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The Relationship of Cataract and Cataract Extraction to Age-related Macular Degeneration: The Beaver Dam Eye Study

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Abstract

Objective—To examine the associations of cataract and cataract surgery with early and late age-related macular degeneration (AMD) over a 20-year interval.

Design—Longitudinal population-based study of age-related eye diseases. **Participants:** Beaver Dam Eye Study participants.

Methods—All persons 43–84 years of age were recruited in 1987–1988. Participants were followed up at five year intervals after the baseline examination in 1988–1990. Examinations consisted of ocular examination with lens and fundus photography, medical history, measurements of blood pressure, height, and weight. Values of risk variables were updated, and incidences of early and late AMD were calculated for each 5-year interval. Odds ratios were computed using discrete linear logistic regression modeling with generalized estimating equation methods to account for correlation between the eyes and multiple intervals.

Main Outcome Measures—AMD.

Results—After controlling for age and sex, neither cataract nor cataract surgery was associated with increased odds for developing early AMD. Further controlling for high risk gene alleles (*CFH* and *ARMS2*) and other possible risk factors did not materially affect the odds ratio (OR). However, cataract surgery was associated with incidence of late AMD (OR 1.93; 95% CI 1.28, 2.90). This OR was not materially altered by further controlling for high risk alleles (*CFH* *Y402H*, *ARMS2*) or for other risk factors. The OR for late AMD was higher for cataract surgery performed 5 or more years prior as compared to less than 5 years prior.

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This article contains additional online-only material. The following should appear online-only: Table 1.

Conclusions—These data strongly support the past findings of an association of cataract surgery with late AMD independent of other risk factors including high risk genetic status, and suggest the importance of considering these findings when counseling patients regarding cataract surgery. These findings should provide further impetus for the search for measures to prevent or delay the development of age-related cataract.

Age-related macular degeneration (AMD) increases in prevalence with increasing age and thus is likely to be increasingly prevalent with increasing longevity worldwide.¹⁻⁶ While there are effective treatments for neovascular AMD, treatment is expensive and commonly requires intravitreal injections with attendant costs⁷ and risks.^{8,9} There is currently no successful treatment for atrophic AMD.

Cataract is the most common age-related eye disease worldwide and is a significant cause of visual impairment and legal blindness.¹⁰ Cataract surgery results in improved visual function and satisfaction with vision.¹¹

Age-related cataract and AMD often develop concurrently, being that they are both problems associated with aging. Combined cross sectional data from the Salisbury Eye Evaluation Project, Proyecto VER and the Baltimore Eye Survey indicated that the odds ratio (OR) for late AMD in the presence of cataract surgery was 1.7 (95% CI 1.1, 2.6). The OR for late AMD in the presence of severe cataract was 1.4 (95% CI 0.8, 2.4).¹² Combined 5-year incidence data from the Beaver Dam Eye Study (BDES) and the Blue Mountains Eye Study (BMES) indicated an OR of 5.7 (95% CI 2.4, 13.6) for late AMD associated with cataract surgery at the baseline examination. By the 10-year follow-up in the BDES, the OR was 3.81 (95% CI 1.89, 7.69) and in the BMES it was 3.3 (95% CI 1.1, 9.9).¹³ Neither the Visual Impairment Project nor the Age-Related Eye Disease Study found an association of cataract surgery with progression of AMD.^{14,15} Cataract itself at baseline was associated with incident early AMD in 10-year incidence data from the BDES (relative risk [RR] 1.3; 95% CI 1.04, 1.63).¹⁶ Chakravarthy and colleagues reported increased odds for late AMD associated with previous cataract surgery.¹⁷ However, neither cataract nor cataract surgery were associated with either early or late AMD in the Beijing Eye Study.¹⁸ Thus, there is no clear consensus as to whether cataract surgery is associated with increased risk of AMD and, if so, whether this is due to confounding by indication (presence of cataract) or due to an effect of cataract that is further exacerbated by cataract surgery. The purpose of this paper is to elucidate these relationships in the context of the BDES, a long term ongoing study of age-related eye conditions over 20 years of follow-up.

Methods

Participants

A private census of Beaver Dam, Wisconsin, was performed in 1987-1988 to identify all residents eligible for the study.¹⁹ Of the 5,924 eligible, 4,926 (83%) persons 43-86 years of age participated in the baseline examination in 1988-1990. Ninety-nine percent of the population was white and 56% were female. The cohort was re-examined at 5- (n=3,722), 10- (n=2,962), 15- (n=2,375) and 20-year (n=1,913) follow-up examinations. There was greater than 80% participation among survivors at each examination (Klein R, personal communication, 2011).²⁰⁻²² Differences between participants and non-participants have been presented elsewhere (Klein R, personal communication, 2011).²⁰⁻²² In general, participants at each examination were younger, and while controlling for age and sex had lower blood pressure and had fewer comorbid conditions than non-participants. All data were collected with Institutional Review Board approval from the University of Wisconsin-Madison in conformity with all federal and state laws, the work was HIPAA compliant, and the study was in adherence to the tenets of the Declaration of Helsinki.

Participants were examined at the study suite in a local hospital, a nursing home, or in their home. The same protocols for measurements relevant to this investigation were used at each examination.²³ Height, weight, and blood pressures were measured. Date of birth was recorded. A history of place of residence was obtained and used to calculate ambient sunlight exposure as greater or less than 1 Wisconsin sun year.²⁴ Smoking, drinking, and education histories were obtained using a standard questionnaire. All medications and supplements (prescription and over-the-counter) currently being taken by the participant were brought to each examination and recorded.

Photographs of the ocular fundus²³ and the lens²⁵ were taken after pupillary dilation according to protocol and graded in masked fashion by experienced graders. Slit lamp photographs were taken to grade the degree of nuclear sclerosis. Retroillumination photographs were taken to grade presence and severity of cortical and posterior subcapsular cataracts. The protocols for photography and for the grading procedures have been previously described.²⁵ Scores for nuclear sclerosis were based on comparisons with standard photographs, which resulted in a 5-step scale of severity based on opacity of the nucleus. Severities greater than standard 3 were considered nuclear cataract. Scores for cortical and posterior subcapsular cataracts were based on estimated amount of involvement of the lens. Cortical cataract was considered present if 5% of the lens was involved. Posterior subcapsular cataract was considered present if 5% of a segment (lens area divided into nine segments) was involved. Presence of cataract surgery was determined by history along with the date of surgery, and was corroborated by red reflex photographs.

The Wisconsin Age-Related Maculopathy Grading System was used to assess the presence and severity of lesions associated with AMD from the fundus photographs.^{1,25,26} Grading procedures, lesion descriptions, and detailed definitions for the presence and severity have appeared elsewhere.²⁵ Early AMD was defined by the presence of either soft indistinct drusen or the presence of any type of drusen associated with pigmentary abnormality (PA), defined as retinal pigment epithelium depigmentation or increased retinal pigment. Late AMD was defined by the presence of neovascular macular degeneration and/or pure geographic atrophy (GA). Quality control procedures were ongoing throughout the study.

The Y402H polymorphism for *CFH* was classified as absent or present for at least one high-risk allele, and this information was available for 4479 participants. The A69S polymorphism for the *ARMS2* gene was defined similarly, and was available for 4600 participants. The absence and presence of the *CFH* and *ARMS2* polymorphisms were combined into a single 4-level categorical variable for analyses (no *CFH* or *ARMS2* risk alleles; at least one *CFH* risk allele but no *ARMS2* risk alleles; no *CFH* risk alleles but at least one *ARMS2* risk allele; at least one *CFH* risk allele and at least one *ARMS2* risk allele). The distribution of other characteristics of the population by presence or absence of information about these markers did not differ from each other or from the rest of the population.

Population for Analysis

For these analyses, we examined the relationship between cataract and cataract surgery as risk factors for incidence of early or late AMD in the presence of other known risk variables. Data were pooled over each of the four 5-year intervals: baseline to the first follow-up, first follow-up to the second follow-up, and so on. There were 973 eyes that developed (were incident for) early AMD and 200 eyes that developed (were incident for) late AMD, 111 for neovascular AMD and 89 for GA. Cataract status, AMD severity level, and other risk variables were assessed at the start of each interval, and incidence of early or late AMD was assessed from the beginning to the end of that interval. In this way, risk variables are assessed at the first visit in the interval, and therefore reflect change from the baseline visit.

For example, consider a participant who smoked at the baseline visit and then stopped smoking by the time they were seen at the first follow-up visit. Their smoking status in the first interval would be “current smoker” and in the second interval would be “past smoker”. The model would then capture this change in risk for incidence of AMD.

To be included in analyses, a participant must have been eligible for incidence of early or late AMD in at least one eye in at least one 5-year interval, and have information on cataract and cataract surgery status available at the start of that interval for the same eye(s) that contributed AMD data. Participants were excluded in a given interval if they were seen at the visit beginning the interval but not at the end. An eye was excluded from incidence calculations for early or late AMD if it already had early or late AMD, respectively, at the start of the interval. Eyes were also excluded if the photos were ungradable due to confounding lesions at the first visit for cataract, or either visit for AMD. Overall, for early AMD, there were 2626 participants contributing data for both eyes, 347 contributing right eye data only, and 333 contributing left eye data only in at least 1 interval. Similarly, there are 3329 participants contributing data from both eyes, 144 with right eye data only, and 145 with left eye data only for late AMD in at least one interval. Of the 3619 participants included in analyses, 3234 had a known *CFH* and *ARMS2* polymorphism status.

Statistical Analysis

For the models presented, data were pooled for each of the four 5-year intervals for all eligible eyes. All odds ratios, 95% confidence intervals, and P values reported use discrete linear logistic regression models²⁷ with generalized estimating equation (GEE) methods to account for correlations between the eyes at multiple intervals. Overall P values reported for categorical variables refer to a type 3 likelihood ratio statistic or test of main effects.²⁸ SAS software version 9.2 (SAS Institute, Cary, NC) was used for all analyses.

Comparisons of characteristics for those included and excluded from analysis are given for each interval (Table 1, available at <http://aaojournal.org>). Differences between the inclusion and exclusion groups were tested by pooling data from all intervals, using GEE methods to account for correlations. P values reported for the pooled analysis are similar to those seen when comparing included and excluded participants at each separate interval (data not shown). Comparisons between those included and excluded report overall P values both before and after adjusting for age, age² and sex.

All models for risk of early (Table 2) or late (Table 3) AMD by cataract and cataract surgery status adjust for age, age² and sex. UVB light exposure, outdoor light exposure, and supplement use were not significant in the multivariable modeling and therefore were not included in the models. The genetics model further adjusts for *CFH* and *ARMS2* genotype using the combined 4-level categorical variable. The maximally adjusted models we report further control for education, smoking, heavy drinking, CVD history, diabetes, and diastolic blood pressure.

Results

Characteristics of importance to our analyses are given for each study visit interval (Table 1, available at <http://aaojournal.org>). For some characteristics, the difference between those included and excluded is not significant over the 4 intervals but is significant after adjusting for age and sex. Thus, those excluded were more likely to be women, to have less than a complete high school education, to currently be or have been smokers, to have been heavy drinkers, to have hypertension, cardiovascular disease, cancer, and/or diabetes, to be taking a vitamin supplement, and to have had cataract or cataract surgery than those included. Inclusion status was not related to presence of *CFH* or *ARMS2* risk alleles. Those excluded

from analyses were also more likely to be older and to have higher systolic blood pressure than those included (data not shown). By design, those excluded were more likely to have had AMD in at least one eye, as those with prevalent AMD at the beginning of a 5-year interval were not at risk for incidence of AMD.

Preliminary models for specific types of cataract showed no significant differences in the risk of developing AMD by cataract type (data not shown); therefore all cataract types were pooled to form the “any cataract” level of the cataract variable.

To determine the relationship of cataract and cataract surgery to AMD outcomes, we initially developed models that included only age, age², and sex adjusted ORs (Table 2). Having at least one type of cataract was considered the referent category. For early AMD, not having any cataracts was minimally associated with lower OR. Having cataract surgery was associated with a non-significant increase in the OR for early AMD. Including the presence of a gene risk allele in the model did not materially alter the risk of early AMD nor did including all of the other potential risk factors. When including time since cataract surgery, those that had cataract surgery 5 or more years ago had a higher OR than those who had cataract surgery within the past 5 years, although neither was significantly different from the referent group. We compared the OR for less than 5 years to the OR for 5 or more years and found that they were not significantly different from each other.

For late AMD (Table 3), not having any cataracts was associated with lower odds compared to those with at least one cataract type present. Cataract surgery was associated with an OR for late AMD of 1.93 (95% CI 1.28, 2.90) compared to having at least one type of cataract in the age, age² and sex adjusted model. The ORs were not materially affected by the presence of a high risk AMD allele or by controlling for all other potentially important characteristics. As with early AMD, the greater the length of time since cataract surgery (5 years vs. <5 years), the greater the OR for late AMD; both of the ORs were significantly different from the referent group but not significantly different from each other. The relationship with cataract surgery 5 years before remained unchanged when those with aphakia and those with lenses implanted before 1993 were omitted. Modeling risk of neovascular AMD and GA separately by cataract and cataract surgery status showed ORs similar to those presented in Table 3.

Discussion

We have found strong evidence that cataract surgery is associated with increased odds of the incidence of late AMD. It should be noted that the effect was present when we included all participants at risk of developing late AMD at the beginning of an interval. However, we have noted in the past that greater severity of early AMD at the start of an interval is associated with greater likelihood of developing late AMD by the end of the interval.²⁹ When we add severity of AMD at the beginning of an interval to the model we described, the ORs for incident late AMD are only slightly diminished. Nevertheless, this suggests that cataract surgery may be a more important risk factor in those who are already at relatively high risk of incident late AMD. We found that the greater the length of time since cataract surgery, the greater the odds were of incidence of late AMD. However, when we compare the longer interval (5 years) with the shorter interval (<5 years) those odds are not significantly different from each other. A larger number of cases might render those odds to be significantly different.

We did not find increased odds of early AMD to be significantly related to cataract, as we had in our earlier publication with shorter follow-up.¹⁶ This may be because in the previous paper we used the more severely affected eye for analyses, whereas in the current paper we

included each eye in the analyses separately. It is also possible that this is due to the different method of analysis used in the current paper (time updating using GEE approach), which we chose because it makes the fullest use of all our longitudinal data with regard to updating of potential risk factors as well as the outcome. Also, including an age² term as we did in the current paper may better model the effects of the vulnerability of biological aging on the eye, as the relationship of age with cataract and AMD incidence is not linear.

The analytic paradigm we used in this paper that differs from our prior approaches was to model the cataract variable as ordered categories. This permitted the examination of the different odds associated with classes of the exposure and permits data from individuals to be considered for the incremental risk category.

Our findings should be viewed with some caution. First is the possibility that mortality has affected our findings. Mortality may be related to the risk factors and outcomes under study. It is unclear whether cataract or cataract surgery on their own are significant biomarkers of aging such that selective survival has altered our finding. While some studies suggest this, others do not. To the extent that this may be true, it is likely to have caused us to underestimate the relationship (OR) of cataract and cataract surgery with late AMD. Larger samples than ours and possibly longer follow-up may give further evidence as to the likely causal or at least temporal association of cataract with early AMD, but as with late AMD, an effect may still be underestimated. In addition, persons who were excluded by design were those who had AMD. We also noted that those who were excluded were more likely to have had cataract or cataract surgery. It is possible that this has led to an underestimate of the relationships of cataract and cataract extraction to late AMD. It is also possible that unknown confounders that we did not adjust for may have influenced our findings.

The large majority of our participants with cataract surgery had lenses implanted at the time of surgery, so we were unable to examine the possibility of different effects of aphakia versus lens implants on AMD. We did not have specific information on the type of implant used; most of our participants had surgery after the introduction of lenses with some UV light blocking ability. Thus, we could not examine a modifying effect of UV light blocking agents (or specifics of cataract surgery techniques) on our findings.

In summary, we have found a substantial effect of cataract surgery on the incidence of late-stage AMD. This finding builds upon past evidence. Further, our data suggest that time since surgery may further increase the risk. If this finding is replicated in other studies and is found to be significant, it would suggest that cataract surgery ought to be put off for as long as is compatible with acceptable vision for patients who are at increased risk of developing late AMD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 2

Odds of Early Age-related Macular Degeneration by Cataract Outcome, and Accounting for Length of Time Since Cataract Surgery.

Cataract Outcome	Age and Sex Adjusted* (n=3306)				Genes Adjusted† (n=2949)				Maximally Adjusted‡ (n=3275)			
	OR	95% CI	P	Overall P	OR	95% CI	P	Overall P	OR	95% CI	P	Overall P
No Cataract	0.89	(0.74, 1.07)	0.20	0.33	0.94	(0.78, 1.13)	0.50	0.65	0.90	(0.75, 1.08)	0.27	0.45
1 Cataract	Ref											
Cataract Surgery	1.06	(0.82, 1.38)	0.64		1.07	(0.81, 1.42)	0.64		1.06	(0.81, 1.38)	0.70	
	Age and Sex Adjusted* (n=3298§)				Genes Adjusted† (n=2943§)				Maximally Adjusted‡ (n=3268§)			
	OR	95% CI	P	Overall P	OR	95% CI	P	Overall P	OR	95% CI	P	Overall P
No Cataract	0.89	(0.74, 1.06)	0.20	0.26	0.94	(0.77, 1.13)	0.50	0.56	0.91	(0.76, 1.09)	0.29	0.22
1 Cataract	Ref											
Cataract Surgery												
<5 years	0.93	(0.66, 1.30)	0.67		0.95	(0.66, 1.36)	0.76		0.88	(0.62, 1.25)	0.48	
5 years	1.31	(0.89, 1.91)	0.17		1.28	(0.85, 1.92)	0.24		1.38	(0.94, 2.05)	0.10	
5 years vs. <5 years	1.41	(0.87, 2.27)	0.16		1.35	(0.81, 2.25)	0.25		1.57	(0.96, 2.57)	0.07	

AMD, age-related macular degeneration; CI, confidence interval; OR, odds ratio; P, P value.

* Adjusted for age, age², and sex.

† Adjusted for age, age², sex, *CFH* and *ARMS2*.

‡ Adjusted for age, age², sex, education, smoking status, history of heavy drinking, history of cardiovascular disease, history of diabetes, and diastolic blood pressure.

§ Numbers are smaller because some participants did not have information available on time since cataract surgery.

Table 3

Odds of Late Age-related Macular Degeneration by Cataract Outcome, and Accounting for Length of Time Since Cataract Surgery.

Cataract Outcome	Age and Sex Adjusted* (n=3618)				Genes Adjusted† (n=3233)				Maximally Adjusted‡ (n=3585)			
	OR	95% CI	P	Overall P	OR	95% CI	P	Overall P	OR	95% CI	P	Overall P
No Cataract	0.85	(0.55, 1.32)	0.47	0.008	0.83	(0.52, 1.32)	0.43	0.01	0.84	(0.54, 1.32)	0.46	0.01
1 Cataract	Ref											
Cataract Surgery	1.93	(1.28, 2.90)	0.002		1.91	(1.23, 2.95)	0.004		1.96	(1.28, 3.02)	0.002	
	Age and Sex Adjusted* (n=3605§)				Age and Sex Adjusted* (n=3605§)				Maximally Adjusted‡ (n=3574§)			
	OR	95% CI	P	Overall P	OR	95% CI	P	Overall P	OR	95% CI	P	Overall P
No Cataract	0.85	(0.55, 1.33)	0.48	0.02	0.83	(0.52, 1.33)	0.43	0.03	0.85	(0.54, 1.33)	0.47	0.02
1 Cataract	Ref											
Cataract Surgery												
<5 years	1.79	(1.10, 2.91)	0.02		1.83	(1.10, 3.06)	0.02		1.81	(1.09, 3.01)	0.02	
5 years	2.19	(1.30, 3.68)	0.003		2.07	(1.18, 3.65)	0.01		2.28	(1.32, 3.95)	0.003	
5 years vs. <5 years	1.22	(0.69, 2.17)	0.49		1.13	(0.61, 2.10)	0.70		1.26	(0.69, 2.28)	0.45	

AMD, age-related macular degeneration; CI, confidence interval; OR, odds ratio; P, P value.

* Adjusted for age, age², and sex.

† Adjusted for age, age², sex, CFH and ARMS².

‡ Adjusted for age, age², sex, education, smoking status, history of heavy drinking, history of cardiovascular disease, history of diabetes, and diastolic blood pressure.

§ Numbers are smaller because some participants did not have information available on time since cataract surgery.