Progression of Age-Related Macular Degeneration After Cataract Surgery

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Objective: To document age-related macular degeneration (AMD) progression after cataract surgery.

Methods: Surgeons prospectively enrolled patients with nonneovascular AMD who were awaiting cataract surgery. Fluorescein angiography was performed preoperatively and at the postoperative week 1, month 3, and month 12 visits. Incidence of neovascular AMD development within 12 months after operation was the primary outcome measure.

Results: A total of 108 subjects were enrolled. Of 86 eyes with preoperatively photographically confirmed nonneovascular AMD, 71 had gradable images by month 12. Neovascular AMD was observed in 9 of 71 eyes (12.7%; 95% confidence interval, 6.0%-22.7%). The progression rate between week 1 and month 12 decreased to 3 of 65 eyes (4.6%; 95% confidence interval, 1.0%-12.9%) after excluding 5 neovascular events identified on the postoperative week 1 visit and 1 case with missing photographs at this visit.

Conclusion: The low incidence rate of neovascular AMD development between 1 week and 1 year after cataract surgery did not support the hypothesis that cataract surgery increases the risk of AMD progression. Several eyes appeared to have disease progression on postsurgery week 1 fluorescein angiograms, suggesting that many cases of presumed progression to neovascular AMD following cataract surgery may have been present prior to cataract surgery, but not recognized owing to lens opacity.


Cataract is the leading cause of blindness globally.\(^1\) Associated with aging, it caused blindness in 17.6 million people and accounts for 48% of blindness worldwide.\(^1\) Surgery is the most effective and common treatment to restore vision in people with cataract. Age-related macular degeneration (AMD) is the leading cause of blindness in people aged 65 years or older in the United States.\(^2,3\) Because both conditions are strongly age-related, many individuals with cataract also have AMD. There has been a long-standing controversy among clinicians as to whether cataract surgery is contraindicated in eyes with nonneovascular AMD.\(^3,8\) A major concern has been whether cataract surgery increases the risk of progression to neovascular AMD in eyes at risk of progression such as those with intermediate AMD (extensive medium-sized drusen, large drusen, or nonfoveal geographic atrophy).

While some researchers observed higher rates of advanced-stage AMD in eyes with a history of cataract surgery,\(^9,12,17\) others have cited an association between progression to neovascular AMD and performance of cataract surgery.\(^9,13,17\) Van der Schaft et al.\(^10\) observed more frequent disciform scar formation secondary to AMD in postmortem pseudophakic eyes when compared with age-matched phakic eyes. In 3 population-based studies,\(^11\) higher prevalence of advanced AMD (neovascular AMD and geographic atrophy) was found among nonphakic eyes. Researchers from the Beaver Dam Eye Study and the Blue Mountain Eye Study reported that a history of cataract surgery at baseline increased the risk of advanced AMD at the 5-year examination 3- to 10-fold.\(^13-15\) A positive association between cataract surgery and 10-year incidence of advanced AMD from the Blue Mountain Eye Study was also reported.\(^16\) These observations have led many to suspect a cause-and-effect relationship between cataract surgery and incident neovascular AMD; however, observational studies have methodological limitations in controlling bias compared with prospective studies.

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Additional findings from case series have suggested that patients with AMD...
who have cataract surgery are at higher risk for AMD progression.6,17 Pollack et al8 followed up 47 subjects who had bilateral symmetric stages of nonneovascular AMD and underwent cataract surgery in only 1 eye. Color fundus photographs and fluorescein angiography were done preoperatively and postoperatively up to 1 year. The rate of progression to neovascular AMD within 1 year of surgery was higher in the eyes that received surgery (19%) when compared with the observed fellow eyes (4.3%). However, selection of the eye to undergo cataract surgery was not random, potentially permitting bias into the selection. It is possible that a systematic bias occurred that entailed selecting the eye at greater risk of progression or already harboring neovascular AMD to undergo the cataract surgery.

Alternatively, some studies have not provided support for the hypothesis that cataract extraction hastens progression of AMD.10,12 Armbrecht et al18 followed up 2 groups for the hypothesis that cataract extraction hastens progression of AMD. One group consisted of 40 patients who were scheduled for cataract surgery and a control group of 43 patients with AMD who did not have plans for cataract surgery. No progression to neovascular AMD was observed in the study eyes, while 2 cases of progression to neovascular AMD were observed in the control eyes. The Age-Related Eye Disease Study compared phakic nonneovascular eyes that underwent cataract surgeries during study follow-up with a group of eyes that did not in 342 participants. Participants were matched by supplement treatment, gender, age, baseline AMD characteristics, and years of follow-up. No increase in rates of progression to neovascular AMD were identified following cataract surgery when compared with individuals who remained phakic.20 In a case-control study of 499 subjects with recent-onset unilateral nonneovascular maculopathy, Sutter and colleagues20 found no differences in the phakic status of the eyes with neovascular AMD vs the fellow eyes without neovascular AMD. A recent retrospective case-control study also did not find a difference between the pseudophakic and phakic groups with early AMD in the development of neovascular AMD within 1 year of cataract surgery.21

The literature to date provides inconsistent information regarding a relationship between cataract surgery and progression to neovascular AMD. With more than 1.6 million cataract operations performed annually in the United States,22 some of which likely occur in the 8 million individuals with intermediate-stage AMD, there is sufficient reason to explore this issue further. The aim of this article is to evaluate the course of AMD during a 1-year period following cataract surgery in individuals with nonneovascular AMD confirmed prior to cataract surgery.

METHODS

SUBJECTS AND PROCEDURES

The study protocol was approved by the Johns Hopkins University Institutional Review Board. Outpatients at the Wilmer Eye Institute, Baltimore, Maryland, undergoing preoperative cataract surgery assessments primarily by 1 cataract surgeon (W.J.S.) between November 2000 and April 2002 were invited to participate if they had nonneovascular AMD and cataract surgery was planned for within 3 months of the examination. The AMD features at the time of enrollment could consist of any of the following in the absence of choroidal neovascularization (CNV) or disciform scarring, based on clinical examination conducted by the cataract surgeons: drusen, geographic atrophy, or any other retinal pigment epithelium abnormalities judged to be consistent with the diagnosis of AMD. Exclusion criteria included compromised ocular media (with the exception of lens opacity) that would prevent reasonable quality photography in the preoperative eye. Only 1 eye of each subject was eligible for enrollment. Written consent was obtained from all participants before enrollment.

Clinical examination, stereoscopic film color fundus photographs of field 1 and 2, fluorescein angiography transiting the study eye, and lens photographs were performed preoperatively and at visits 1 week, 3 months, and 12 months postoperatively. Indocyanine green (ICG) angiography of the study eye was performed at the preoperative and 1-week postoperative visits to identify CNV, potentially through the cataract, and to identify any questionable cases of neovascular AMD in the immediate postoperative period via the near infrared imaging of ICG fluorescence. Phacoemulsification with the placement of a posterior chamber intraocular lens was performed according to the cataract surgeon’s standard care of performing phacoemulsification.

GRADING OF PHOTOGRAPHIC MATERIALS

All retinal and lens images were graded independently by 2 graders. Postoperative week 1 images were specifically obtained because of the often-compromised quality of preoperative fundus images in the setting of a visually significant cataract. These early postoperative images were presumed to still reflect the preoperative AMD macular status visualized through improved ocular media. When grading the week 1 images, graders did not have access to the preoperative images or to their previous assessments to eliminate the possible influence of the preoperative grading on week 1 assessment. In contrast, prior to grading month 3 and month 12 images, graders were required to review preoperative and week 1 images and the corresponding case report forms to capture any suspicion of progression. Eyes were classified by their most advanced AMD feature in the following order: neovascular AMD, geographic atrophy, or drusen and/or pigmentary abnormalities. Size (in disc areas [DA]) and location of neovascular lesions or geographic atrophy were also graded.

DATA COLLECTION AND ANALYSIS

Demographic data, medical history, and medication use information were collected. Information on cataract surgery, intraoperative and postoperative complications, and ocular examinations, including Snellen visual acuity measurements, was extracted from medical records. All acuities were converted to the logMAR scale for analyses and then back to Snellen equivalents for reporting.

Included in the analysis were study eyes with photographically confirmed preoperative nonneovascular AMD, ie, eyes with drusen, geographic atrophy, or eyes without drusen but with AMD features in the fellow eye. The primary outcome was the progression to neovascular AMD by the 12-month examination. Progression of AMD was defined as going from not having to having neovascular AMD, based on photographic evidence from color fundus photographs and fluorescein angiography. Progression of geographic atrophy was considered in each of the following circumstances: (1) incident geographic atrophy in an eye with-
out neovascular AMD or geographic atrophy at the preoperative visit or (2) in an eye with geographic atrophy preoperatively in the absence of neovascular AMD or extension of nonfoveal geographic atrophy present preoperatively to foveal center involvement by the postoperative month 12 visit. Progression rates were calculated and their exact binomial confidence intervals (CIs) were estimated using SAS version 9.1 (SAS Inc, Cary, North Carolina).

RESULTS

Of 108 subjects enrolled, 86 were included in this analysis. Twenty-two participants were excluded for lack of fluorescein angiograms owing to fluorescein allergy at enrollment (1); ungradable preoperative fundus images (1); absence of AMD on review of baseline images (4, pattern dystrophy, and 4, pathologic myopia that presumably had been misinterpreted as AMD by the cataract surgeons); absence of preoperative AMD in the study eye and no confirmed AMD in the fellow eye (3); or definite (4) or probable (5) neovascular AMD on the preoperative images (Figure 1). Two eyes were retained in the analysis cohort despite the absence of AMD features or ungradable images to determine AMD in the study eye at the presurgery or week 1 postsurgery visits because the fellow eyes of these individuals had either neovascular or nonneovascular AMD. Another 11 eyes for which preoperative AMD status could not be determined owing to compromised image quality in the presence of cataract were also retained in the analysis cohort because AMD was identified on the postoperative week 1 images.

BASELINE CHARACTERISTICS AND SURGICAL COMPLICATIONS

The study cohort consisted of participants with a median age of 76.0 years (range, 58 to 92 years) at enrollment; 48% were women and 97% were white (not Hispanic) (Table 1). Use of systemic corticosteroids, aspirin, warfarin, and antihypertension medication are presented in Table 1. Nearly two-thirds of the participants were current or former cigarette smokers. The median preoperative visual acuity (Snellen equivalent) of the study eyes was 20/50 (range, ∃20/40 to 20/400) (Table 1).

Characteristics of AMD of the 86 study eyes included in the analyses and the fellow eyes of these participants are presented in Table 2. All except 2 study eyes had photographic confirmation of nonneovascular AMD at the preoperative visit. The fellow eyes had a similar distribution of AMD characteristics, with the exception that 12% of fellow eyes manifested neovascular AMD. Surgery complications were few; there was 1 intraoperative posterior capsular tear with vitreous loss and more mild iris injury and resuturing of the surgical incision to repair a wound leak from the posterior chamber intraocular lens, with sutures performed postoperatively for 1 eye.

PROGRESSION TO CNV WITHIN 12 MONTHS

Of the 86 eyes with nonneovascular AMD at baseline, 71 (83%) had photographic documentation of AMD status at the 12-month visit and 66 (77%) completed a clinical

Figure 1. Example of a case enrolled in which the enrolling ophthalmologist did not identify any choroidal neovascularization (CNV), but the reading center graders identified CNV at baseline. The top row of images shows a hazy color fundus photograph (A), hazy bright fluorescence judged by reading center graders to be caused by CNV (B), and hazy bright fluorescence judged by reading center graders to be leakage from CNV (C). D, One week after cataract surgery, obvious CNV recurring at the edge of a prior area of laser treatment is identified. E, Bright fluorescence from CNV adjacent to hypofluorescence of a prior area of laser treatment is seen. F, Staining of laser treatment shows additional leakage from recurrent CNV along the foveal side of the laser-treated area.
examination at this visit (Table 3). Four deaths occurred during the follow-up period. Fifteen (17%) eyes had to be excluded from the analysis owing to missing or ungradable images at follow-up.

Of the 71 eyes at risk for neovascular AMD at the preoperative assessment, for which follow-up images demonstrating AMD status were available through month 12, neovascular AMD was observed in 9 eyes (12.7%; 95% CI, 6.0%-22.7%) by 12 months, including 1 that was graded as probable rather than definite neovascular AMD at the month 12 visit, all with large drusen (≥125 µm). The progression to neovascular AMD during the same period of time among the phakic contralateral eyes was 3 of 65 cases (4.6%; 95% CI, 1.0%-12.9%).

The progression to neovascular AMD during the same period of time among the phakic contralateral eyes was investigated. Of the 86 contralateral eyes of the study eyes with nonneovascular AMD preoperatively, 36 were nonphakic at enrollment, 6 had neovascular AMD, and 11 had incomplete information either at enrollment or follow-up. Neovascular AMD developed in only 1 eye (3.0%) at 3 months, of the remaining 33 phakic eyes with absence of neovascular AMD at the 12-month 12 visit. Five cases were initially identified at the week 1 assessment (Figure 2), none at month 3, 3 at month 12 (Figure 3), and 1 at month 12, but they had missed the week 1 and month 3 postoperative visits, so the date of incident neovascular AMD could not be accurately captured. The rate of confirmed progression to neovascular AMD between week 1 and month 12 was 3 of 65 cases (4.6%; 95% CI, 1.0%-12.9%).

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graphic atrophy preoperatively, and a subfoveal neovascular AMD lesion no greater than 4 DA that was diagnosed at month 12. It is unclear whether neovascular AMD was present in this eye at the week 1 or month 3 visits owing to missing photographs at both visits. It is possible an atrophic disciform lesion may have been present preoperatively and was misinterpreted as foveal geographic atrophy posterior to a cataract.

In the 5 eyes in which neovascular AMD was not observed at the preoperative visit by the clinician or the reading center, but was confirmed on week 1 postoperative color and fluorescein angiogram images at the reading center, ICG angiograms at the preoperative and postoperative week 1 visit did not show a definite plaque or hot spot. Only 1 eye was graded as having a questionable plaque at the preoperative visit, but when the cataract was removed and the image clarity improved, no plaque or hot spot was noted at postoperative week 1. In 6 other eyes, ICG angiograms had plaque or hot spots either at the preoperative visit or postoperative week 1, even though no neovascular lesion was noted on fundus photographs or fluorescein angiograms in these eyes throughout follow-up in the study.

At the 12-month visit, visual acuity in the study eyes was 20/40 or better in 83% of the eyes and 20/100 to 20/200 in 7% of the eyes. Visual acuity improved by 2 or more lines in 83% of the eyes. Only 1 eye (1.4%) experienced loss in visual acuity greater than 1.5 lines. A CNV of 5 DA was identified immediately after the surgery in this eye.

**PROGRESSION OF GEOGRAPHIC ATROPHY**

The cohort of 86 subjects at risk for neovascular AMD was further refined to include only subjects without preoperative evidence of geographic atrophy and with photographic documented geographic atrophy status through month 12. Twenty-five subjects with the following conditions were removed from this analysis: preoperative geographic atrophy in any macular location (8), no available images at any follow-up visits (4), no geographic...
atrophy prior to month 12 and missing or ungradable images at the month 12 examination (6), or development of neovascular AMD at follow-up and no geographic atrophy prior to neovascular AMD (7).

Only 2 of 61 eyes (3.3%; 95% CI, 0.4%-11.4%) had definite or probable geographic atrophy by month 12; 1 was no greater than 1 DA at week 1 and its size remained stable through month 12, and 1 had ungradable photographs at week 1 and questionable geographic atrophy of a size no greater than 2 DA at month 3. This eye developed neovascular AMD at month 12. Therefore, there were no confirmed cases of incident geographic atrophy developing between 1 week and 12 months postoperatively.

Five of 8 eyes with confirmed preoperative geographic atrophy could be evaluated through the month 12 visit. Geographic atrophy progressed in 3 eyes, including extension to the foveal center in 1 eye and increasing in size by at least 1 DA in 2 eyes. Progression of geographic atrophy by either of these parameters was noted between the preoperative and postoperative week 1 visits in 2 of these 3 cases. In both cases, geographic atrophy could have existed before cataract surgery, but may not have been detected from the photographs because of lens opacity before the removal of cataract. Geographic atrophy progression was found between 1 week and 12 months after surgery in only 1 eye in which the size of geographic atrophy involving the foveal center increased from 6 DA at week 1 to 9 DA at month 3.

**COMMENT**

Our follow-up study of cataract surgery in eyes with non-neovascular AMD identifies a low rate of AMD progression during the first year after cataract surgery. Only 3 of 65 eyes (4.6%) that were free of neovascular AMD at the preoperative and postoperative visit at week 1 developed neovascular AMD within 12 months after surgery. During the same period of time, no new cases of geographic atrophy developed in any of the 59 eyes in which geographic atrophy was absent prior the cataract surgery and 1 week after cataract surgery. Of the 5 eyes with geographic atrophy at a presurgery visit and gradable im-

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**Figure 3.** Example of no choroidal neovascularization (CNV), noted by ophthalmologist or reading center graders at baseline or at week 1, with CNV identified by reading center graders at month 12. The top row shows a color fundus photograph (A) that is hazy from cataract but shows no CNV, as documented on fluorescein angiography in the early and late phase (B and C). One week after cataract surgery, fundus photograph (D) and early- and late-phase fluorescein angiogram frames (E and F, respectively) show staining of drusen and retinal pigment epithelium abnormalities, but no leakage. One year after cataract surgery, a color fundus photograph shows no obvious CNV (G), but fluorescein angiography in the early and late phases (H and I, respectively) shows a small area of leakage caused by CNV just inferotemporal to the foveal center.
ages at postsurgery visits, only 1 had an increase in the size of geographic atrophy between week 1 and month 12, and no case with foveal sparing geographic atrophy at the preoperative and week 1 postsurgical visits progressed into the center point of the macula at follow-up.

More cases of AMD progression, either the development of neovascular AMD, development of geographic atrophy, or progression in geographic atrophy, were observed between the preoperative visit and the immediate postsurgical visit. In eyes free of neovascular AMD preoperatively, 5 cases of neovascular AMD were identified on images with clear media 1 week after surgery. For these 5 cases, the preoperative photographs were taken 0 to 15 days before the surgery. It was unlikely that neovascular AMD developed in the week following cataract surgery, based on the characteristics of the lesions identified, including their sizes and location. It was more likely that these lesions existed prior to the cataract surgery and were not captured by the preoperative images in the presence of opaque media. For the same reasons, the geographic atrophies that were found to have progressed at week 1 postsurgically in 3 eyes (including 1 new lesion, 1 lesion that increased in size, and 1 lesion extending into the fovea), were also more likely to be preexisting conditions and were overlooked at the preoperative assessment.

Our findings suggest that previous reports of the association or progression of nonneovascular AMD to advanced AMD after cataract surgery could be biased with the absence of immediate preoperative and postoperative fluorescein angiography to rule out preexisting neovascular AMD or geographic atrophy. Subtle signs of neovascular AMD or geographic atrophy, even on an angiogram, may be obscured by lens opacity just prior to cataract surgery. In such cases, the neovascular disease or the geographic atrophy may contribute to the individual’s vision loss, and this may erroneously be ascribed to the cataract and contribute to a decision to proceed with cataract surgery. Diagnosis of these late features of AMD was hampered on clinical examination as well as on review of fundus images at an experienced reading center. In our study, the AMD status of the study eye changed from absence of neovascular AMD or geographic atrophy to presence of either manifestation of late AMD in 6 eyes of our cohort on review of the immediate postoperative fundus photographs and fluorescein angiograms. We have revised the 12-month AMD progression rates in our study to exclude these eyes as well as 2 eyes with unknown status at 1 week, resulting in a rate of 4.6% for progression to neovascular AMD and 0% for progression to geographic atrophy. If immediate postoperative photographs had not been done and these eyes had been considered incident cases, the estimated rates of progression to advanced AMD between the presurgery and 12 months postsurgery visits would be much higher; the rate of progression to neovascular AMD was 12.7% (9 of 71 cases), and the rate of progression to geographic atrophy was 3.3% (2 of 61 cases). This scenario may explain, in part, why the 12-month CNV progression rate of 4.6% in this study was lower than the 19% incidence of neovascular AMD progression reported by Pollack and colleagues.7 While all subjects in Pollack and colleagues’ study had either preoperative or immediate postoperative fluorescein angiography to confirm the absence of CNV, only some subjects included in Pollack and colleagues’ series had fluorescein angiography within 1 week after cataract surgery to confirm absence of neovascular AMD.

To obtain an expected rate of progression in the general population similar to ours, we applied the Age-Related Eye Disease Study severity score23 to our 71 subjects at risk for neovascular AMD and estimated the 1-year progression rate. With only 7 subjects with a severity score of 3 and only 5 subjects with a severity score of 4, we would have expected a progression rate of less than 5% after 1 year.

The strengths of this study include its prospective design, with carefully documented stereoscopic color fundus photographs and fluorescein angiograms immediately before and after cataract surgery and their evaluation by experienced graders who adhere to uniform standards of image interpretation. Most findings published to date that suggested a possible association between cataract surgery and progression of AMD originated from population-based studies, and these studies were not designed prospectively to address the question of whether the removal of cataract promotes progression of earlier forms of AMD to late forms of AMD. Of the few prospective follow-up studies in patients with earlier stages of AMD, this study is the only one, to our knowledge, that had color fundus photographs and fluorescein angiograms.

Table 4. Characteristics of Neovascular AMD Lesion at the Time of First Observation in Surgery Eyes

<table>
<thead>
<tr>
<th>Subject</th>
<th>Most Advanced AMD at the Preoperative Visit</th>
<th>Characteristics of CNV When First Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neovascular AMD observed 1 wk after cataract surgery</td>
<td>1</td>
<td>Drusen, ≥125 µm</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Drusen, ≥125 µm</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Drusen, ≥125 µm</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Drusen, 64-124 µm</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Drusen, cannot grade</td>
</tr>
<tr>
<td>Neovascular AMD observed 12 mo after cataract surgery and no CNV 1 wk after surgery</td>
<td>6</td>
<td>Drusen, ≥125 µm</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Drusen, ≥125 µm</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Drusen, ≥125 µm</td>
</tr>
<tr>
<td>CNV observed 12 mo after cataract surgery and missing in week 1 and month 3 photographs</td>
<td>9</td>
<td>Foveal geographic atrophy</td>
</tr>
</tbody>
</table>

Abbreviations: AMD, age-related macular degeneration; CNV, choroidal neovascularization; DA, disc area. *Image quality precludes determination of the presence of drusen.
grams on all subjects both immediately before and after cataract surgery. The immediate postoperative images allowed the elimination of cases of advanced AMD apparently not noted preoperatively in the presence of cataract, and consequently led to a more accurate estimation of the true incidence of AMD progression following cataract surgery. In addition, cataract surgeons in this study were responsible for diagnosing and enrolling subjects who they thought had AMD. This study design is more likely to mimic the real-life clinical scenario of cases diagnosed as having AMD by a cataract surgeon when cataract surgery is planned for that patient.

The limitations of this study include the small size of the cohort defined to be at risk and evaluated for the critical endpoints of AMD progression and the follow-up duration being limited to 12 months. Fifteen eyes (17%) at risk for neovascular AMD had to be excluded because their post-surgery AMD status at 12 months could not be determined owing to unavailable or ungradable images. The preoperative or immediate postoperative images indicated that 4 of 15 eyes (27%) had geographic atrophy, 6 (40%) had drusen of 125 µm or greater, and 5 had drusen of 64 to 124 µm; none had drusen of 63 µm or less. Compared with eyes included in the analyses, these eyes may be at higher risk for neovascular AMD and therefore may have led to a higher rate of neovascular AMD if the follow-up images were available. Another limitation of the study is the lack of a control group that remains phakic; however, our findings still strongly suggest that there is no great increase in the risk for neovascular AMD and therefore may have led to a more accurate estimation of the true incidence of AMD progression following cataract surgery because of the relatively low rates of AMD progression observed in participants considered at risk for AMD progression based on their preoperative fundus characteristics who underwent cataract surgery and were carefully monitored for disease progression.

Only a small percentage of study participants with AMD had definite progression to either neovascular AMD or geographic atrophy within 1 year after cataract surgery when eyes were carefully monitored with immediate preoperative and postoperative fundus photographs and fluorescein angiograms. Our findings do not support the hypothesis that cataract surgery accelerates the progression of AMD.

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