The New Epidemiology of Cataract

Alison G. Abraham, MHS\textsuperscript{a}, Nathan G. Condon, MD, MPH\textsuperscript{b},
Emily West Gower, PhD\textsuperscript{a,*}

\textsuperscript{a}Dana Center for Preventive Ophthalmology, Wilmer Eye Institute, Johns Hopkins School of Medicine, 600 North Wolfe Street, 116 Wilmer Building, Baltimore, MD 21287, USA
\textsuperscript{b}Helen Keller International, 352 Park Avenue South, 12th Floor, New York, NY 10010, USA

Cataract poses a substantial economic and public health burden and is the leading cause of blindness worldwide, accounting for nearly 48% of all blindness \cite{1}. As such it is also a disease that has been and will continue to be a target of epidemiologic research. Insights into causative factors amenable to intervention, genetic factors that predispose to disease, and avenues for novel treatment serve to reduce the disease burden.

As a result of decades of research into factors that may cause age-related cataract, several risk factors have been well-identified and reviewed in detail in other manuscripts \cite{2–6}. More recent studies, however, have found conflicting results for some risk factors, and have identified other potential risk factors of interest that need further study. This article reviews evidence for well-known risk factors, but focuses primarily on more recent findings and factors in which research is still evolving.

The burden of disease

Many surveys have been conducted in various countries to estimate the prevalence of blindness and low vision in diverse populations. Data on the causes of visual impairment yield estimates of the contribution of cataract to disability. The World Health Organization estimates that the current global prevalence of blindness is 0.57% \textsuperscript{(range: 0.2\textendash}1\%), with more than 82% of all blindness occurring in individuals aged 50 and older. Cataract accounts for 47.8% of the world’s roughly 37 million blind individuals \cite{1}. Of note, approximately 90% of the contribution of cataract to blindness in this study was seen in developing countries \cite{1}.

The three subtypes of cataract (nuclear, cortical, and posterior subcapsular [PSC]) are seen to various extents in different populations. Prevalence and incidence estimates across populations are summarized in Table 1. In the United States, nuclear cataract is seen more commonly in whites, whereas cortical is seen more commonly in African Americans; however, PSC cataract is prevalent at roughly the same, much lower, rate in both groups \cite{7}. In studies of populations outside the United States, various prevalence estimates for each cataract subtype have been reported that may reflect differences in either environment or predisposition (see Table 1) \cite{7–9}.

Impact of disease

Although 90% of cataract cases are found in developing countries, the disease has a substantial impact in developed world countries as well from social, physical, and financial perspectives. In the early 1990s, Steinberg and coworkers \cite{10} estimated that Medicare spent more than $3.4 billion dollars annually on routine cataract procedures. Furthermore, approximately 60% of Medicare spending in the 1990s was devoted to cataract surgery and associated costs \cite{11}. With the graying of the United States population, it is expected that this number will continue to rise dramatically.

The burden of cataract extends beyond the financial costs to society. Patients with prevalent cataract are likely to have significantly reduced
quality of life resulting from low vision. Cataract is primarily a disease of older age groups. Often, decreases in functional abilities are attributed to other age-related processes and not recognized as the onset of cataract. In a United States–based study of nursing homes, cataract was the leading cause of low vision (as defined by visual acuity worse than 20/40 in the better-seeing eye), responsible for 37% of low vision among white subjects and 54% of low vision among African American subjects [12]. Similarly, in the Netherlands, binocular low vision was present in 31.3% of nursing home residents, and 78% of this low vision was caused by cataract [13]. These data suggest that cataract represents an important contributor to disability in older populations in developed countries despite treatment availability.

Inequality in access to care in the United States leads to differential cataract surgical uptake, resulting in unequal distribution of the disease burden in these populations. Several investigators have examined factors related to receiving cataract surgery among individuals who were eligible for surgery [14–17]. Such factors as facility with the English language, medical insurance, and access to regular medical care are all predictive of receiving cataract surgery when surgery is of benefit [14].

As with any medical procedure, cataract surgery has associated risks including a suboptimal outcome. Several studies have demonstrated that a success rate of good clinical outcomes of over 90% is attainable in both developed and developing countries [18–21]. Other studies, however, have reported surgical success rates closer to 50% [22,23]. Zhao and coworkers [23] report that in Shunyi County, China, 45% of eyes had vision worse than 6/60 at follow-up. Given the large number of individuals undergoing cataract surgery, surgical failure rates of even 10% translate to a significant number of individuals with poor surgical outcomes and continued visual disability.

The need for further research into pathways for prevention and delay of disease is highlighted by the impact of cataract. Finding alterable factors that could delay disease by as few as 10 years would have a substantial effect on quality of life and economic burden, reducing the rate of cataract development by an estimated 14% and decreasing the number of cataract surgeries by nearly 50% [2,24].

Well-established risk factors for cataract

Some risk factors for the development of age-related cataract, including smoking, diabetes, and UV light exposure, have been consistently reported across multiple studies and summarized in previous reviews [2–6]. Briefly, smoking consistently has been found to be associated with both nuclear and PSC cataract [6], and several studies have demonstrated a dose-dependent relationship between pack-years of use and degree of opacification [25–30]. Most recently, a new analysis including 13 years of follow-up from the Physicians Health Study cohort indicated that smoking cessation reduced risk primarily by limiting cumulative dose and smoke-related damage, although there was some indication that there also may be a reversible component of damage [28].

Research into the link between UVB radiation exposure and cataract dates back several decades, with most studies showing a significant relationship between UVB exposure and cortical cataract, using various exposure and outcome assessment strategies [3]. Oxidative damage

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Prevalence and incidence of cataract, by subtype across populations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group studied (y)</td>
<td>Nuclear</td>
</tr>
<tr>
<td>Population</td>
<td></td>
</tr>
<tr>
<td>American whites (7)</td>
<td>65+</td>
</tr>
<tr>
<td>African Americans (7)</td>
<td>65+</td>
</tr>
<tr>
<td>Singaporeans (9)</td>
<td>50+</td>
</tr>
<tr>
<td>Japanese (9)</td>
<td>50+</td>
</tr>
<tr>
<td>Icelandic (9)</td>
<td>50+</td>
</tr>
<tr>
<td>Prevalence (%)</td>
<td></td>
</tr>
<tr>
<td>Incidence (%)</td>
<td></td>
</tr>
<tr>
<td>Population (length of follow-up)</td>
<td></td>
</tr>
<tr>
<td>Barbados whites (9 y) (8)</td>
<td>40–84</td>
</tr>
<tr>
<td>Barbados blacks (9 y) (8)</td>
<td>40–84</td>
</tr>
<tr>
<td>Beaver Dam, Wisconsin (10 y) (8)</td>
<td>43–86</td>
</tr>
</tbody>
</table>

---

ABRAHAM et al
resulting from UVB exposure is hypothesized to be the mechanism through which UVB may induce cataract, and the anterior cortical surface likely receives the most radiant energy, explaining the predominant findings of higher cortical cataract risk with less or no effect on rates of nuclear cataract and PSC [31]. Furthermore, three studies characterized the distribution of the position of opacities, and each found increased risk of cortical cataract in the lower nasal quadrant compared with other areas of the lens [32–34]. It has been hypothesized that the lower nasal quadrant of the lens is the most affected by solar UV exposure given the angle of the sun during peak UV hours. Quantifying the magnitude of the association is difficult, however, given that methodology for determining exposure varies widely across studies. Odds ratios range from 1.10 (95% confidence interval [CI], 1.02–1.20) per 0.01 Maryland sun-year [35] to 2.48 (95% CI, 1.24–4.99) for cortical cataract comparing annual exposures greater than 564.5 KJ/cm² with exposures of less than 516.7 KJ/cm² [36].

Study results are highly dependent on the method used to quantify the exact UV dosage received by the lens. Ambient levels are an imperfect surrogate, because individual behaviors greatly modify actual lens exposure given constant ambient UVB. Some studies have attempted to overcome this problem by asking detailed questionnaires that can be used to quantify lifetime sun exposure. Such questionnaires are time-consuming to administer, however, and are limited by the difficulty that respondents may have with accurately reporting behaviors from the distant past. Personal traits, such as iris color and nutritional status, also may alter the effect of UVB radiation that reaches the eye. UVB radiation may act primarily as a synergistic effect, increasing the rate of an ongoing opacification process or adding to other oxidative insults to exceed a threshold for cataract formation.

Research into the association between diabetes and cataract formation dates back to the 1960s. It was not until much more recently that prospective studies were conducted that allowed examination of the temporal association between diabetes and incident cataract. Three population-based prospective studies have reported that diabetes is a risk factor for both cortical and PSC cataract. In the Beaver Dam Eye Study, diabetes mellitus was associated with the 5-year incidence of both cortical and PSC cataract [37]. The Blue Mountains Eye Study yielded similar results, finding a twofold higher 5-year incidence of cortical cataract in participants with impaired fasting glucose (odds ratio, 2.2; 95% CI, 1.1–4.1) and more frequent PSC incident cataract among diabetics with newly diagnosed diabetes (odds ratio, 4.5; 95% CI, 1.5–13) [38]. A history of diabetes was associated with incident cortical cataract (relative risk = 2.4; 95% CI, 1.8–3.2) and PSC (relative risk = 2.9; 95% CI, 1.9–4.5) in the Barbados Eye Study in addition to the finding of a dose-response relationship between these incident opacities and increased levels of glycosylated hemoglobin at baseline [39].

Different effect estimates for diabetes on cataract formation have been reported both from age groups less than approximately 60 years and those older than approximately 60 years. This finding has been repeated in a number of studies [40–42]. A diminishing effect of diabetes on cataractogenesis in older age groups may indicate either an increasing influence of other factors thereby washing out the effect of diabetes or a survivor bias, such that severe diabetes leads to early mortality leaving only healthier survivors in the older age groups. An interaction has also been noted in some studies with glycated hemoglobin such that an association between glycated hemoglobin and cataract is seen only in diabetics [37,43]. Such a result may indicate tight glucose control can minimize the risk of cataract in those with diabetes, as has been demonstrated with other diabetes-associated ocular conditions [44].

Risk factors where current understanding is evolving or reflects conflicting results

Myopia

Population studies suggest that the prevalence of myopia may be increasing over time in some areas, the implication of which is higher rates of some of the myopia-associated ocular pathologic conditions [45]. Recent research provides clinical evidence for an association between myopia and nuclear cataract formation. Several cross-sectional studies reported an association between myopia and prevalent nuclear cataract; however, prospective studies were needed to confirm the temporality of the association because nuclear cataract itself can contribute to increased lens power and myopia. Indeed, recently published prospective studies have reported somewhat different results from cross-sectional studies of the same population. In the prevalence study of the
Visual Impairment Project conducted in Australia, an association between myopia and all types of cataract was reported [46]. In the prospective study published in 2006, myopia was only a risk factor for cortical cataract, reporting a 2.2-fold increased risk (95% CI, 1.4–3.4) of incident cortical cataract [47]. This study is the first to report an association between myopia and incident cortical cataract. In Beaver Dam, an association between myopia and prevalent nuclear cataract was seen; however, no association was seen between myopia and incident cataract [48]. The Blue Mountains Eye Study reports a 3.3-fold increased risk of incident nuclear cataract among individuals with high myopia (−6 diopter [D]) and a 5.4-fold increased risk of PSC (95% CI, 2.5–11.9) cataract formation among individuals with moderate to high myopia (−3.5 D). Furthermore, for persons aged 70 years or older, a myopic shift in refraction was associated with incident nuclear cataract, cortical cataract, and PSC [49,50]. In the Barbados Eye Study, myopia, defined as less than −0.5 D, was associated with incident nuclear cataract (relative risk = 2.8) [51].

Recent findings reported from the Salisbury Eye Evaluation demonstrate the importance in the temporality of this association. Cross-sectional associations were reported for both nuclear cataract and PSC. An additional finding was an association between early spectacle wear and PSC, a possible indicator of the temporality of the relationship between myopia and PSC [52]. The mechanism through which myopia may act to cause cataract is unknown, although damage-induced lipid-peroxidation has been hypothesized [45].

Nutrition and supplement usage

Oxidative damage is a putative contributor to the mechanisms of cataractogenesis for both nuclear and cortical cataract. Much interest has been generated by dietary constituents that have antioxidative properties. Levels of many antioxidants exist naturally in the various structures of the eye, protecting tissues from the myriad oxidative insults to which the eye is subject [53]. Many epidemiologic studies have evaluated the role of vitamins and micronutrients in preventing cataract, with nutrient measurements varying from dietary intake to supplement use and plasma levels of the vitamins in question. The types of measurement used and the outcome types, ranging from cataract extraction to prevalence of cataract at 5-year follow-up, make comparisons across studies difficult. Additionally, teasing out the association of an individual nutritional factor is difficult because of the colinearity among various nutritional factors. Individuals who are nutritionally replete in one factor are likely replete in most factors of interest.

A 2000 review of the literature of observational studies conducted by Wu and Leske [54] highlights the conflicting data on nutrients in prevention of cataract and demonstrates that even within the same study population, results may vary over time. For instance, within their own studies, the Lens Opacities Case-Control Study (LOCS) [55] and the Longitudinal Cataract Study [56], a longitudinal study of the LOCS population, discrepant results were found. In LOCS, dietary intake of vitamin C seemed to provide protection against nuclear cataract [55], whereas in the longitudinal study more recently reported [56], the association was not found. On the contrary, when evaluating vitamin E supplementation, no association was seen in the case control study [55] but a protective association with nuclear opacification was reported in the longitudinal study [56]. Similar conflicting results have been reported for the Nurses’ Health Study and the Physicians’ Health Study.

Researchers have hoped that clinical trials would help to clarify the role of nutrients and cataract prevention, and would demonstrate protection against cataract development or progression. The Physicians’ Health Study II evaluating betacarotene, vitamin A and E, and multivitamins [57] and the Italian-American Clinical Trial of Nutritional Supplements and Age-related Cataract evaluating multivitamin use [58] are currently underway, and follow-up will be completed in the next few years; however, most recently reported trial results do not support the hypothesis of protection from vitamins. The Age-related Eye Disease Study reported no association between supplementation with vitamin C, vitamin E, and betacarotene and 7-year risk of development or progression of lens opacities [59]; likewise, the Vitamin E, Cataract and Age-related Maculopathy Trial evaluating vitamin E given for 4 years reported no overall association between supplementation and incidence or progression of lens opacities [60]. These findings are in contrast to two earlier clinical trials of vitamin supplementation in a population in China with borderline nutritional status, which demonstrated a protective effect of supplementation on development of nuclear opacities, albeit in only one supplement
combination out of several studied [61]. These conflicting results highlight the importance of the nutritional status of the population being studied. Although evidence of a role for nutritional supplementation in retarding the progress of cataract is currently lacking for nutritionally replete populations, an ongoing study in southern India, the Antioxidants and Prevention of Cataract Study, may provide further insight into the potential role of supplementation in less well-nourished groups, where the bulk of cataract blindness exists.

Weight status and fat consumption

Many factors relating to health and nutrition are interrelated, making the individual association of a specific factor difficult to tease apart. Several studies have evaluated the relationship between body mass index and cataract. The Nurses’ Health Study cohort, the Physicians Health Study cohort, the Framingham cohort, and the Beaver Dam Eye Study cohort have all reported associations between body mass index and PSC cataract [37,62–65]. The nature of the relationship between body mass index and cataract has not been fully elucidated; however, some studies suggest a U-shaped relationship. Numerous other studies have reported associations with cortical and nuclear cataracts and null findings [63,66–69]. The role of central adiposity is even more unclear [41,62].

Research also has focused on the contribution of dietary fat and serum lipids to cataract risk [70,71]. Of particular interest may be the contribution of fatty acids to both cataract development and protection. One cross-sectional study in the Nurses Health Study cohort found a higher risk of nuclear cataract among nurses who consumed the highest amount of linoleic and linolenic acid [72]. Lens research has confirmed a cytotoxic effect of these and other unsaturated, cis-configured fatty acids on lens epithelial cells, an effect that seems to be moderated by aqueous albumin concentrations that may rise with age [73]. Such results could have implications for diseases, such as diabetes where plasma free fatty acid levels tend to be elevated. In a second longitudinal study of the Nurses Health Study cohort eicosapentaenoic and docosahexaenoic acid were found to be protective against cataract extraction, whereas linoleic and linolenic acid were not strongly associated with the outcome [74].

Findings from the various studies of lipid metabolism, obesity, diabetes, and opacification of the lens may be scratching the surface of a complex etiologic web. Animal studies may indicate that these factors interact to promote cataract development and modification of one factor may be used to reduce risk from another [75].

Corticosteroids

Numerous studies have reported associations between oral corticosteroid use and cataract formation. As early as 1960, studies indicated a causal role of systemic steroids in PSC development [76]. Many reviews have been written on the topic summarizing the evidence for an association between cataract and both oral and inhaled steroids [77–81]. Evidence for oral steroid use as a risk factor for cataract is stronger than that for inhaled steroids. The use of oral corticosteroids for the treatment of inflammatory and immune disorders, such as asthma, rheumatoid arthritis, and lupus erythematosus, provided early evidence of an increased prevalence of PSC formation in exposed individuals, particularly children [76,82–87]. Controlled trials of steroids used in combination with other therapy have strengthened the case for a causative role of oral steroids in PSC progression. Patients randomized to receive oral steroids for immunosuppression showed consistently higher rates of PSC [80,88,89]. The prevalence of PSC seems to be sensitive to both the dose and duration of steroid administration [76,80,82,83,90].

More recent literature has focused on the role of inhaled corticosteroids on cataract formation. A review by Allen and coworkers [81] summarizes the data through 2003. A cursory review of the literature might suggest conflicting information because multiple studies report no association between inhaled corticosteroids and cataract [90–92]. These studies are based on small populations of primarily children and young adults who are unlikely to develop this typically age-related condition [91,92], however, or they focus on a small population in which oral steroids were used, making it more difficult to isolate the association with inhaled steroids [90]. Three case-control studies examining cataract diagnosis and extraction without regard to type found participants taking inhaled steroids to be at higher risk of prevalent cataract [93–96]. Most recently, a large cross-sectional survey of the Blue Mountains Eye Study cohort found a relative prevalence of 1.9 (95% CI, 1.3–2.8) for PSC and 1.5 (95% CI, 1.2–1.9) for nuclear cataract among subjects using
inhaled corticosteroids compared with those with no inhaled corticosteroid use [95]. Cumming and Mitchell [97] suggest that the evidence for inhaled steroid on cataract formation is at least as strong as that for oral steroid use in their cross-sectional study and that future studies should evaluate whether direct entry of corticosteroid into the eye because of poor inhaler technique may play a role. Prospective studies of inhaled steroid users may help to confirm the role of their use in cataract development.

It should be noted that several factors may complicate the detection of small effects from inhaled steroids. The particular lesions associated with steroid use may have a reversible component and can be difficult to detect because they rarely affect vision [80,98]. In addition, there may be a large degree of variability in individual susceptibility, and synergism with other cataractogenic factors may ultimately determine any individual’s PSC outcome [78,80,99].

**Exogenous estrogens**

A large body of evidence suggests that across racial groups, women have higher rates of cataract, even when adjusting for women’s greater longevity [31,39,46,100–104]. Postmenopausal estrogen decline has been hypothesized to play a role. Research into the causal relationship of exogenous hormone use and cataract risk, however, has provided conflicting results. In both the Beaver Dam and Salisbury populations, prevalence data suggested a relationship between current hormone-replacement therapy use and decreased nuclear cataract. In Salisbury, an association also was seen with PSC. Recently published prospective evaluations of both of these two populations reported no association, however, between hormone-replacement therapy and any cataract formation. Additionally, whereas the Blue Mountains research group concludes that there is some evidence of a protective association between estrogen use and incident cataract formation [105], the recently reported Visual Impairment Project found no association between female hormonal use and cataract [47]. Clearly, the role of hormone-replacement therapy in cataract prevention has not been fully elucidated.

**Genetics**

The role of genetics in the development of cataract is a question of increasing interest. Finding genes that contribute to the mechanism of cataractogenesis may eventually lead to gene product targets for intervention. Further, such information could aid in identifying predisposed individuals who might be more susceptible to other cataract risk factors, such as UV exposure [24]. The Framingham Eye Study examined familial aggregation of lens opacities and found that the odds of a nuclear cataract or PSC were three times higher among those with affected siblings compared with those without an affected sibling [106]. In the Beaver Dam Eye Study, the contribution of a single gene to the variability in sex- and age-adjusted measures of nuclear and cortical cataract was estimated to be as high as 35% and 58%, respectively [107,108].

The Twin Eye Study went one step further, estimating both the contribution of genetic and environmental factors to various cataract phenotypes. The authors found that the total variability in nuclear cataract development was partitioned as follows: heritability accounted for 48% (95% CI, 42%–54%); age accounted for 38% (95% CI, 31%–44%); and unique environmental effects accounted for 14% (95% CI, 12%–18%) [109]. A similar investigation of cortical cataract found that dominant genes were estimated to contribute to 38% (95% CI, 1%–64%); additive genes contributed to 20% (95% CI, 0%–57%); age contributed to 16% (95% CI, 12%–21%); and the environment accounted for 26% (95% CI, 22%–31%) [110]. Two studies in the Salisbury cohort estimated the magnitude of heritability to be 35.6% (95% CI, 21%–50.3%) for nuclear cataract and 24% (95% CI, 6%–42%) for cortical cataract [111,112].

At least two genes have been reported to be associated with an increased risk for age-related cataract itself among Japanese populations; however, the relationships have not been replicated in other populations. Sekine and coworkers [113] found a significantly higher frequency of deletion of the gene for glutathione-S-transferase, a key enzyme involved in free-oxygen radical scavenging, among Japanese patients with typical age-related cataract as compared with age-matched controls. The mean age of cataract patients with the gene deletion was significantly younger than for patients possessing the normal gene. Alberti and coworkers [114] failed to replicate these results in an Italian population, and the role of this gene also seems variable in other populations [115,116].

Another candidate gene currently available for age-related cataract is galactokinase. A deficiency of this enzyme is the cause of a disorder involving hypergalactosemia and early cataract formation. A novel variant of galactokinase, identified during...
newborn screening for hypergalactosemia, has been associated with a twofold increased risk for age-related nuclear cataract among Japanese individuals [117]. The original investigators failed to find evidence of this particular variant among blacks and whites in the United States, and other investigators have failed to find an association between galactokinase alleles and cataract in an Italian population [118]. Finally, a locus associated with cortical cataract on chromosome 6 has been reported from the Beaver Dam population [119].

Markers of inflammation

A very recent interest in markers of inflammation and vascular endothelial dysfunction as predictors of cataract has yielded some results. Inflammation is thought to play a role in the pathogenesis of at least PSC. A study by Klein and coworkers [120] using serum samples obtained between 1988 and 1990 from the Beaver Dam cohort found that higher levels of tumor necrosis factor-α, interleukin-6, and serum soluble intercellular adhesion molecule-1 were associated with prevalent nuclear cataract. Little previous evidence exists concerning these and other markers of inflammation and the risk of cataract. It is hoped that further studies will follow.

Future directions

Recent research supports the theory that the development of any cataract phenotype is likely the result of a multifactorial process except in rare instances of very large occupational exposures. The future of cataract research will be in more complex study designs looking at multiple factors that contribute to a single mechanism of cataractogenesis.

The need to standardize exposure and outcome measurements will become more important as clinicians seek to synthesize data better from multiple studies. Standardizing exposure assessment entails finding a consensus on the most biologically meaningful measure of the exposure of interest. Not only must an appropriate measurement instrument be considered but also finding a relevant exposure time window. For exposures with a hypothesized long lag period between exposure and a detectable preclinical phase of disease, such as smoking and environmental UV, quantifying the appropriate magnitude of exposure can be challenging. Measurements may be subject to recall bias in nonprospective study designs. Further, systemic or environmental measures of an exposure may not be linearly related to ocular exposures, such as in studies of antioxidants and dietary constituents.

Outcome assessment is complicated by the many systems of cataract severity measurement. These systems rely on different standards for judging levels of severity. Often these ordinal scales are reduced to a dichotomous measure of cataract or no cataract and information regarding the progression of early disease is lost.

Cataract research is still a fertile field for investigation. The high prevalence of the disease in older age groups makes the elucidation of even weak modifiable risk factors clinically significant. Few diseases have as great an impact on public health worldwide.

References


