Is Pseudophakia a Risk Factor for Neovascular Age-Related Macular Degeneration?

Florian K. P. Sutter, Moreno Menghini, Daniel Barthelmes, Johannes C. Fleischbauer, Malaika M. Kurz-Levin, Martina M. Bosch, and Horst Helbig

PURPOSE. To examine the possible association between pseudophakia and neovascular age-related macular degeneration (AMD).

METHODS. Reports of all patients undergoing fluorescein angiography in the authors' department over a 6-year period were retrospectively reviewed. Four hundred ninety-nine patients with recent onset of neovascular AMD in one eye and early age-related maculopathy (ARM) in the fellow eye were included in the study. Lens status (phakic or pseudophakic) in both eyes at the time of onset of neovascular AMD and the time between cataract surgeries (if performed) and onset of neovascular AMD were determined.

RESULTS. There was no significant difference in lens status between early AMD and fellow eyes with early ARM (115/499 [23.0%] vs. 112/499 [22.4%] pseudophakic; P = 0.88, odds ratio 1.035, 95% CI 0.770–1.391). Subgroup analysis revealed no difference between the groups with large drusen, small drusen, or pigmentary changes only (resectively, 20.3% vs. 19.6% pseudophakic, P = 0.92; 20.5% vs. 23.3% pseudophakic, P = 0.84; 33.3% vs. 31.7% pseudophakic, P = 1.0). Pseudophakic eyes with neovascular AMD had not been pseudophakic for a significantly longer period at the time of onset of neovascular AMD than their pseudophakic fellow eyes at the same time point (225.9 ± 170.4 vs. 209.9 ± 158.2 weeks, P = 0.27).

CONCLUSIONS. The results do not support the hypothesis that pseudophakia is a major risk factor for the development of neovascular AMD. (Invest Ophthalmol Vis Sci. 2007;48:1472–1475) DOI:10.1167/iovs.06-0766

Cataract and age-related maculopathy (ARM) are among the most common diseases that affect elderly people. Ninety percent of patients older than 70 years have some degree of cataract.1 Thus, cataract surgery is the most commonly performed operation worldwide, with an estimated >2 million procedures performed in the United States per year. Up to 90% of people older than 80 years have ARM.2,3 The advanced stages of the disease, termed age-related macular degeneration (AMD), are the leading cause of legal blindness in Western countries.4,5

Recently, serious concerns have been raised about whether cataract surgery may cause or trigger late-stage AMD.6 Various pathophysiological mechanisms have been discussed to explain a possible positive correlation between cataract surgery and late-stage AMD, including light toxicity during the operation,7 surgical trauma, or inflammatory factors after surgery,8 and increased light exposure after removal of the crystalline lens.9 Several large epidemiologic studies report some degree of positive association of lens opacities, cataract, or cataract surgery with AMD.10–13 Such a causative relationship would have widespread clinical, economic, and possibly legal implications. Cataract surgery would become a “gamble”6 for surgeons and patients alike. In the present study, we investigated the possible relationship of pseudophakia and neovascular AMD, in a retrospective case–control study.

METHODS. This study complied with the tenets of the Declaration of Helsinki. The database of fluorescein angiographies in our hospital from July 1998 to April 2004 was analyzed for patients with newly diagnosed neovascular AMD in one eye and no signs of advanced AMD (neovascular AMD, geographic atrophy, or fibrotic scar) in the fellow eye. One eye of each patient was defined as the “case eye,” the fellow eye in the same patient without advanced AMD was defined as the “control eye.” Accordingly, each patient in this study was equally represented in both groups, and the groups were therefore exactly matched for known and unknown systemic risk factors. Exclusion criteria included eyes with choroidal neovascularization due to conditions other than AMD and cases in which insufficient information was available. Patients with visual symptoms of neovascular AMD (metamorphopsia and/or visual loss) for >3 months before fluorescein angiography were excluded, to eliminate “old” cases of neovascular AMD with undetermined time of onset. Lens status (phakic or pseudophakic) and date of cataract surgery (if performed) was determined for each eye by correspondence with the referring ophthalmologist in cases in which the information was missing in the files.

To exclude eyes in which neovascular AMD may have been present before surgery and to test the robustness of the study findings, we performed an additional analysis after exclusion of 12 cases with <3 months between surgery and diagnosis of neovascular AMD.

Different clinical subtypes of ARM are known to be at different risk for the progression to neovascular AMD.14 To exclude that the heterogeneity of the study group may influence the overall result, subgroup analysis was performed. For each patient the type of early AMD (small drusen, large drusen, or pigmentary changes only) in the eye without neovascular AMD was noted from the angiogram reports. When this information was missing, color fundus photographs were assessed again. Patients were grouped based on the findings in the fellow eye without advanced AMD, because in many eyes with recent-onset neovascular AMD, underlying early ARM changes cannot be recognized due to edema or exudation, but there is a high degree of symmetry of early ARM changes between fellow eyes.15,16 Patients for whom grading was not possible (lack of or insufficient quality of fundus photographs) were excluded from subgroup analysis (67 patients, 14.4%).

In patients with bilateral pseudophakia the period between cataract operation in each eye and the onset of neovascular AMD in one eye was determined.

From the Department of Ophthalmology, University Hospital, Zurich, Switzerland.

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Corresponding author: Florian K. P. Sutter, Department of Ophthalmology, University Hospital, CH-8049 Zurich, Switzerland; florian.sutter@usz.ch.
Pseudophakia and Neovascular AMD

There was no significant difference in lens status between eyes with neovascular AMD and fellow eyes without advanced AMD within the entire study population (23.0% vs. 22.4% pseudophakic; odds ratio 1.035, 95% CI 0.770 –1.391, \( P = 0.88 \)) nor in any of the subgroups analyzed. To exclude cases with preexisting neovascular AMD diagnosed only after surgery and to test the robustness of the study findings, we performed an additional analysis after excluding 12 patients in whom neovascular AMD was detected within 3 months of surgery. This analysis did not find a significant difference between the groups. A detailed analysis is shown in Table 2.

In a separate subgroup analysis we looked at the time interval between cataract surgery and the onset of neovascular AMD in one eye in all patients with bilateral pseudophakia \( (n = 64) \). Pseudophakic eyes with neovascular AMD had been pseudophakic for 225.9 ± 170.4 weeks at the time of onset of neovascular AMD. In their pseudophakic fellow eyes cataract surgery had been performed 209.9 ± 158.2 weeks before. This difference of 16 weeks was not statistically significant \( (P = 0.27) \).

**DISCUSSION**

The question of whether cataract extraction is a risk factor or trigger for development of neovascular AMD is an important issue in today’s clinical practice. On the one hand, surgeons do not want to harm patients by triggering severe vision loss due to neovascular AMD when removing opaque lenses. On the other hand, patients with early ARM and cataracts should not be excluded from cataract surgery (which may significantly improve vision) based only on vague data.

Several different lines of evidence have been raised for a possible role of cataract surgery in triggering advanced AMD. First hints came from small observational case series. In 1979 Blair17 reported six eyes with drusen in which neovascular AMD progressed to a manifest stage and could be improved vision) based only on vague data.

The strongest evidence of a possible deleterious effect of cataract surgery on the development of advanced AMD comes from population-based epidemiologic studies. Pooled data from the Blue Mountain Eye Study and the Beaver Dam Eye

### Table 1. Demographic Data of the Eyes in the Study Population

<table>
<thead>
<tr>
<th></th>
<th>( n )</th>
<th>Age Range</th>
<th>Average Age</th>
<th>Median Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>352</td>
<td>55.75–94.36</td>
<td>77.67</td>
<td>78.13</td>
</tr>
<tr>
<td>Men</td>
<td>174</td>
<td>55.73–92.42</td>
<td>76.65</td>
<td>76.89</td>
</tr>
</tbody>
</table>

Data are expressed in years.

Statistical analysis was performed in commercial software (Instat 3.02; GraphPad Inc., San Diego, CA). The significance level was defined as \( P < 0.05 \). The two-sided Fisher exact test was used for contingency table analysis. In a comparison of pairs of eyes with bilateral pseudophakia, data did not follow a Gaussian distribution. The two-tailed Wilcoxon matched-pairs, signed-ranks test was therefore used for the analysis.

### RESULTS

Between 1998 and 2004, a total of 11,427 fluorescein angiographies were performed and the reports were entered in a commercial database (FileMaker Pro, Santa Clara, CA). The database was searched for the key words “CNV,” “occult,” and “classic.” The key word “neovascularization” was avoided, because this would have included too many “hits” for patients with diabetic retinopathy and other vascular diseases. The search brought up 3154 angiography reports. Six hundred ten reports were selected during the database search because the report said “no sign of CNV . . . .” Some reports were found due to misspellings only (CNV instead of CMV for example) and were excluded. Of the remaining 2544 reports, 1048 were follow-up reports (not new onset of the disease) and were excluded, 1496 were confirmed to be fluorescein angiograms documenting the first diagnosis of recent onset neovascular AMD. Of these 499 cases were unilateral with no late-stage AMD in the fellow eye (no atrophy and no choroidal neovascularization). We analyzed the 1496 unpaired cases as well and compared them with 512 control eyes (partner eye in the same group of patients). These results (no significant difference) have been presented at the 99th annual meeting of the Swiss Ophthalmology Society (Lugano, Switzerland, September 2006).

The present study included 499 patients with recent-onset neovascular AMD in one eye and no signs of advanced AMD in the fellow eye. According to the study design (only pairs of eyes included with one eye in each group), the two groups were identical in demographic characteristics (Table 1) and possible systemic risk factors.

### Table 2. Comparison of Proportions with Pseudophakia between Eyes with and without Neovascular AMD

<table>
<thead>
<tr>
<th>Type of Early AMD</th>
<th>Eyes with Neovascular AMD*</th>
<th>Eyes without Neovascular AMD*</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>( P^\dagger )</th>
</tr>
</thead>
<tbody>
<tr>
<td>All types ( n = 499 )</td>
<td>23.0</td>
<td>22.4</td>
<td>1.035</td>
<td>0.770 –1.391</td>
<td>( P = 0.88 )</td>
</tr>
<tr>
<td>Large drusen ( n = 296 )</td>
<td>22.3</td>
<td>19.6</td>
<td>1.043</td>
<td>0.697 –1.562</td>
<td>( P = 0.918 )</td>
</tr>
<tr>
<td>Small drusen ( n = 73 )</td>
<td>20.5</td>
<td>23.3</td>
<td>0.842</td>
<td>0.388 –1.869</td>
<td>( P = 0.842 )</td>
</tr>
<tr>
<td>Pigmentary changes only ( n = 63 )</td>
<td>33.3</td>
<td>31.7</td>
<td>1.075</td>
<td>0.510 –2.266</td>
<td>( P = 1.0 )</td>
</tr>
<tr>
<td>Female patients ( n = 325 )</td>
<td>24.3</td>
<td>22.8</td>
<td>1.089</td>
<td>0.758 –1.565</td>
<td>( P = 0.712 )</td>
</tr>
<tr>
<td>Male patients ( n = 174 )</td>
<td>20.7</td>
<td>21.3</td>
<td>0.966</td>
<td>0.576 –1.619</td>
<td>( P = 1.0 )</td>
</tr>
<tr>
<td>Subgroup analysis‡ ( n = 487 )</td>
<td>21.1</td>
<td>21.4</td>
<td>0.988</td>
<td>0.727 –1.343</td>
<td>( P = 1.0 )</td>
</tr>
</tbody>
</table>

There are no significant differences in any of the analyzed subgroups.

* Data are the percentage of subjects with pseudophakic eyes.

† Fisher exact test.

‡ Analysis was performed by excluding cases with <12 weeks between surgery and diagnosis of neovascular AMD.
Study showed a substantially increased incidence of late-stage AMD in pseudophakic eyes compared with phakic eyes. This study has limitations, however. Development of neovascular AMD was a rare event, even in the pooled data. Although 11,391 eyes at risk were studied over a 5-year period, only a small number (54 eyes total, 41/11,076 phakic and 13/315 nonphakic eyes) with neovascular AMD was observed. Moreover, epidemiologic surveys cannot differentiate if neovascular AMD is associated with cataract surgery or if it is associated with cataract itself, which was the reason for the cataract surgery. Older small case series have postulated a protective effect of lens opacities for the development of advanced AMD. Recent larger studies, however, found a positive correlation of cataract and AMD, even if corrected for known risk factors, which suggests that cataract and AMD indeed share common risk factors in addition to age, sex, and smoking, such as genetic predisposition, light exposure, and others. Such predisposing factors common in AMD and cataract would necessarily create a correlation between cataract surgery and AMD and can hardly be adequately corrected for in epidemiologic studies. Furthermore, not all subjects studied in epidemiologic studies may be at risk for the disease studied. The comparison of healthy subjects and patients at risk may introduce further biases in epidemiologic studies. Thus, even with the pooled data from two large epidemiologic studies, it remains unclear whether cataract and AMD just share common etiological factors or if cataract surgery indeed may trigger the development of end-stage macular disease.

The best method for answering this question would therefore be a large prospective randomized controlled trial (RCT) with random allocation of eyes for cataract surgery or observation and long follow-up. Such a study, however, is difficult to perform for several reasons. Patients in developed countries have easy access to bilateral cataract surgery. It is therefore not easy to randomize one eye with reduced vision due to cataract for observation for several years. Moreover, a hypothetical sample size calculation shows that such an RCT would require a large number of patients to power the study sufficiently (Table 3).

We therefore attempted to examine this question by means of a retrospective case-control study, as has been done in other fields of medicine, when the effect of risk factors on a disease was tested. When, for example, the role of smoking as a risk factor for lung cancer was studied, primarily no prospective randomized controlled trial was performed. A group of patients with lung cancer was assessed for history of smoking and these data were compared with the smoking habits of a control group without lung cancer. This group should be closely matched for other possible risk factors (e.g., age, sex, genetic risk). The concept of our study can be compared with that of a retrospective twin study about smoking and lung cancer. We compared retrospectively which percentage of eyes with neovascular AMD had a history of cataract surgery (the possible risk factor), compared with their "identical twin" fellow eyes without neovascular AMD.

Table 3. Hypothetical Sample Size Calculation for an RCT

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Natural Risk</th>
<th>Effect (40%)</th>
<th>Eyes Needed per Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>AREDS category 2 5-year follow-up</td>
<td>1.3% 1.82%</td>
<td>8,916</td>
<td></td>
</tr>
<tr>
<td>AREDS category 3 5-year follow-up</td>
<td>18.5% 25.62%</td>
<td>501</td>
<td></td>
</tr>
<tr>
<td>AREDS category 2 2-year follow-up</td>
<td>0.5% 0.7%</td>
<td>23,409</td>
<td></td>
</tr>
<tr>
<td>AREDS category 3 2-year follow-up</td>
<td>8.8% 12.32%</td>
<td>1,196</td>
<td></td>
</tr>
</tbody>
</table>

Data are for a trial powered to detect an effect of +40% with a power of 0.80 and a type I error of 0.05, in the scenarios shown.

Assuming that a causative relationship between cataract surgery and subsequent development of neovascular AMD exists, we would expect a higher prevalence of pseudophakia in eyes with neovascular AMD than in eyes with early ARM. We found no such difference. The results show an odds ratio of 1.035 with a 95% CI of 0.770–1.391, which means that, with a probability of 95%, we can assume that pseudophakia did not increase the risk for the development of neovascular AMD by more than 40% in our study population. Recent analysis of the AREDS (Age-Related Eye Disease Study) data supports this conclusion (Bressler SB et al. IOVS 2006;47:ARVO E-Abstract 2175).

In the present study, we wanted to assess the time of onset of neovascular AMD in our cases as precisely as possible, to determine exactly the relationship with prior surgery. Most of the angiography request forms from referring ophthalmologists contained information about the patient’s history and complaints or the time frame of vision loss. Sometimes patients were referred for fluorescein angiography when scars and exudation in the central retina was an incidental finding during routine examination, and patients did not see the ophthalmologist when the loss of vision occurred. We wanted to exclude the cases in which the disease was newly diagnosed but the time of onset of the disease was undetermined.

One could argue that an exclusion criterion of the time since cataract surgery to fluorescein angiography or since surgery to the onset of symptoms should be introduced to eliminate cases in which neovascular AMD was present but undiagnosed before surgery.

To exclude cases with a short time delay between surgery and onset of neovascular AMD, however, may introduce a bias rather than exclude one. Intraoperative trauma has been suggested as a possible mechanism by which cataract surgery triggers the onset of neovascular AMD. The fluctuation of intraocular pressure during surgery may create breaks in the diseased Bruch’s membrane and trigger subretinal growth of the choroidal vascularization. Cases with onset of choroidal neovascularizations after LASIK have been reported and pressure fluctuations during the use of the keratome seems to be a plausible mechanism in these cases. In these post-LASIK cases the interval was 30.2 ± 19.3 months, but has been reported to be as short as 3 weeks. In elderly cataract patients with ARM and more diffuse disease of Bruch’s membrane and a preexisting proangiogenic stimulus, the onset could be faster than average after LASIK.

To exclude cases with possible preexisting neovascular AMD diagnosed only after surgery and to test the robustness of the study findings, we performed an additional analysis after excluding patients with less than a 3-month delay between surgery and diagnosis of neovascular AMD. This analysis did not reveal a difference between the two groups (Table 2).

The design of the study primarily did not cover how long the possible risk factor (pseudophakia) exerts its effect. We therefore tested a subgroup of 64 patients who were pseudophakic in both eyes, but had neovascular AMD only in one eye. If the risk for neovascular AMD increases with the time an eye is pseudophakic, we have to expect that eyes with neovascular AMD had their cataract surgery earlier than the fellow eye without advanced AMD. We found a difference of 16 weeks between the two groups, which was not statistically significant, which suggests that the risk for neovascular AMD does not increase significantly with the time the eye is pseudophakic.

Based on the design of the study, we are not able to draw any conclusions about atrophic forms of late AMD.

In summary, this large study of paired eyes has its limitations due to the retrospective design and the possibly limited quality of the data, but the strengths are a high number of...
events (eyes with neovascular AMD) being studied, nearly 10 times that of the Blue Mountain Eye Study and the Beaver Dam Eye Study, and a well-matched control group (the fellow eye without advanced AMD). Data from this study do not support the hypothesis that pseudophakia is a major risk factor for the development of neovascular AMD.

References