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Commentary

Does Cataract Surgery Accelerate the Progression to Late Age-Related Macular Degeneration?

Emily Y. Chew, MD - *Bethesda, Maryland*
Gui-shuang Ying, MD, PhD - *Philadelphia, Pennsylvania*
Susan Vitale, PhD, MHS - *Bethesda, Maryland*

Cataract and age-related macular degeneration (AMD) often coexist and share common risk factors, including increasing age, smoking, and genetic associations. An important clinical question debated for decades is whether cataract surgery accelerates the progression of AMD, especially to its late stages of neovascular AMD (nAMD) or geographic atrophy. Prior studies have resulted in mixed findings, with the older population-based epidemiologic studies reporting increased risk of progression to late AMD after cataract surgery, while long-term follow-up of clinical trials such as the Age-related Eye Disease Study (AREDS), AREDS2,[1] and other clinic-based studies[2] found no increased risk.

In this issue (p. 1409), researchers using the American Academy of Ophthalmology IRIS® Registry (Intelligent Research in Sight) again examined this potential association.[3] Using propensity score matching to match eyes 1:1 on age, sex, race, ethnicity, laterality, AMD severity, and smoking status, cataract surgery was modeled as a time-varying exposure in a Cox proportional hazards model to estimate the hazard ratio (HR) of conversion to nAMD among eyes undergoing cataract surgery compared to those without cataract surgery. After matching, 40 053 eyes (1 eye per patient) were included in each group. Cataract surgery was found to be associated with a higher risk of nAMD, with an HR of 1.22 (95% confidence interval, 1.16-1.30; $P < 0.001$). Importantly, the risk of cataract surgery varied significantly according to baseline AMD severity (for early AMD, 1.33; for intermediate AMD, 1.11). Time-varying Cox regression analysis provided additional insight, demonstrating that the risk was strongest during the first year of follow-up (HR = 2.5) but diminished over time and became nonsignificant by year 4 (HR = 1.0). By year 6, the cumulative incidence of nAMD was 16.7% vs. 15.2% among eyes with and without cataract surgery, respectively. As the authors stated, there may be surveillance bias from closer postoperative follow-up.

As in any large clinic-based big data set, there is potential for misclassification, as diagnosis codes such as International Classification of Diseases 9/10 codes were used to define AMD severity and the primary outcome of nAMD, instead of the use of ophthalmic images, which are lacking in IRIS and other data sets. This potential misclassification of AMD severity and nAMD status could bias the estimated association between cataract surgery and the risk of nAMD. In this era of big data and the use of artificial intelligence/machine learning, a collection of ophthalmic images would indeed be a major asset in providing greater precision of the baseline status and a more precise definition of the primary outcome. Providing a precise diagnosis, for example, of geographic atrophy associated with AMD, using diagnosis codes would be more difficult because the probability of misclassification could be quite high. In the prospective Australian Cataract Surgery and Age-related Macular Degeneration Study, 1851 participants underwent cataract surgery in 1 eye, and 1244 (70.7%) had 36-month post-operative visits documented with ophthalmic images.[4] The paired comparisons between the operated eye vs. the phakic eye found no increased risk of development of late AMD, soft large drusen, or reticular drusen, but there was an increased risk of development of hyperpigmentation in eyes that underwent cataract surgery.

The authors of the present study are to be commended for their cautions against the overinterpretation of the findings of a rather small association of increased risk of developing nAMD after cataract surgery, likely due to increased surveillance after operation. Patients with existing AMD, especially those with intermediate AMD, which can be quite heterogeneous, are at high risk of developing late AMD. It is important to inform patients with coexisting AMD and cataract that vigilant follow-up is key for the management of their AMD after cataract surgery because the risk of progression may be inherently high and coincidental. Timely intravitreous treatment of nAMD is essential in maintaining good visual acuity after cataract surgery. A study of postoperative visual acuity in AREDS2 during the era of anti-VEGF therapy demonstrated visual acuity improved even in those eyes with late AMD, as measured using best-corrected visual acuity employing a standardized protocol.[5] The authors of the present study have identified risk factors associated with the development of nAMD after cataract surgery, including older age, female sex, non-Hispanic ethnicity, active smoking, more severe stage of AMD, and poorer visual acuity at baseline. These data may help counsel patients who may be encouraged now to undergo cataract surgery despite the presence of AMD. It is important to emphasize the importance of follow-up after cataract surgery in patients with AMD to ensure good visual outcomes for all patients.

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Correspondence:
Emily Y. Chew, MD, Division of Epidemiology and Clinical Applications, National Eye Institute/National Institutes of Health, Building 10, CRC, Room 3-2531, 10 Center Drive, MSC-1204, Bethesda, MD 20892-1204. E-mail: echew@nei.nih.gov.

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