Cataract Surgery and the Risk of Aging Macula Disorder: The Rotterdam Study

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PURPOSE. To investigate still-controversial associations between prior cataract surgery and aging macula disorder (AMD) in a general population.

METHODS. Baseline lens status and risk of incident AMD (IAMD) were examined in participants of the prospective population-based Rotterdam Study at risk for AMD (n = 6032). Slit lamp examination was used to determine lens status and stereoscopic color fundus photography to determine the presence of AMD. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were estimated with generalized estimating equation (GEE) models. Stratified analyses were also performed for CFH Y402H genotype.

RESULTS. After adjusting for age, sex, follow-up time, and the correlation between eyes, a history of cataract surgery was associated with incident dry late AMD (OR, 3.43; 95% CI, 1.82–6.49). This association remained significant after additional adjustment for smoking status and AMD stage at baseline (OR, 3.44; 95% CI, 1.68–7.08). No statistically significant association was found between prior cataract surgery and the incidence of wet late AMD or early AMD. Homozygous CFH Y402H carriers had higher risks for all types of AMD compared to heterozygotes and noncarriers after cataract surgery, particularly for dry AMD.

CONCLUSIONS. The findings imply that cataract surgery increases the risk of dry AMD, particularly in homozygous CFH Y402H carriers. The risk of AMD progression should be considered before recommending cataract surgery to patients with cataract and early AMD. (Invest Ophthalmol Vis Sci. 2008;49:4795–4800) DOI:10.1167/iovs.08-2066

Cataract and aging macula disorder (AMD) are the two leading causes of visual impairment in the elderly.1–4 Today, cataract surgery is the most commonly performed surgical procedure in ophthalmology, generally resulting in good visual acuity. Studies have shown controversial results regarding the relationship between cataract surgery and the risk of development of late AMD.5–15

In clinical practice, ophthalmologists have observed the occurrence of wet late AMD shortly after cataract surgery. An increased risk of wet AMD after cataract surgery was first suggested by a cross-sectional postmortem histopathologic study.5 Later, finding was confirmed in a clinical setting.5 The 5- and 10-year incidence data of the Beaver Dam Eye Study (BDES) showed that cataract surgery before the baseline examination was associated with a higher incidence of both dry and wet late AMD, as well as with progression of early AMD.7,8 Similar findings were reported by other studies.9–11 In contrast, the Age-Related Eye Disease Study (AREDS; Milton RC, et al. IOVS 2007;48:ARVO E-Abstract 2104)12 and Armbrecht et al.,13 found no clear evidence of increased risk of either dry or wet AMD after cataract surgery. The Visual Impairment Project16 also did not find an association between prior cataract surgery and AMD in multivariate analyses.

In view of our rapidly aging population, greater life expectancy, and the clinical importance of these findings, we also investigated the association between cataract surgery and subsequent AMD in the population-based Rotterdam Study.

METHODS

Population

The Rotterdam Study is a prospective, population-based cohort study of cardiovascular, locomotor, neurologic, and ophthalmologic diseases in the elderly.17

In summary, all inhabitants aged 55 years or older living in Ommoord, a suburb of Rotterdam, the Netherlands, were invited to participate in the study. Of the 10,275 eligible individuals, 7935 (78%) participated. The ophthalmic part of the study started after screening of the participants had begun, leading to 6780 ophthalmic participants—again a 78% response rate. The study was conducted according to the tenets of the Declaration of Helsinki, and the medical ethics committee of the Erasmus University approved the study protocol. A written informed consent was obtained from all participants. Baseline examination, including a standardized home interview and physical examination at the research center took place between March 1990 and July 1993. This was followed by a first follow-up examination from September 1993 to the end of 1994 (response rate 88%), a second from 1997 to 1999 (response rate 80%), and a third follow-up examination from 2000 to the end of 2004 (response rate 74%).
Assessment of Cataract Surgery and Potential Confounders

History of cataract surgery was obtained from the home interview, and confirmed with slit lamp examination during the ophthalmic examination at the research center. Lens status was recorded at baseline, at the second and third follow-up visits. The exact date of cataract surgery was not available in our study. Aphakia was defined as the absence of any lens (natural or artificial) after cataract surgery, whereas pseudophakia was defined as the presence of an artificial intraocular lens (IOL) after cataract surgery. In the study, 5681 participants were genotyped for the CHF Y402H polymorphism (1277 T→C, rs1061170) in 2-ng genomic DNA extracted from leukocytes (Taqman assay; Applied Biosystems, Foster City, CA). Potential confounders included age, sex, follow-up time, AMD stage (stages 0–1, 2, or 3), and smoking status (current, former, or never). Additional adjustment was made for systolic and diastolic blood pressure, total and high-density lipoprotein (HDL) cholesterol. Information on all potential confounders was collected at baseline and updated at the second follow-up visit.

AMD Definition

To diagnose AMD, we took 35° color photographs of the macular area of each eye at each follow-up examination (TRV-50VT fundus camera; Topcon Corp., Tokyo, Japan) after pharmacologic mydriasis. These images (digitized from the last follow-up examination to the present) were graded with 12.5× magnification according to the International Classification and Grading System for age-related maculopathy (ARM) by the same two trained professionals who graded AMD from baseline to the present, who were masked for all other determinants.18–21 We changed only the terminology from early and late ARM to early and late AMD. We categorized the range of AMD fundus signs into five mutually exclusive stages 0 to 4 that had an increasing risk of late AMD.18,21 Stage 0 was defined as stage 0, no signs of AMD at all or only hard drusen (≥63 μm); stage 1 was soft distinct drusen (≥63 μm) or only pigmentary abnormalities. Because many participants with only one large druse or one hyperpigmentation in this system are classified as stage 1 and because we wanted to separate participants with marked AMD from those with only limited signs, we considered stage 1 as no AMD in the present analyses. Early AMD included stage 2, soft indistinct drusen (≥125 μm), reticular drusen only, or soft distinct drusen (≥63 μm) with pigmentary abnormalities; and stage 3, soft indistinct drusen (≥125 μm) or reticular drusen with pigmentary abnormalities.

Stage 4 was similar to late AMD, subdivided into dry (geographic atrophy) and wet (neovascular) AMD. Dry AMD was defined as any sharply demarcated round or oval area of apparent absence of the retinal pigment epithelium (RPE), larger than 175 μm, with visible choroidal vessels and no wet AMD. Wet AMD was defined as the presence of a serous or hemorrhagic detachment of the RPE, and/or a subretinal neovascular membrane, and/or subretinal hemorrhage, and/or perifoveal fibrous scar. An eye was classified according to the highest stage of AMD, and in cases where both dry and wet AMD were present, as wet AMD. Incident early AMD was defined as the absence of AMD at baseline and the presence of early AMD at follow-up. Incident late AMD was defined as either no AMD (stage 0–1) or early AMD at baseline and the presence of late AMD at follow-up. Incident (i)AMD was defined as no AMD at baseline and presence of early or late AMD at follow-up. All types of iAMD were defined as being incident in the same eye that had undergone cataract surgery. Lesions that were considered to be the result of generalized disease, such as diabetic retinopathy, chorioretinitis, high myopia, trauma, congenital diseases, or photocoagulation for reasons other than for wet AMD, were excluded from AMD classification.

Population for Analysis

For the incidence analyses, the data were pooled over two periods: (1) baseline visit to the second follow-up visit; (2) the second follow-up visit to the third follow-up visit (Fig. 1). Lens status and other determinants were assessed at the start of each period (baseline and second follow-up visit, respectively). Lens status at the first follow-up visit was not taken into account, because it was not confirmed by slit lamp examination. iAMD was assessed at the end of each period (second follow-up and third follow-up visit). At baseline, gradable fundus photographs were available on 6418 participants, of whom 174 (2.7%) had early AMD and 50 (0.8%) late AMD in both eyes. Of the 6368 persons at risk for late AMD, 3627 (57.0% of those at risk) participated in the second follow-up examination. The study population for the incidence analyses consisted of 3608 (56.7% of those at risk) participants of whom data on lens status were available at baseline. At the second follow-up visit, gradable fundus photographs were available on 3636 participants, of whom 161 (4.4%) had early AMD and 24 (0.7%) late AMD in both eyes. Of the 3612 persons at risk for late AMD, 2425 (67.1%) participated in the third follow-up examination. The study population for the incidence analyses was extended with 2424 participants of whom data on lens status were available at the second follow-up examination. In total, the study population for the incidence analyses consisted of 6032 participants, of whom we included 12,002 eyes. Persons did not participate in follow-up examinations due to refusal, death or loss to follow-up. In addition, we performed age-adjusted incidence analyses stratified by CHF Y402H genotype. Genotypic data were available on 10,428 eyes. For the cross-sectional analyses, the data were pooled over two time points: the baseline visit and the second follow-up visit. Lens status, other determinants, and prevalence of AMD were assessed at both time points. The study population for the cross-sectional analyses consisted of 6561 participants whose data on lens status were available at baseline. This group was augmented with 3627 participants whose data on lens status were available at the second follow-up visit. In total, the study population for the cross-sectional analyses consisted of 9988 participants, of whom we included 19,915 eyes. Persons with both eyes aphakic were excluded in the incidence (n = 0) and cross-sectional (n = 1) analyses, to avoid unstable point estimates due to the small numbers.

Data Analysis

Characteristics of eyes with and without prior cataract surgery were compared with analysis of covariance for continuous variables and with logistic regression analysis for discrete variables adjusting for age and sex (SPSS, ver. 11.0; SPSS Inc., Chicago, IL). To exploit the data in an optimal way, all available data were combined into one analysis. The unit in the incidence analysis was one eye (left or right) per period (baseline to second follow-up visit, second follow-up to third follow-up visit). Thus, each participant yielded a maximum of four units in the data set: (1) the left eye in first period, (2) the left eye in second period, (3) the right eye in first period, and (4) the right eye in second period. The association between determinants and incident AMD was studied by logistic regression. To adjust for the correlation of the units corresponding to the same subject, the generalized estimating equation (GEE) approach was followed, with an independent or unstructured working correlation matrix (SAS, ver. 8.2; SAS Institute, Inc., Cary, NC). Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) are provided. The unit in the cross-sectional analyses was one eye (left or right) per time point (baseline and second follow-up visit). Thus, each participant yielded a maximum of four units in the dataset: (1) the left eye at baseline, (2) the left eye at second follow-up visit, (3) the right eye at baseline, and (4) the right eye at second follow-up visit. The association between determinants and prevalent AMD at either time point was also studied by the GEE approach.

RESULTS

General characteristics of the eyes in the incidence study population are presented in Table 1. Participants with pseudophakic eyes were older than participants with phakic eyes (P < 0.001) and were more often former smokers (P < 0.001). Mean follow-up time was significantly longer in the phakic
group than in the pseudophakic group (5.8 vs. 5.1 years, \(P < 0.001\)). Other baseline characteristics were not significantly different between these two groups. The average follow-up time was 5.7 years with a range of 2.8 to 9.7 years. Of the 12,002 eyes at risk, 63 right and 56 left eyes were pseudophakic at baseline. Between baseline and second follow-up examination, 108 right and 108 left eyes had undergone cataract surgery. A total of 693 phakic eyes and 45 pseudophakic eyes were diagnosed with any iAMD.

In Table 2 ORs and corresponding 95% CIs are presented for the association between prior cataract surgery and iAMD. After adjustment for age, sex, follow-up time, and the correlation between the fellow eyes, a history of cataract surgery was associated with an increased risk of dry late AMD (OR, 3.43; 95% CI, 1.82–6.49). This association remained significant after further adjustment for smoking status and AMD stage at baseline (OR, 3.44; 95% CI, 1.68–7.08). No statistically significant association was observed between prior cataract surgery and the development of wet or early AMD (OR, 0.93; 95% CI, 0.35–2.49, and OR, 1.31; 95% CI, 0.88–1.95, respectively). Further adjustment for systolic and diastolic blood pressure, total and HDL cholesterol did not essentially alter our results. Stratified analyses for CFH Y402H genotype are shown in Table 3. The OR of AMD after cataract surgery increased in an allele-dose manner for dry AMD with 2.30 (95% CI, 0.28–18.83) for noncarriers, 3.31 (95% CI, 1.23–8.91) for heterozygotes, and 4.02 (95% CI, 1.37–11.79) for homozygous CFH Y402H carriers. In homozygotes the postoperative risk tended to be higher for all subtypes of AMD.

The cross-sectional analyses are presented in Table 4. Pseudophakic eyes had an increased prevalence of stage 3, early AMD (OR, 1.96; 95% CI, 1.28–2.99) compared with phakic eyes. After multivariate adjustment, the prevalence of both wet AMD (OR, 0.51; 95% CI, 0.24–1.07) and dry AMD (OR, 0.72; 95% CI, 0.37–1.37) tended to be lower in pseudophakic than in phakic eyes.

**DISCUSSION**

Data from this population-based study show that history of cataract surgery increases the risk of dry AMD. We did not find
any significant associations between prior cataract surgery and incidence of wet or early AMD. Homozygous CFH Y402H carriers had higher risks of all types of AMD. Risks of dry AMD after cataract surgery were significantly increased in an allele-dose manner. These data suggest that cataract surgery may be a risk factor for AMD, particularly for homozygous CFH Y402H carriers and dry AMD.

There is still no consistent evidence regarding the association between cataract surgery and the risk of AMD. An increased risk of wet AMD after cataract surgery was first suggested in a postmortem histopathologic study. The incidence data of the Beaver Dam Eye Study (BDES) and Blue Mountains Eye Study (BMES) showed that prior cataract surgery was associated with a higher incidence of both dry and wet AMD. Similar findings were reported by other studies. In contrast, the population-based Visual Impairment Project, Armbrrecht et al., and AREDS (Milton RC, et al. IOVS 2007;48:ARVO E-Abstract 2104) found no association between cataract surgery and the progression to wet or dry AMD. The cross-sectional data of the BDES found no consistent association between prior cataract surgery and early or late AMD. The results of our study, Baatz et al., and Sutter et al. showed no association between pseudophakia and wet AMD. As in our study, the cross-sectional data of the BDES found only a positive association between prior cataract surgery and early AMD. The strengths of our study include its prospective population-based design and the large study sample with long follow-up. By using data on cataract surgery at two time-points (i.e., at baseline and the second follow-up visit), we increased the power. In addition, reassigning the lens status of the eyes at the follow-up were older and less healthy, which indicates that the association between cataract surgery and the risk of AMD, because of the small number of aphakic eyes. Persons who refused to participate or were lost to follow-up were older and less healthy, which indicates that study participants were at a lower risk of development of AMD compared than were the total eligible study population.

There are several possible explanations for the association between cataract surgery and dry late AMD. Shared risk factors for AMD and cataract form potential confounders. However, the association between cataract surgery and incident dry AMD remained significant after controlling for age, sex, smoking status, and AMD stage at baseline examination. Further adjustment for systolic and diastolic blood pressure, HDL, and total cholesterol did not essentially alter our results. Nonascertained risk factors (e.g., light exposure and genetic factors) may explain the association. Detection bias may have influenced our results since drusen, RPE abnormalities and subtle signs of early advanced AMD are more likely to be missed in phakic eyes with lens opacities than in clear pseudophakic eyes.

Any AMD
- Risks were determined by the generalized estimation equation model.

### Table 1. Characteristics of the 12,002 Eyes of the Study Participants with and without Prior Cataract Surgery

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>With Prior Cataract Surgery (n = 454)</th>
<th>Without Prior Cataract Surgery (n = 11,548)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>75.1 (6.95)</td>
<td>67.3 (6.71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>271 (59.7)</td>
<td>6,596 (57.1)</td>
<td>0.93</td>
</tr>
<tr>
<td>Right eye, n (%)</td>
<td>234 (51.5)</td>
<td>5,764 (49.9)</td>
<td>0.49</td>
</tr>
<tr>
<td>Follow-up time, mean (SD)</td>
<td>5.10 (1.06)</td>
<td>5.76 (1.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>138 (30.5)</td>
<td>3,660 (31.9)</td>
<td>—</td>
</tr>
<tr>
<td>Former</td>
<td>274 (60.5)</td>
<td>5,652 (49.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current</td>
<td>41 (9.1)</td>
<td>2,158 (18.8)</td>
<td>0.78</td>
</tr>
<tr>
<td>AMD stage at baseline, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 0–1</td>
<td>409 (90.1)</td>
<td>11,007 (95.3)</td>
<td>—</td>
</tr>
<tr>
<td>Stage 2</td>
<td>34 (7.5)</td>
<td>472 (4.1)</td>
<td>0.90</td>
</tr>
<tr>
<td>Stage 3</td>
<td>11 (2.4)</td>
<td>69 (0.6)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Continuous variables are expressed as mean (SD). Categorical variables are expressed as n (%).
* P was calculated using ANCOVA for continuous variables and logistic regression for discrete variables, adjusted for age and sex.
† P for trend.

### Table 2. Risk of iAMD in Pseudophakic Eyes

<table>
<thead>
<tr>
<th>Incident AMD</th>
<th>Phakic Eyes</th>
<th>Pseudophakic Eyes</th>
<th>OR (95% CI) Adjusted for Age, Sex, and Follow-up Time</th>
<th>OR (95% CI) Further Adjusted for Smoking and AMD Stage at Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right (n = 5764)</td>
<td>Left (n = 5784)</td>
<td>Right (n = 234)</td>
<td>Left (n = 220)</td>
</tr>
<tr>
<td>Any AMD</td>
<td>351 (6.4%)</td>
<td>342 (6.2%)</td>
<td>20 (9.4%)</td>
<td>25 (12.7%)</td>
</tr>
<tr>
<td>Early AMD</td>
<td>324 (5.9%)</td>
<td>327 (5.9%)</td>
<td>18 (8.6%)</td>
<td>24 (12.2%)</td>
</tr>
<tr>
<td>Dry AMD</td>
<td>22 (0.4%)</td>
<td>27 (0.5%)</td>
<td>9 (3.9%)</td>
<td>6 (2.8%)</td>
</tr>
<tr>
<td>Wet AMD</td>
<td>33 (0.6%)</td>
<td>24 (0.4%)</td>
<td>3 (1.3%)</td>
<td>2 (0.9%)</td>
</tr>
</tbody>
</table>

Risk was determined by the generalized estimation equation model.
TABLE 4. Risk of Prevalent AMD in Pseudophakic Eyes: Generalized Estimation Equation Model

<table>
<thead>
<tr>
<th>Eye Status</th>
<th>Phakic Eyes (9392)</th>
<th>Pseudophakic Eyes (9431)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalent AMD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any AMD</td>
<td>673 (7.2%)</td>
<td>660 (7.0%)</td>
</tr>
<tr>
<td>Early AMD</td>
<td>569 (6.1%)</td>
<td>559 (6.0%)</td>
</tr>
<tr>
<td>Stage 2 AMD</td>
<td>478 (5.2%)</td>
<td>484 (5.1%)</td>
</tr>
<tr>
<td>Stage 3 AMD</td>
<td>91 (1.0%)</td>
<td>75 (0.8%)</td>
</tr>
<tr>
<td>Dry AMD</td>
<td>59 (0.6%)</td>
<td>47 (0.5%)</td>
</tr>
<tr>
<td>Wet AMD</td>
<td>45 (0.5%)</td>
<td>54 (0.6%)</td>
</tr>
</tbody>
</table>

Risk was determined by the generalized estimation equation model.
tical technique, and implantation of different kinds of intraocular lenses in the different countries. In conclusion, in this large, population-based cohort study we found an increased risk of development of dry AMD after cataract surgery. This risk appears to be highest for homozygous CFH Y402H carriers. Ophthalmologists should assess the risk of AMD progression in patients considered for cataract surgery, especially in patients with early AMD and genetic predisposition to a malfunctioning CFH.

References