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Changes in Lens Opacities on the Age-Related Eye Disease Study Grading Scale Predict Progression to Cataract Surgery and Vision Loss

Age-Related Eye Disease Study Report No. 34

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Purpose: To investigate whether the 2-year change in lens opacity severity on the Age-Related Eye Disease Study (AREDS) lens grading scale predicts progression to cataract surgery or loss of visual acuity by 5 years.

Design: Prospective cohort study within a randomized clinical trial of oral supplements.

Participants: The AREDS participants whose eyes were phakic at baseline and free of late age-related macular degeneration throughout the study.

Methods: Baseline and annual lens photographs of AREDS participants (n = 3466/4757; 73%) were graded for severity of cataracts using the AREDS system for classifying cataracts from photographs. Clinical examinations conducted semiannually collected data on cataract surgery and visual acuity. Association of the change in lens opacities at 2 years with these outcomes at 5 years was analyzed with adjusted Cox proportional hazard models.

Main Outcome Measurements: Progression of lens opacities on stereoscopic lens photographs at 2 years, cataract surgery, and visual acuity loss of 2 lines or more at 5 years.

Results: The adjusted hazard ratios (HRs) for association of progression to cataract surgery at 5 years were: nuclear cataract increase of 1.0 unit or more compared with less than 1.0-unit change at 2 years, 2.77 (95% confidence interval [CI], 2.07−3.70; $P < 0.001$); cortical cataract increase of 5% or more in lens opacity in the central 5 mm of the lens compared with less than 5% increase at 2 years, 1.91 (95% CI, 1.27−2.87; $P = 0.002$); and posterior subcapsular cataract increase of 5% or more versus less than 5% in the central 5 mm of the lens, 8.25 (95% CI, 5.55−12.29; $P < 0.001$). Similarly, HRs of vision loss of 2 lines or more at 5 years for this degree of lens changes at 2 years were the following: nuclear, 1.83 (95% CI, 1.49−2.25; $P < 0.001$); cortical, 1.13 (95% CI, 0.78−1.65; $P = 0.519$); and posterior subcapsular cataract, 3.05 (95% CI, 1.79−5.19; $P < 0.001$).

Conclusions: Two-year changes in severity of lens opacities on the AREDS lens grading scale are predictive of long-term clinically relevant outcomes, making them potential surrogate end points in follow-up studies. *Ophthalmology 2015;122:888-896 © 2015 by the American Academy of Ophthalmology.*

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The Age-Related Eye Disease Study (AREDS) system for classifying cataracts was used in a large multiyear, multicenter follow-up study.[1] The classification system is sufficiently detailed to detect small differences in the severity of age-related nuclear, cortical, and posterior subcapsular (PSCs) cataracts. Like other grading systems for the lens,[2−4] the AREDS lens grading system has shown a high degree of cross-sectional reproducibility.[1] An unanswered question is whether movement along the severity scale for the 3 types of cataract, especially at the less severe end of the spectrum, is predictive of the need for cataract surgery and loss of visual acuity. Developing a surrogate outcome is desirable because of the slow rate of progression from the earliest stages of lens opacities to clinically important end points. Documentation that progression along the AREDS severity scale is clinically important could decrease the sample size and duration requirements of studies of cataract. Moreover, such documentation validates the clinical relevance of the lens classification systems that have been central to cataract research.

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In this study, we used gradings from baseline and annual lens photographs of the AREDS cohort to evaluate whether increases in the severity of lens opacities at 2 years for the 3 major types of age-related cataract predict risk of progression to clinically important end points, that is, cataract surgery and loss of visual acuity.

Methods

The AREDS study design is presented in detail elsewhere.[5] Briefly, 4757 participants between 50 and 80 years of age were enrolled at 11 clinical centers. Participants were followed up for a median of 10 years for the long-term clinical course of age-related macular degeneration (AMD) and age-related cataract and also were evaluated for the effect of high-dose nutritional supplements on the progression of the 2 conditions in a randomized clinical trial. Institutional review board approval was obtained at each clinical site, and participants signed informed consent for the study.

Participants both with and without signs of AMD, cataract, or both were enrolled between 1992 and 1998 and followed up at 6-month intervals. To qualify for the study, at least 1 eye of each participant had to have visual acuity of 20/32 or better at baseline, media sufficiently clear for good-quality fundus photographs to allow assessment of AMD severity, and an absence of any other ocular disorders that could interfere with the evaluation of either AMD or lens opacities. Unlike the recruitment strategy for the AMD component of the study, in which specific numbers of participants were recruited into 4 AMD categories to ensure adequate power for the AMD clinical trial, there were no prespecified recruitment goals for lens status except that lenses, when present, had to be clear enough for adequate fundus photography.

We focused this report on analyses of 6054 eyes of 3466 AREDS participants in which late AMD or other ocular conditions that could have resulted in loss of visual acuity during the course of the study did not develop. Eyes with a diverse array of baseline opacity grades for the 3 types of age-related cataract were included in the analyses. Eyes with a history of cataract surgery or 2-line loss of visual acuity before the 2-year evaluation of opacity change were excluded from the analyses.

Procedures

Standardized color lens photographs were obtained by certified photographers at baseline and then annually, starting with the second annual visit using specially modified Topcon slit-lamp cameras (Topcon Corp, Tokyo, Japan) and Neitz cameras (Neitz Instruments Co, Ltd., Tokyo, Japan).[1] Photographs were assessed for the presence and severity of nuclear, cortical, and PSC opacities by certified graders at the University of Wisconsin reading center. Based on a series of 7 slit-lamp standard photographs showing increasingly severe nuclear opacification, nuclear opacity grades ranged from 0.9 (less severe than standard 1) to 7.1 (more severe than standard 7; Fig 1).[1,6] As in previous reports, moderate nuclear cataract was defined as a grade of 4.0 or more.[6] The extent of cortical and PSC opacities was graded by estimating the area of lens involvement (range, 0%−100%) in sectors of a grid overlay on the Neitz retroillumination photographs (Fig 2).[1] Individual sector percentages were combined to estimate an overall percentage of involvement within the central 5 mm of the lens. In our analyses, moderate cortical and moderate PSC cataracts were defined as at least 5% involvement of the central 5 mm.

Demographic information and medical history were obtained at baseline. Ophthalmic examinations, including measurement of best-corrected visual acuity according to the Early Treatment Diabetic Retinopathy Study protocol,[7] slit-lamp examinations, and ophthalmoscopy, were performed at annual visits. At nonannual visits, data were collected on interim cataract surgery and visual acuity. Visual acuity was measured using the refraction from the previous visit, unless there was a decrease in visual acuity of more than 10 letters from baseline using the Early Treatment Diabetic Retinopathy Study scoring system, in which case a refraction was performed and best-corrected visual acuity was measured.

Outcomes and Statistical Analyses

The 2 primary outcomes, progression to cataract surgery and a 2-line or more loss of visual acuity by 5 years, were assessed by ophthalmic history and examination every 6 months. Change in lens opacity by year 2 was based on the baseline and annual reading center grades for each type of opacity. Baseline covariates that may affect the primary outcomes were taken into account in the analyses: age of the participant as a continuous variable; gender; smoking, both formerly and currently as reported by the participant; the presence of diabetes mellitus type 2 according to medical history; baseline AMD severity as measured using the AREDS categorization system[5]; baseline lens opacity grade; history of cataract surgery in the fellow eye; and the presence of multiple cataract types. According to the AREDS categorization system for AMD severity, category 1 included participants who were free of any age-related macular changes; category 2 included those with mild or borderline AMD changes, such as small or intermediate drusen (<125 μm), pigment abnormalities, or both, in 1 or both eyes; category 3 included those who had large drusen (≥125 μm), extensive intermediate drusen, geographic atrophy that did not involve the center of the macula, or a combination thereof and who did not have advanced AMD in either eye; finally, category 4 included those who had advanced AMD (geographic atrophy in the center of the macula, neovascular changes, or both) or who had decreased vision (<20/32) attributable to lesions of nonadvanced AMD in only 1 eye.

Cox proportional hazard regression was used to assess the association of a change in lens opacity by year 2 with the 2 primary outcomes by year 5. Change in lens opacity was categorized into 2 groups for the 3 types of cataract: less than 1 and 1 or more for nuclear cataract, and less than 5% and 5% or more in the central 5 mm of the lens for cortical and PSC cataract changes. The unit of analysis is the eye. The Wei-Lin-Weissfeld method[8] for analyzing repeated measures was applied to take into account the correlation between the 2 eyes of each participant for applicable models. Models also were adjusted for the covariates described previously. To evaluate the effect of history of cataract surgery in the fellow eye, we used a model with 1 randomly selected eye per participant. These analyses were performed using the proportional hazards regression (PHREG) procedure in SAS software version 9.2 (SAS Inc, Cary, NC). Finally, concordance probability estimates and their associated standard errors were calculated using the method from Gönen and Heller to evaluate the discriminatory power of models.[9] Concordance probability estimate values measure how accurately the models predict the 2 primary end points based on the variables and covariates being examined. A concordance probability of 1.0 represents a model that has perfect discrimination, whereas a value of 0.5 represents one that is no more predictive than a coin flip.[9]

Results

Baseline characteristics of participants are displayed in Table 1. Characteristics are similar in all 6 sets of analyses: progression to cataract surgery for all 3 lens opacity types by 5 years and