The Association of Age-Related Macular Degeneration and Lens Opacities in the Aged

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Abstract: Data from 3,087 persons age 45 or older in the National Health and Nutrition Survey, 1971–74, showed that subjects with lens opacifying disease had an increased odds for age-related macular degeneraton (AMD) compared to those who had no lens opacities. The crude odds ratio for aphakic patients was 4.6 (95% CI = 2.5, 8.6). The association remained after controlling for age, sex, and systolic blood pressure (a common risk factor) in a logistic regression model. These data are consistent with the hypothesis that light-induced damage may contribute to both lens and retinal disease and suggest that cataract extraction without implantation of ultra-violet/blue light absorbing intraocular lens may place subjects at increased risk of AMD. (*Am J Public Health* 1989; 79:765–769.)

Introduction

Age-related macular degeneration (AMD) and cataracts are two of the most common causes of visual impairment in older persons. Differing sampling methods and diagnostic criteria make prevalence estimates difficult, but the World Health Organization estimated in 1982 that 17 million persons in the world were blind as a result of cataracts. Ferris notes that AMD was the leading cause of registered blindness in the United States and Great Britain as early as 20 years ago.[1] While each disease affects a separate structural component of the eye, their dramatic increase in prevalence with aging suggests common or related processes may be responsible for both conditions.

Although the pathogenesis of neither condition is well understood, mechanisms that involve light-mediated damage have been theorized for both.[2–4] According to these theories, damage to the lens and/or retina occurs when the body's defenses, such as antioxidant stores and enzyme systems, fail or are overwhelmed. Light has been shown to induce retinal lesions in many mammals.[5–7] A role for free-radical-mediated damage in the development of cataracts is supported by the finding of deficient superoxide dismutase activity in cataractous human lenses.[8]

Since light must pass through the lens to reach the retina, cataracts may actually retard the development of AMD. The yellow pigmentation that characterizes nuclear cataracts may filter out blue light that is felt to be especially damaging.[9] Zigman and Collier noted in the diurnal gray squirrel that the yellow pigmented lens filtered near-ultraviolet (UV) radiant energy and protected the retina from physical and functional damage.[5]

There have been very few population-based studies examining this theory. Sperduto, *et al*, found no association between cataracts and AMD in the Framingham Study when the various age-related lens changes were pooled.[10] On reexamination of the same data, when specific types of cataracts were studied, they found a positive association between AMD and cortical changes and a negative association with nuclear sclerosis.[11]

An interesting and important corollary, if some lens opacification is protective of the macula, is that an increased risk may be imposed by surgical removal of cataractous lens. The Report of the Cataract Panel in Vision Research—A National Plan: 1983–87 suggests that aphakic eyes may be at special risk for retinopathy and maculopathy.[12]

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The current study uses data from the first National Health and Nutrition Examination Survey (NHANES-I) to examine whether there is an association between the occurrence of AMD and lenticular opacities and whether aphakics compose a special risk group for AMD.

Methods

NHANES-I was a cross-sectional study of a probability sample (and partial oversample) of the civilian noninstitutionalized coterminus US population, designed to assess the prevalence of certain conditions. Details of the design and conduct of the survey are available elsewhere.[13] The visual component included a short ocular history and detailed examination for visual acuity, motility, and pathology, including tonometry and dilatation. Right and left eyes were examined and rated separately.

For this study, subjects having "senile macular degeneration," "senile disciform macular degeneration," or "senile circinate macular degeneration" were classified as having AMD, while all other persons served as controls (Table 1). A diagnosis of macular degeneration required pathological findings of "loss of macular reflex, pigment dispersion and clumping, and drusen"[14] as well as visual acuity of 20/25 or worse (best corrected) that was felt by the examiner to be due to the disease.

Lens conditions were grouped into four mutually exclusive groups—aphakic eyes, eyes with cataract and associated visual impairment, eyes with lens opacities but no visual impairment, and eyes with no lens opacifying disease (reference group). The cataract group was formed from all immature, intumescent, mature, hypermature, and morgagnian cataracts which the examiner felt were responsible for vision loss to the level of 20/25 or more (best corrected). The definitions for macular degeneration, cataracts, and aphakia are all consistent with those used by Klein in previous analyses of this data.[15]

The study population was restricted to subjects 45 years of age or older. The odds of having AMD for each of the lens opacifying conditions was calculated for right eyes and left eyes independently, as well as for persons with the condition in either eye. The reference group for the latter "person-measure" analysis was defined as those individuals with normal lenses bilaterally.

The relation of AMD with cataract was also examined for cataract subgroups based upon type of cataract. To be classified in either the "nuclear sclerosis" or "cortical cataract" subgroups, eyes were required to have cataracts identified in either the nuclear region or cortical region exclusively (as determined by a precoded variable in the data

TABLE 1—Frequencies of Persons with AMD and other Retinal Conditions by Lens Conditions, National Health and Nutrition Examination Survey, 1971–74

	AMD		NON-AMD			
			Other Retinal Abnormalities		No Retinal Abnormality	
	OD	OS	OD	OS	OD	OS
No Lens Opacifying Disease	57	61	676	670	1144	1125
Total Lens Opacifying Disease	103	95	614	638	493	498
Aphakics	6	6	21	25	25	26
Total Lens Opacities	97	89	593	613	468	472
Opacities without Visual Impairment	60	63	385	400	290	290
Total Cataracts	37	26	208	213	178	182
Nuclear	8	5	29	35	36	38
Cortical	5	3	58	53	55	54
Other	24	18	121	125	87	90
Total # Eyes	160	156	1290	1308	1637	1623

OD = oculus dexter (right eye)
OS = oculus sinister (left eye)

set). All other cataracts were placed in a category designated as "other" which included eyes with mixed nuclear and cortical cataracts.

Crude weighted and unweighted odds ratios were initially calculated for all age groups combined and then after stratification by 10-year age groups. The results for weighted and unweighted analyses were not appreciably different. Unweighted odds ratios based upon actual frequencies with confidence limits calculated using Woolf's method[16] are presented in the tables. Finally the relationship of AMD with lens opacities was examined using a logistic model controlling for age, sex, and a common suspected risk factor for both: systolic hypertension.[15] The model was run using both unweighted data and a supplementary logistic regression program in SAS designed to incorporate sampling weights and take the complex sample design into account.[17] Results were similar and presented for both weighted and unweighted data.

Results

The study population included 3,738 persons (6,174 eyes) (Table 1). The prevalence of both lens opacifying disease and AMD increased dramatically with age (Figure 1). Lens disease was generally bilateral. AMD was found in 185 persons (316 retinas). In 131 (70.8 per cent) subjects the disease was bilateral.

In the univariate analysis, persons with cataracts were substantially more likely to have AMD than were persons with no lens abnormalities (Table 2). Similarly, persons with lens opacities but no visual impairment had an odds ratio of 2.5 (95% CI = 1.8, 3.5) when compared with persons with no lens opacities. A person with at least one aphakic eye had an even higher odds ratio for AMD (OR = 4.6; 95% CI = 2.5, 8.6).

Estimates of odds ratios measuring the strength of association between AMD and three categories of lens abnormality (opacities without visual impairment, cataracts, aphakics) are presented for three age strata in Table 3. All estimates remain greater than 1.0, with lower bounds of the 95 per cent confidence limits excluding 1.0 in the highest age stratum (where most of the cases were found) for the opacity without visual impairment and aphakic groups. The data shown in Table 3 are for individuals, with a person defined as having the condition if it was observed in either eye. Similar results were observed when analyses were conducted for the left and right eyes separately. These estimates suggest that

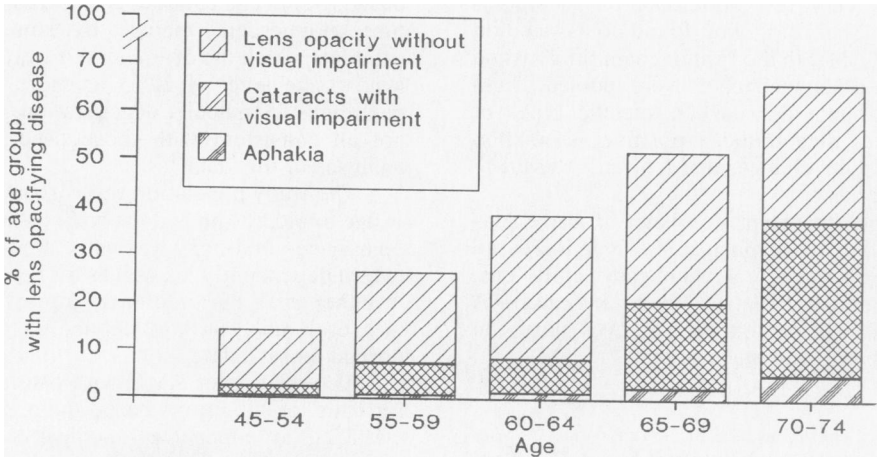

FIGURE 1a—Prevalence of Lens Opacifying Disease by Age Group in the Non-institutionalized Elderly Population of the Coterminus United States.
SOURCE: Data from the National Health and Nutrition Survey, 1971–74.

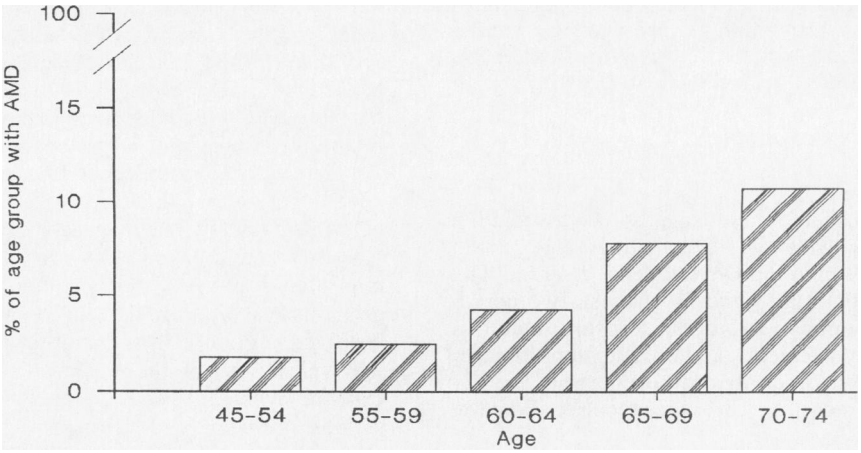

FIGURE 1b—Prevalence of Age-related Macular Degeneration by Age Group in the Non-institutionalized Elderly Population of the Coterminus United States.
SOURCE: Data from the National Health and Nutrition Survey, 1971–74.

TABLE 2—Crude Odds Ratios and 95% Confidence Intervals ( ) for Association of AMD and Various Lens Opacifying Conditions in the National Health and Nutrition Examination Survey, 1971–74

	OD	OS	Either eye
No Lens Opacity	1.0	1.0	1.0
Lens Opacity without Visual Impairment	2.8 (2.0, 4.1)	2.7 (1.9, 3.8)	2.5 (1.8, 3.5)
Cataract	3.1 (2.0, 4.7)	2.0 (1.3, 3.2)	2.4 (1.6, 3.7)
Nuclear Sclerosis	2.5 (1.6, 4.1)	2.4 (1.5, 3.8)	2.2 (1.4, 3.5)
Cortical Cataract	2.8 (1.8, 4.4)	2.3 (1.5, 3.6)	2.4 (1.6, 3.6)
Other Cataract	3.7 (2.3, 6.1)	2.5 (1.4, 4.2)	2.9 (1.9, 4.7)
Aphakia	4.2 (1.8, 9.5)	3.5 (1.4, 8.4)	4.6 (2.5, 8.6)

OD = Oculus dexter (right eye)
OS = Oculus sinister (left eye)

the odds for having AMD may be increased 50 percent among persons with cataracts, 80 percent among persons with non-visually impairing opacities, and 200 percent among aphakic persons.

Multiple logistic regression analyses were conducted to appraise the association between lens abnormalities and AMD while simultaneously taking into account other major predictors of macular degeneration. The effects of each of the three primary categories of lens disease were simultaneously tested in a model containing age, sex, and systolic blood pressure. As shown in Table 4, odds ratios determined by this approach were similar to those described above with age stratification. Again, the strongest effect was associated with aphakia which had a weighted odds ratio of 2.0, followed by non-visually impairing lens opacities with a weighted odds ratio of 1.8. These results suggest that the increment in odds ratio associated with aphakia (as an example) is similar to that associated with 10 years of additional age.

The number of persons with exclusively nuclear or

TABLE 3—Age-Stratified Odds of Association between AMD and Lens-Opacifying Disease, National Health and Nutrition Examination Survey, 1971–74

	Lens Opacity without Visual Impairment		
Age (years)	Cataract	(LO)	Aphakia
45–54	*	3.0 (0.9, 9.8)	*
55–64	1.5 (0.3, 7.1)	1.4 (0.5, 3.8)	*
65–74	1.5 (1.0, 2.4)	1.8 (1.2, 2.8)	3.2 (1.5, 6.5)
Mantel-Haenzel Age Adjusted Odds Ratio with 95% Confidence Intervals	1.5 (1.0, 2.3)	1.8 (1.3, 2.6)	3.3 (1.7, 6.5)

*insufficient data.
95% CI in parentheses.

TABLE 4—Weighted and Unweighted Multivariate Logistic Regression of AMD on Lens Opacifying Disease, Age, Sex, and Systolic Blood Pressure in NHANES I Elderly Population, 1971–74

	Weighted OR	Unweighted OR
Lens Opacifying Disease		
None	1.00	1.00
Opacity without Visual Impairment	1.80 (1.40, 2.30)	1.75 (1.22, 2.51)
Cataract	1.14 (0.84, 1.55)	1.29 (0.85, 1.95)
Aphakia	2.00 (1.44, 2.78)	2.46 (1.24, 4.88)
Age (per year)	1.07 (1.05, 1.10)	1.08 (1.05, 1.11)
Sex		
Male	1.00	1.00
Female	0.73 (0.54, 0.99)	0.76 (0.56, 1.03)
Systolic BP (per 10 mm Hg)	1.08 (1.04, 1.13)	1.06 (1.00, 1.12)

95% CI in parentheses.

cortical cataracts was small in this study, making detailed stratified analysis impossible. However, the crude odds ratios relating AMD to both cataract subtypes were strong and statistically significant. Neither the strength nor direction of the relationships differed, as has been suggested in other studies.[11]

Discussion

The analyses presented here suggest an association between two age-dependent eye abnormalities: age-related macular degeneration, and opacifying lens disease. The finding suggests that the pathogeneses of these two conditions may involve a common etiologic (exposure) factor, a common susceptibility element, and/or common disease-modulating risk factors. Since the pathogenesis of neither condition is well understood, we can only speculate about the nature of the common factor(s).

Development of lens and retinal diseases might reflect the independent or combined effects of such factors as: excessive light exposure, especially over a period of years; an inefficient constitutional anti-oxidant system such as the enzyme superoxide dismutase (SOD); the influence of deficient dietary antioxidants such as vitamins A, E, or C; and/or the damaging effects of oxidation-potentiating factors such as dietary psoralens or certain drugs.[18] These concepts suggest that some patients with concurrent lens and retinal disease might reasonably be viewed as suffering from accelerating aging, a formulation in line with prior speculations that cataracts may be a marker for advanced physiologic age.[19]

In the logistic regression, the presence of cataracts was weakly associated with AMD (OR = 1.1, p = 0.4), possibly reflecting the difficulty of visualizing maculas in eyes with dense cataracts, even with dilatation. It is appealing to theorize that the weak association between cataracts and AMD in this study may be due to the fact that cataracts retard the transmission of light to the retina, decreasing the extent of light damage. Unfortunately, limitations of the data regarding the severity of either AMD or cataracts preclude investigating this possibility more completely. An alternative explanation of the weak relation involves the possibility that different kinds of cataracts may have differing pathogeneses. For some types, no common factors may be shared with macular degeneration.

The very strong association of AMD with aphakia suggests that a sudden increase in light transmittance after cataract removal may reinitiate and dramatically accelerate the progression toward frank macular degeneration. This speculation provides additional reason to support the trend toward routine implantation of intraocular lens following cataract extraction, particularly with a lens capable of reducing the transmittance of ultraviolet or blue light. Alternatively, it has been suggested that cataract extraction can produce retinal changes resembling AMD.* It has also been suggested that exposure to bright surgical lights at the time of cataract extraction may be responsible for damage to the macula.[20] Serial examinations comparing patients with intraocular lens implants and those without lens implants would help resolve this question.

By defining all retinas without frank AMD as controls, there is a high probability of misclassifying retinas with subclinical AMD in the control group. The conservative nature of this approach enhances the believability of the association of AMD and lens opacifying disease which was found. When the analyses presented above were conducted using disease-free retinas as a control group, the relationships between AMD and all lens opacifying disease were stronger (higher estimates and tighter confidence limits).

The association between lens and macular disease independent of age is consistent with the theory of ultraviolet/near-ultraviolet light damage to the eyes. Until the actual risk factors for both conditions are clearly known, the most important implication of these findings is perhaps that surgical removal of cataracts, while improving vision in the short term, may actually place patients at greater risk of irreversible visual loss in the long run. With the increased life expectancy of the general population, this may become a serious problem, and warrants further investigation. The cheapest and most effective public health measure may be to encourage use of protective eyewear at early ages.

*Sperduto R: Personal communication, 1988.

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