with many common chronic diseases, some of the risk factors for cataract are likely to have operated over a long time, so that an individual's lifetime exposure needs to be determined. Current behavioural exposure may or may not reflect past exposure. An example of this may be diet. Dietary habits can fluctuate quite widely and also change quite quickly. The assessment of the current diet of an octogenarian may bear little relationship to their dietary practices and dietary intake when they were younger. This is particularly important in the assessment of the potential role of dietary supplements such as antioxidants. For example, a single measurement of serum or aqueous vitamin C at the time of cataract surgery would not give a reflection of lifetime vitamin C consumption! The assessment of lifelong dietary habits and nutritional intake is very difficult, but fortunately there are methods and instruments that have been developed by nutritionists in their study of other diseases that can be applied to the study of cataract.[18,19]

The exposure of the eye to ultraviolet-B (UV-B) radiation is an area that presents a different set of problems. There has been relatively little work on the overall assessment of exposure of individuals to UV-B radiation, let alone work on factors that might specifically affect ocular exposure.[20–24] Although the global annual ambient UV-B radiation levels vary across the temperate zones by a factor of approximately 4, there is the potential for an 18-fold variation between the ocular exposure of a typical indoor and outdoor worker. However, the use of eyewear and a hat will reduce the ocular exposure of the outdoor worker by 9-fold, so that it becomes only twice the exposure of the indoor worker. The assessment of the association between UV-B exposure and cataract must be based on the assessment of individual lifetime ocular exposure.

Table 1. *Some putative risk factors for cataract*

Gender
Ethnicity
Family history
Iris colour
Education
Employment
Socioeconomic status
Diabetes
Glaucoma
Dehydration
Severe diarrhoea
Ocular UV exposure
Smoking
Alcohol consumption
Analgesic use
Steroid use
Hormone replacement therapy
Presence and/or treatment of:
Arthritis
Gout
Hypertension
Mental illness
Intake of:
Vitamin A
Vitamin C
Vitamin E
Selenium
Zinc

Risk factors for cataract

Even a partial list of putative risk factors for cataract is very long (Table 1). It includes some factors such as gender which cannot readily be altered, although the mechanism by which gender exerts an effect could potentially be ascertained and then manipulated. Other factors, such as age, almost certainly represent the cumulative effect of factors not yet identified. A number of studies have identified the duration of education as an important risk factor for cataract. However, education is probably confounded by factors that were omitted or that are not yet understood.

Many cross-sectional studies of cataract risk factors have now been performed (see the review by West and Valmadrid[25]). The results from some longitudinal studies have started to become available.[26] However, at this time I think one can still conveniently summarise the risk factors for cataract as being the six Ds (Table 2):

Table 2. *The aetiology of cataract*

Daylight
Diet
Drugs
Diabetes
Dehydration
Don't know

1. *Daylight* (UV-B radiation) is well established as a cause for cortical opacity[27,28] and may have an attributable risk of about 20%. The role for UV-B in the formation of either nuclear or posterior subcapsular cataract needs confirmation from further studies.[29,30]
2. The main impact of *Diet* seems to be on the intake of three antioxidant vitamins, specifically β-carotene (vitamin A), vitamin C and vitamin E (ACE).[31] The evidence for the importance of these dietary antioxidants is still somewhat equivocal, although a consistent body of information seems to be developing around the protective role of high levels of vitamin E.[32–35] Previous studies in India have shown that severe protein-calorie malnutrition is more common in people with cataract,[36] although the significance of this finding is unclear. In the United States a high body mass index has been found to increase the risk of developing posterior subcapsular cataract.[37]
3. The rôle of severe *Dehydration*, associated usually with diarrhoea, is still to be determined. Some studies in the Indian sub-continent have shown an association between cataract and severe diarrhoea or cholera,[38,39] where other studies have not.[40] The attributable risk for dehydration/diarrhoea may vary from none to 37%.
4. *Diabetes* is associated with an increased risk of cortical opacities and posterior subcapsular cataract.[25,41] This is particularly seen in younger patients, in whom, overall, cataract is less common. Presumably in older people this effect is masked as cataract from other causes becomes more common. In addition, people with diabetes are also more likely to have early cataract surgery because of reduced vision, often associated with macular oedema. The population attributable risk of diabetes is of the order of 6%.[42]
5. Therapeutic *Drugs*, specifically steroids, are a potent cause of posterior subcapsular cataract.[43] This seems true whether they are taken orally, topically or possibly by inhalation.[44,45] The effect of steroids has a linear dose-response and is not an idiosyncratic drug reaction. Recreational drugs are also linked to cataract. Cigarette smoking is strongly linked to nuclear sclerosis[46] and high alcohol intake has been associated with posterior subcapsular cataract.[47,48]
6. The largest group by far is *'Don't know'*, and this is the category that keeps lens researchers in business.

Intervention studies

The most definitive confirmation that a particular factor is directly linked with the development of cataract is the demonstration of its impact in a properly conducted clinical trial. This is true whether the rate of development or progression of lens opacities is reduced by either protection from exposure to that factor, such as UV-B radiation, or by the use of a specific supplementation, such as antioxidant vitamins. So far very few prospective, randomised clinical trials have been undertaken on putative cataract risk factors.

The Roche European/American Cataract Trial was recently reported in abstract form.[49] Although this was a relatively small study, preliminary analysis showed that vitamin E had a large differential contribution to slowing the rate of age-related cataract progression.

In the United States a large multicenter study has been funded by the National Eye Institute. The Age Related Eye Disease Study (AREDS) has enrolled nearly 5000 patients who will be followed for from 5 to 10 years.[50,51] This study will examine the effect of undisclosed high-dose antioxidants and zinc supplementation. The code should be broken somewhere between the year 2000 and 2005.

A 4 year, prospective study of 1200 patients was started in 1995 by our group in Melbourne. In the Vitamin E and Cataract Study (VECAT) patients were randomised to receive either vitamin E 500 mg or placebo.[52] The results of this study should be available in the year 2000.

Conclusion

Cataract epidemiology has been an area of intensive research. Over the last 20 years the results of studies have become more meaningful as more attention is directed to improving the assessment and measurement of both cataract and the potential risk factors. Although cigarette smoking, the use of corticosteroids and diabetes have been well established as risk factors for cataract, these factors do not lend themselves to meaningful, specific interventions to prevent cataract. Several randomised clinical trials are being conducted to assess the potential protective effect of antioxidant vitamins. Long-term, prospective studies of the effect of the reduction in exposure to UV-B radiation are daunting in both their duration and scale. However, until further information is available on the rôle of antioxidant vitamins, there are no specific recommendations one can make to patients to reduce the risk of cataract, other than to reduce their ocular exposure to UV-B radiation and to stop smoking.

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