The Genetics of Cataract

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Cataract is the first of the five immediate priority areas for the global initiative to eliminate avoidable blindness by the year 2020, Vision 2020. Cataract was chosen because it is the leading cause of vision impairment in the world and because safe, effective surgical intervention is available that leads to a dramatic improvement in visual function. However, the results of cataract surgery depend on surgical experience, the type of surgery performed, the presence of ocular comorbidities, and environmental and social conditions. For example, a recent population-based study in Australia showed that 85% of eyes had best corrected visual acuity of 6/12 (20/40) or better after cataract surgery. In contrast, a study in India revealed that 32% of eyes had a poor visual outcome (distance visual acuity, <20/60), and 20% of eyes were legally blind after cataract surgery.

Cataract surgery has been estimated to cost $3.4 billion per year in the United States and is the most commonly performed ophthalmic procedure. The incidence of cataract and the total cost associated with cataract will increase as the percentage of older people increases in most countries. For example, by applying age-specific rates of cataract to the estimated Australian population, we find that although the total Australian population is expected to increase by 22% between 1996 and 2021, the number of people with age-related cataract is likely to increase by 76% during that same period (Fig. 1), because of the aging of the population alone.

From age-specific prevalence data, it can be estimated that if exposure to risk factors for cataract could be modified to delay the onset of cataract by just 10 years, the need for cataract surgery would decrease by nearly 50%. Because the median age for the development of cataract is 70 years, a 10-year delay represents only a modest, and not unrealistic, 14% decrease in the rate of development of cataract.

Successful prevention programs require a good understanding of the risk factors for age-related cataract. Numerous papers have been written about the epidemiology of age-related cataract. Two review papers published in 1995 summarized the known risk factors for cataract, which could be categorized as demographic, environmental, lifestyle-associated, disease-related, and miscellaneous. More recent studies have confirmed and extended these findings, but have not identified new categories of risk factors, and several prospective clinical trials are in progress to assess the effect of supplementary antioxidants. Cross-sectional studies have suggested that antioxidants protect against the development of cataract. The most obvious demographic factor is increasing age, but most studies have also shown that women have an increased risk of cataract. Cataract is also generally more common in people of lower socioeconomic status. The primary environmental risk factor is the link between ocular exposure to UV-B and cortical cataract. Lifestyle-associated risk factors include the increased risk of nuclear cataract due to cigarette smoking and the potential increased risk of cataract associated with high alcohol intake. Disease-related risk factors include diabetes, hypertension and antihypertensive medications, and the use of antipsychotic medications or steroids.

At the time that the review articles were published, family history also had been shown to have some association with cataract, but recall bias was suggested as a potential reason for the observed associations. Others had suggested that families that lived a long time were more likely to need cataract surgery, just because of their older age.

More sophisticated analyses of the potential role of genetics in the development of cataract were reported subsequently. In the Framingham Eye Study, strong associations were found between siblings for nuclear and posterior subcapsular cataract. Segregation analyses on the Beaver Dam Eye Study cohort suggested that a single major gene may account for 58% of the variable risk of development of cortical cataract and that another single major gene may account for 35% of nuclear cataract. Neither of these studies measured the relative contribution of genetics versus environmental effects on the development of age-related cataract. Twin studies provide an excellent opportunity to address this question of nature versus nurture.

Despite the extensive research that had been conducted into defining the risk factors for cataract, a large percentage of the disease in the population was still unaccounted for by known risk factors. Then, Hammond et al. published their findings from the Twin Eye Study related to nuclear cataract. They found that the relative contributions of genetics and environment to the development of nuclear cataract were 48% and 14%, respectively, whereas age accounted for the risk in their study group of older female twins. In the March 2001 issue of IOVS, Hammond et al. reported their findings on cortical cataract. They estimate that genetics may account for between 37% and 58% of cortical cataract and that environment accounts for between 11% and 37%. These findings related to the genetic influence on cortical cataract are similar to those of the Beaver Dam Eye Study.

Genetics had been known to explain a number of congenital eye conditions, including congenital cataract, but it was a real surprise to discover that genetics explains such a large part of the variation in age-related cataract after controlling for the other known environmental and demographic risk factors. These new data from investigation of both the nature and nurture elements are a great help in filling the gap in our knowledge about the range of factors associated with the development of age-related cataract. Results from all published studies to date suggest that perhaps 50% of age-related cataract can be explained by genetics, with the remainder due to aging and to systemic and environmental factors.

The challenge now is to use the new genetic information to design studies to decrease the incidence of age-related cataract in the population. Obviously, the race is on to identify genes...
associated with an increased risk of cataract. However, direct gene therapy in relation to preventing the onset of cataract may not be possible in the near future, because further research would be needed first, including identification of the gene product and targets for intervention and methods of delivery to the lens.

The next logical step may be to determine the impact of different risk factors for cataract in those who have a known genetic susceptibility. This information should allow an intervention to be designed for families who have an increased risk of cataract. For example, families with an increased risk of cortical cataract could be involved in a study to specifically reduce ocular exposure to ocular UV-B. On the other hand, families with an increased risk of nuclear cataract could be enrolled in a specific program to stop cigarette smoking to determine whether their risk of development of nuclear cataract is decreased. Clinical trials to quantify the effect of antioxidants in preventing the incidence and progression of cataracts may be better targeted at families at higher risk.

The results of the two Twin Eye Studies of nuclear and cortical cataract are exciting, because they provide us with more information about the cause of age-related cataract and potentially allow us to tailor our interventions. They provide the first really new epidemiologic information about cataract that has been published in some time and suddenly fill in a large gap in the knowledge about factors associated with cataract.

References