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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 (AREDS) Report #34

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Abstract

Purpose—To investigate whether the two year change in severity of lens opacities 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—AREDS participants whose eyes were phakic at baseline and free of late AMD throughout the study.

Methods—Baseline and annual lens photographs of AREDS participants (n=3466/4757; 73%) were graded for severity of cataract using the AREDS System for Classifying Cataracts from Photographs. Clinical exams conducted semi-annually 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 or more lines at 5 years.

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[*]A complete listing of the AREDS Research Group is found in Reference Number 2.

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Results—The adjusted hazard ratios (HR) for association of progression to cataract surgery at 5 years, were: nuclear cataract increase of 1.0 unit or greater compared with < 1.0 unit change at 2 years: 2.77 (95% confidence limit (CL): 2.07–3.70, p<0.001); cortical cataract increase of 5% or greater in lens opacity in the central 5mm of the lens, compared with < 5% increase at 2 years: 1.91 (95% CL: 1.27–2.87, p=0.002) ; and posterior subcapsular cataract increase of 5% or greater vs. <5% in the central 5 mm of the lens: 8.25 (95% CL: 5.55–12.29, p<.001). Similarly, HRs of vision loss of ≥2 lines at 5 years for this degree of lens changes at 2 years were the following: nuclear: 1.83 (95% CL: 1.49–2.25, p<.001); cortical: 1.13 (95% CL: 0.78–1.65, p=.519); and PSC: 3.05 (95% CL: 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 endpoints in follow-up studies.

Introduction

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 (PSC) cataracts. Like other grading systems for the lens,[2,3,4] 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 three 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.

In this report, 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 three major types of age-related cataract predict risk of progression to clinically important endpoints, i.e. cataract surgery and loss of visual acuity.

Methods

The AREDS study design is presented in detail elsewhere.[5] Briefly, 4757 participants between 50 to 80 years of age were enrolled at 11 clinical centers. Participants were followed for a median of 10 years for the long-term clinical course of age- related macular degeneration (AMD) and age-related cataract and also evaluated for the effect of high-dose nutritional supplements on the progression of the two 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 and/or cataract were enrolled between 1992 and 1998 and followed at six-month intervals. To qualify for the study, at least one 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 four AMD categories to ensure adequate power for the AMD clinical trial, there were no pre-specified 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, which 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 three types of age-related cataract were included in the analyses. Eyes with a history of cataract surgery or two-line loss of visual acuity prior to the two-year evaluation of opacity change were excluded from the analyses.

Procedures

Standardized color lens photographs were taken by certified photographers at baseline and then annually, starting with the second annual visit using specially modified Topcon slit-lamp cameras (Topcon Corporation, Tokyo, Japan), and Neitz (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 seven 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 is defined as a grade of 4.0 or greater.[6] The extent of cortical and PSC opacities was graded by estimating the area of lens involvement (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 cataract are defined as at least 5% involvement of the central 5mm.

Demographic information and medical history were obtained at baseline. Ophthalmic examinations, including measurement of best-corrected visual acuity according to the ETDRS protocol,[7] slit-lamp examinations, and ophthalmoscopy were performed at annual visits. At non-annual 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 ETDRS scoring system, in which case a refraction was performed and best corrected visual acuity was measured.

Outcomes and Statistical Analyses

The two primary outcomes, progression to cataract surgery and a two or more line loss of visual acuity by five years, were assessed by ophthalmic history and examination every six months. Change in lens opacity by year two, was based on the baseline and annual reading center grades for each type of opacity. Baseline covariates that might 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 were those with mild or borderline AMD changes, such as small/intermediate drusen (<125 μm) and/or pigment abnormalities, in one or both eyes; category 3 were those who had large drusen (≥125 μm), extensive intermediate drusen, and/or geographic atrophy that did not involve the center of the macula, 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 and/or neovascular changes) or who had decreased vision (<20/32) attributable to lesions of non-advanced AMD in only one eye.

Cox proportional hazard regression was used to assess the association of a change in lens opacity by year two with the two primary outcomes by year five. Change in lens opacity was categorized into two groups for the three types of cataract: <1, 1 or more for nuclear cataract, and <5% and 5% or more in the central 5mm of the lens for cortical and PSC 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 two eyes of each participant for applicable models. Models were also adjusted for the covariates described above. To evaluate the effect of history of cataract surgery in the fellow eye, we used a model with one randomly selected eye per participant. These analyses were performed using the PHREG procedure in the SAS System, version 9.2 (SAS Institute Inc., Cary, NC). Finally concordance probability estimates (CPE) and their associated standard errors (SE) were calculated using the method from Gönnen and Heller in order to evaluate the discriminatory power of models.[9] CPE values measure how accurately the models predict the two primary endpoints 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 three lens opacity types by five years, and progression to two-line or greater visual acuity loss for all three lens opacity types by five years. The numbers of participants in each of these analyses are listed in Table 2. Table 3 shows the distribution of baseline lens opacity grades and change in grades by year two for each of the three cataract types, as wel as the number of eyes that had multiple types of lens opacities by year five and cataract surgery in the fellow eye. At baseline most participants were at the least severe end of the grading spectrum for the three types of cataract. For instance, in the 5-year cataract surgery analysis, 56% of participants had a grade of ≤2 for nuclear cataract, 65% had a grade of 0% for cortical cataract, and 95% had a grade of 0% for PSC cataract. Figure 3 demonstrates the distribution of two-year changes in lens opacity grades for nuclear cataract. The mean changes in grade for all three cataract types by year two were small at: 0.4 for nuclear cataract (n=6054 and 5970 eyes for cataract surgery and visual acuity loss analyses, respectively), 0.5 for cortical cataract (n=6082 and 5995 eyes, respectively), and 0.3 for PSC cataract (n=6069 and 5984 eyes, respectively). Figures 4 a–c demonstrate the rates of progression to cataract surgery at 5 years for different levels of cataract severity at baseline for the 3 cataract types.

Hazards ratios for analyses of progression to cataract surgery

Cox proportional hazard regression results for cataract surgery by year five, based on change in cataract grade at year 2, are summarized in Table 4. The hazard ratio (HR) and 95% confidence limits (CL), after adjusting for the covariates, for the association of progression to cataract surgery by year 5 with an increase in nuclear lens opacity grade of 1.0 or greater, compared with a <1.0 unit of change at 2 years, was 2.77 (95%CL 2.07–3.70, p<.001). For a 5% or greater increase in the severity of cortical lens opacities in the central 5 mm, compared with a <5% increase at 2years, the HR for progression to cataract surgery at 5 years was 1.91 (95%CL 1.27–2.87, p=.002). For this same degree of lens opacity change at 2 years, the HR for progression to cataract surgery at 5 years for PSC was 8.26 (95%CL 5.55–12.29, p<.001). Thus, for all three types of lens opacity, small changes in cataract grade on the AREDS lens grading scale in a relatively short period of time, namely by two years, were associated with a statistically significant increased risk of progression to cataract surgery by five years.

Hazards ratios for analyses of progression to 2-line or greater visual acuity loss

Cox proportional hazard regression results for vision loss of two-lines or greater by year five based on the change in cataract grade are summarized in Table 4. Using the definitions of cataract grade change described above, the adjusted HRs and 95% CLs for progression to two-line or greater visual acuity loss at 5 years were for nuclear cataract: 1.83 (95%CL 1.49–2.25, p<.001); for cortical cataract: 1.13 (95%CL 0.78–1.65, p=.519); and for PSC cataract: 3.05 (95%CL 1.79–5.19, p<.001). Similar to the analyses of progression to cataract surgery, small changes in cataract grade in a relatively short period of time were associated with a significantly increased likelihood of progression to two-line or greater visual acuity loss by five years for nuclear and PSC opacities.

These analyses were repeated using the 4170 participants without missing data and including all participants regardless of development of advanced AMD or other diseases that might result in vision loss. Though somewhat attenuated, increased hazard ratios were in a similar range for progression to cataract surgery (data not shown). Similar analyses were conducted evaluating the relationship of the year 5 change in lens status to the progression of lens opacities, cataract surgery, and vision loss at 10 years. The results show similar but somewhat attenuated hazard ratios.

Concordance Probability Estimates (CPE)

CPE's for the analyses along with their corresponding standard errors (SE are summarized in Table 5. The CPE's are consistent, ranging from 0.64 to 0.73 (SE≤0.1), indicating that the Cox proportional hazard regression models in this study are modestly predictive of progression to cataract surgery and visual acuity loss based on lens opacity grade change as described previously for the three cataract types.

Discussion

Our data demonstrate the slow rate of progression of lens opacities. In an elderly, clinic based population, the mean change in the severity of lens opacities after 2 years of follow up was 0.4 units (scale 0.9–7.1) for nuclear opacity and 0.5 % (scale 0–100%) for cortical and 0.3% (scale 0–100%) for PSC opacities. Clinically important events such as cataract surgery and loss of visual acuity due to lens opacities in a comparable population would be expected to take many more years to develop. As a result, designers of studies of cataract progression have limited choices in selecting endpoints. One can either use slowly developing, but clinically important endpoints or the faster occurring changes in the severity of opacities. Use of clinically important endpoints such as cataract surgery or vision loss is generally not a viable option because of large study size and/or long study duration requirements. The major objection to use of change in opacity status as a surrogate outcome variable has been the lack of documentation that it is a reliable predictor of clinically important events such as cataract surgery and loss of visual acuity.

Our data link movement along the AREDS scales for classifying age related opacities with occurrence of both cataract surgery and loss of visual acuity. Even a modest progression of opacities (a worsening of 1.0 or more units for nuclear or a 5% or more increase in opacity grade for cortical or PSC cataract) at 2 years increased the likelihood of cataract surgery by 5 years. The same modest changes by 5 years increased the risk of progression to cataract surgery by year 10, though the HRs for cataract surgery were somewhat lower in the 10 year data (data not shown).

The results for loss of visual acuity were somewhat less consistent for the three cataract types than the results for cataract surgery. Increased severity of nuclear and PSC opacities was clearly predictive of a two-line or greater loss of visual acuity by five years of follow-up. Less consistent associations between increased opacity grade and loss of vision were noted for cortical opacities.

No assignment of cause of vision loss was made in the AREDS study, so that we could not be certain whether coexisting disease, most notably AMD, might have influenced the visual acuity findings. We addressed this concern by adjusting for baseline AMD status and by excluding eyes that developed advanced AMD during the course of the study. Also, we repeated the analyses using only eyes of participants at low risk (<1%) of developing AMD, those in AREDS categories 1 and 2 (Supplementary Table 6).[10] These are the participants with either no AMD changes or with mild/borderline changes at baseline. Furthermore, to qualify for AMD categories 1 and 2, both eyes of the participants had to have visual acuity of 20/32 or better (75 or more letters read correctly), suggesting no visual acuity impairment because of existing disease. In the smaller cohort at low risk of vision loss from AMD increase in nuclear opacities were significantly associated with loss of vision by 5 years. A ≥5 % increase in PSC opacities was associated with a significantly increased risk of loss of visual acuity by five years. No consistent associations between cataract progression and vision loss were noted in the smaller cohort for cortical cataract.

Our results are largely consistent with clinical expectations. As might be expected, hazard ratios for progression to cataract surgery and loss of visual acuity by 5 years were higher with greater increases in severity grade for PSC and nuclear opacities, the two most clinically important opacities (Table 4). Also, as might be expected, as the baseline opacity grade for nuclear cataract increased, the HRs for progression to the two endpoints at 5 years increased as well. This trend was not seen for cortical cataract and could not be examined for PSC cataract because too few participants had grades >0 at baseline. Because cortical cataracts tend to develop in the periphery of the lens they are probably the least clinically relevant of the three age-related opacities. This might explain some of the differences noted for this type of cataract compared with the others. Hazard ratios for cataract surgery and loss of visual acuity were lower with increasing severity of cortical opacities than with either increasing severity of nuclear or PSC opacities (Table 4). Also, coexisting nuclear or coexisting PSC cataract was associated with a greater risk of progression to the two endpoints than when cortical cataract was the secondary opacity type. Other studies have suggested that cortical cataracts are less important as a cause of cataract surgery than either nuclear or PSC opacities.[11,12] It is important to note though, that for all three cataract types, including cortical cataract, there was a statistically significant increase in the risk of later cataract surgery even for participants with relatively small changes in cataract grade (Supplementary Tables 7 and 8).

Adjusted Cox proportional hazards models suggested that increased age was associated with an increased incidence of cataract surgery and loss of visual acuity.[13–16] Previous studies have demonstrated a higher incidence of cataract, especially cortical and PSC cataract, with diabetes mellitus and elevated serum glucose levels.[16–18] Our analyses demonstrated an association between a history of diabetes mellitus and increased risk of progression to cataract surgery at 5 years for both nuclear and PSC cataracts. The presence of more than one cataract type was associated with a greater risk of progression to the two endpoints, most consistently when the secondary opacity type was PSC or nuclear.

The Age-Related Eye Disease Study is uniquely suited to examine whether progression along a cataract severity scale might serve as an endpoint in clinical studies of cataract. 4757 participants aged 50–80 years were followed for a median of 10 years. Lens photographs were taken in a standardized fashion by certified photographers and graded at a reading center by specially trained and certified observers. The grading system was sufficiently detailed to detect small differences in the severity of age-related nuclear, cortical and PSC cataracts.[1] Inter-grader reliability was high. The data presented here show that relatively short term, modest changes in the severity of all three types of lens opacities on the AREDS scale were predictive of long term clinically relevant outcomes. Use of worsening severity of opacities as surrogate outcome variables is likely to facilitate future longitudinal studies of cataract. Based on these considerations and our findings, we offer increasing severity of lens opacities on the AREDS scale for classifying cataracts as a possible surrogate endpoint in follow up studies of age- related cataracts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Age-Related Eye Disease Study Research Group. The age-related eye disease study (AREDS) system for classifying cataracts from photographs: AREDS report no. 4. American Journal of Ophthalmology. 2001; 131:67–75.
2. Chylack LT Jr, Leske MC, McCarthy D, et al. Lens opacities classification system II (LOCS II). Archives of Ophthalmology. 1989; 107:991–997. [PubMed: 2751471]
3. Maraini G, Pasquini P, Sperduto RD, et al. The effect of cataract severity and morphology on the reliability of the Lens Opacity Classification System II (LOCS II). Investigative Ophthalmology & Visual Science. 1991; 32:2400–2403. [PubMed: 2071351]
4. Grewal DS, Brar GS, Grewal SP. Correlation of nuclear cataract lens density using Scheimpflug images with Lens Opacities Classification System III and visual function. Ophthalmology. 2009; 116:1436–1443. [PubMed: 19500847]
5. Age-Related Eye Disease Study Research Group. The Age-Related Eye Disease Study (AREDS): Design Implications AREDS Report No. 1. Controlled Clinical Trials. 1999; 20:573–600. [PubMed: 10588299]
6. Sperduto RD, Clemens TE, Lindblad AS, et al. Cataract classification using serial examinations in the age-related eye disease study: age-related eye disease study report no. 24. American Journal of Ophthalmology. 2008; 145:504–508. [PubMed: 18201681]
7. Ferris FL 3rd, Sperduto RD. Standardized illumination for visual acuity testing in clinical research. American Journal of Ophthalmology. 1982; 94:97–98. [PubMed: 7091290]
8. Wei LJ, Jin DY, Weissfield L. Regression analysis of multivariate incomplete failure time data by modeling marginal distributions. J Am Stat Assoc. 1989; 84:1065–1073.
9. Gönen M, Heller G. Concordance probability and discriminatory p ower in proportional hazards regression. Biometrika. 2005; 92:965–970.
10. Chew EY, Lindblad AS, Clemons T. Summary results and recommendations from the age-related eye disease study. Archives of Ophthalmology. 2009; 127:1678–1679. [PubMed: 20008727]
11. Adamsons I, Muñoz B, Enger C, et al. Prevalence of lens opacities in surgical and general populations. Archives of Ophthalmology. 1991; 109:993–997. [PubMed: 2064584]
12. Klein BE, Klein R, Moss SE. Incident cataract surgery: the Beaver Dam eye study. Ophthalmology. 1997; 104:573–580. [PubMed: 9111248]
13. Klein BE, Klein R, Lee KE, et al. Incidence of age-related cataract over a 15-year interval the Beaver Dam Eye Study. Ophthalmology. 2008; 115:477–482. [PubMed: 18171585]
14. Kanthan GL, Wang JJ, Rochtchina E, et al. Ten-year incidence of age-related cataract and cataract surgery in an older Australian population. The Blue Mountains Eye Study. Ophthalmology. 2008; 115:808–814. [PubMed: 17900695]
15. Leske MC, Wu SY, Nemesure B, et al. Nine-year incidence of lens opacities in the Barbados Eye Studies. Ophthalmology. 2004; 111:483–490. [PubMed: 15019323]
16. Chang JR, Koo E, Agrón E, et al. Risk factors associated with incident cataracts and cataract surgery in the Age-related Eye Disease Study (AREDS): AREDS report number 32. Ophthalmology. 2011; 118:2113–2119. [PubMed: 21684602]

17. Tan JS, Wang JJ, Mitchell P. Influence of diabetes and cardiovascular disease on the long term incidence of cataract: the Blue Mountains eye study. Ophthalmic Epidemiology. 2008; 15:317–327. [PubMed: 18850468]

18. Sabanayagam C, Wang JJ, Mitchell P, et al. Metabolic syndrome components and age-related cataract: the Singapore Malay eye study. Investigative Ophthalmology & Visual Science. 2011; 52:2397–2404. [PubMed: 21228391]

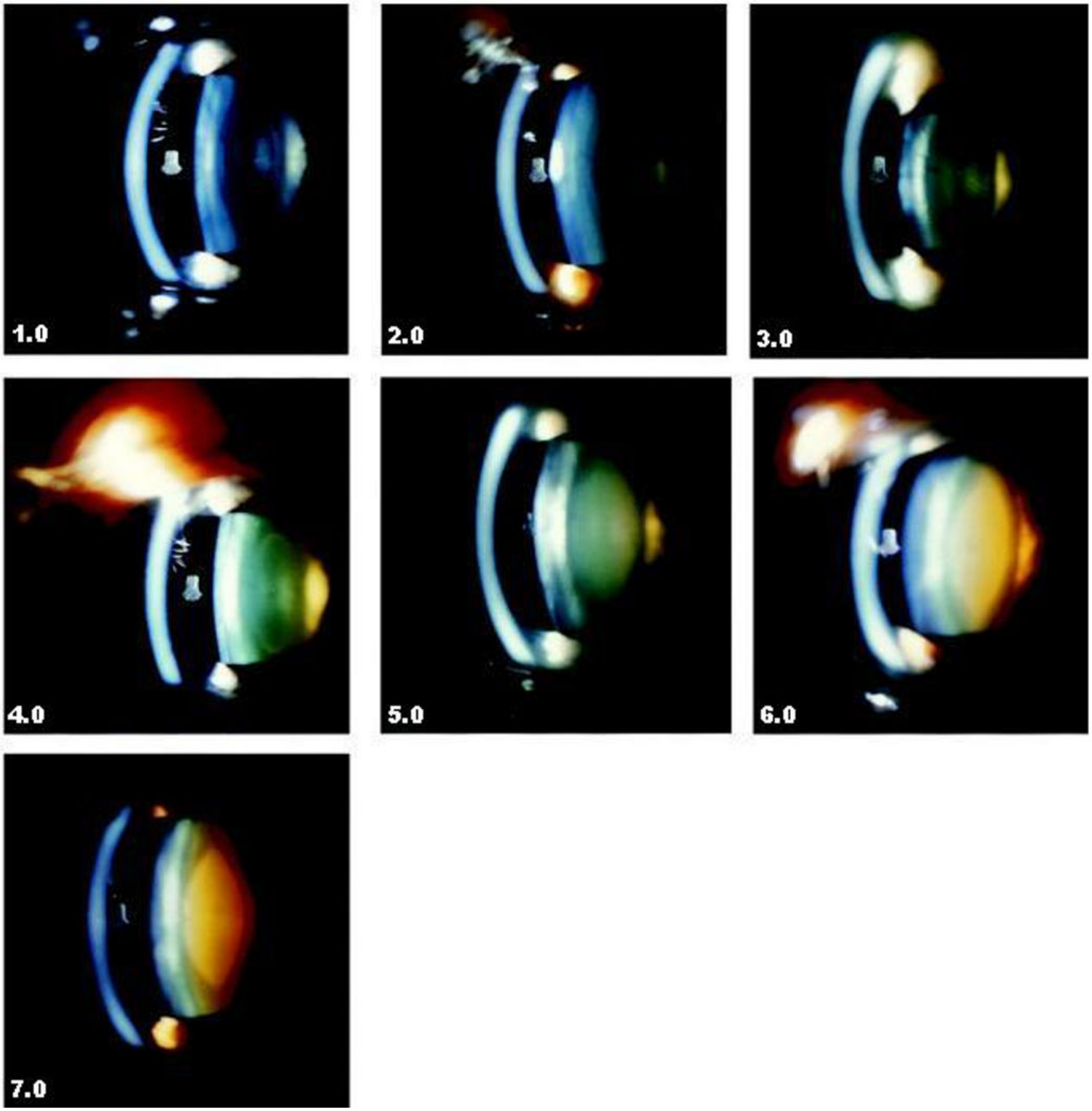


Figure 1. Slit-lamp standard photographs for grading nuclear cataract.[1]

Slit-lamp photographs of participants were compared with the seven standard photographs to grade nuclear opacities on a decimalized scale between 0.9 (less severe than Standard 1) and 7.1 (more severe than Standard 7)

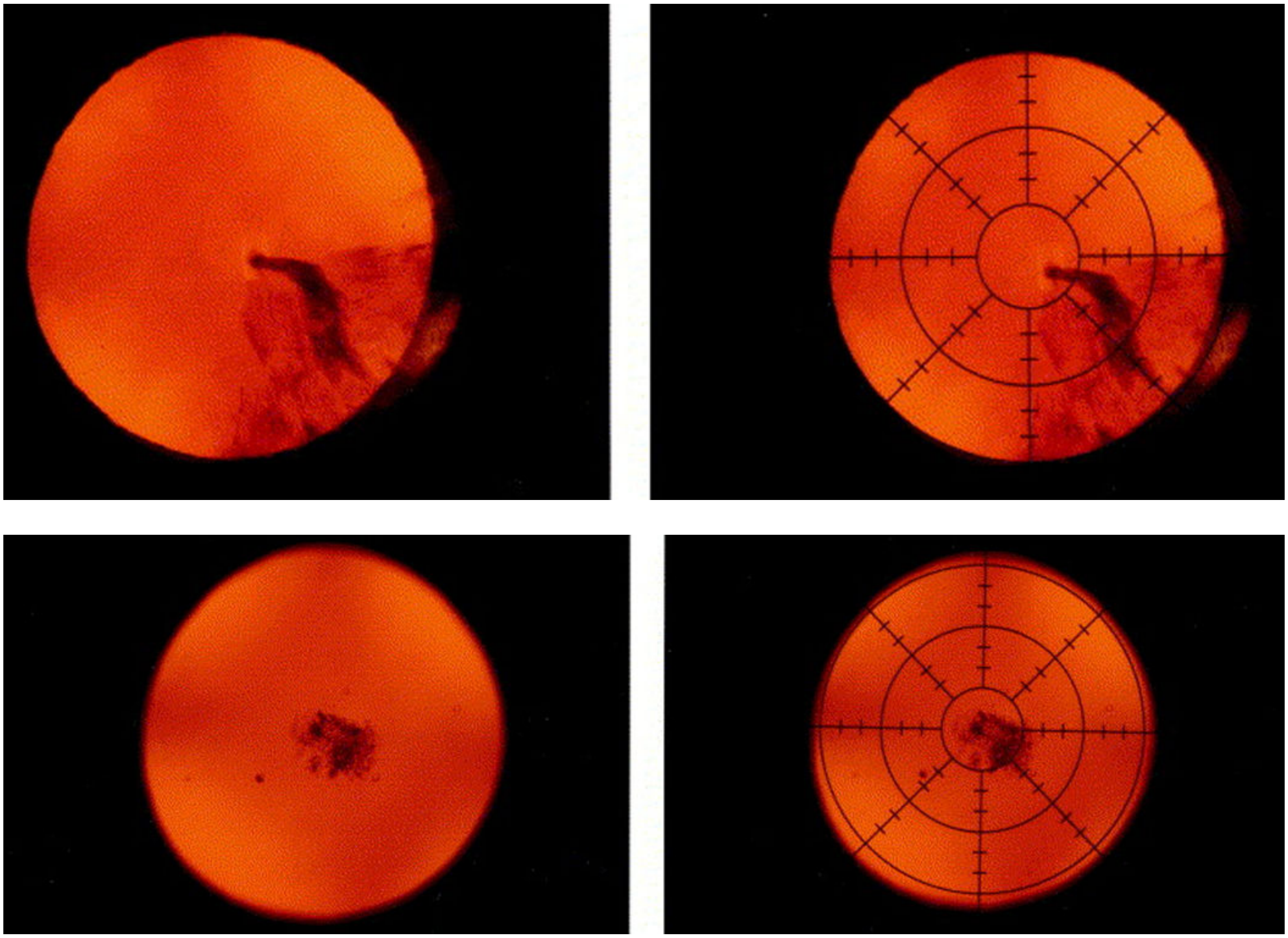


Figure 2. Grading scheme for cortical and PSC cataracts using retroillumination photographs.[1]
Cortical and posterior subcapsular cataract (PSC) opacities appear as darkly shaded interruptions in the red fundus reflex. A grid with three concentric circles which correspond to circles with diameters of 2, 5 and 8 mm on the lens was placed over the photographs. Percent involvement (0–100%) of the central 5mm was estimated for cortical and PSC opacities and percent involvement of the entire visible lens was also estimated for cortical opacities. In this example, the grade of the cortical cataract is 22% (Figure 2a). The grade of the PSC cataract is 15% (Figure 2b).

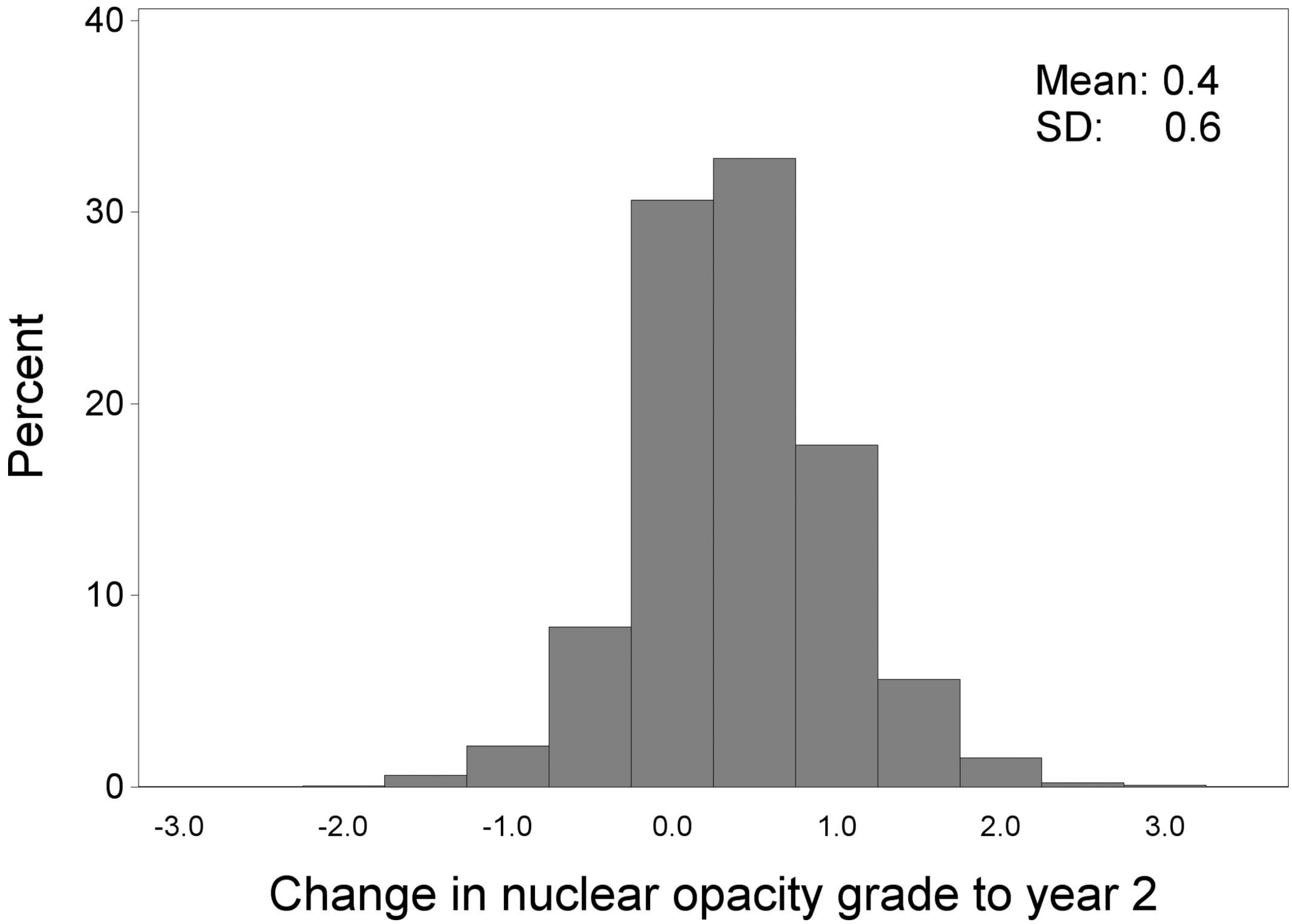
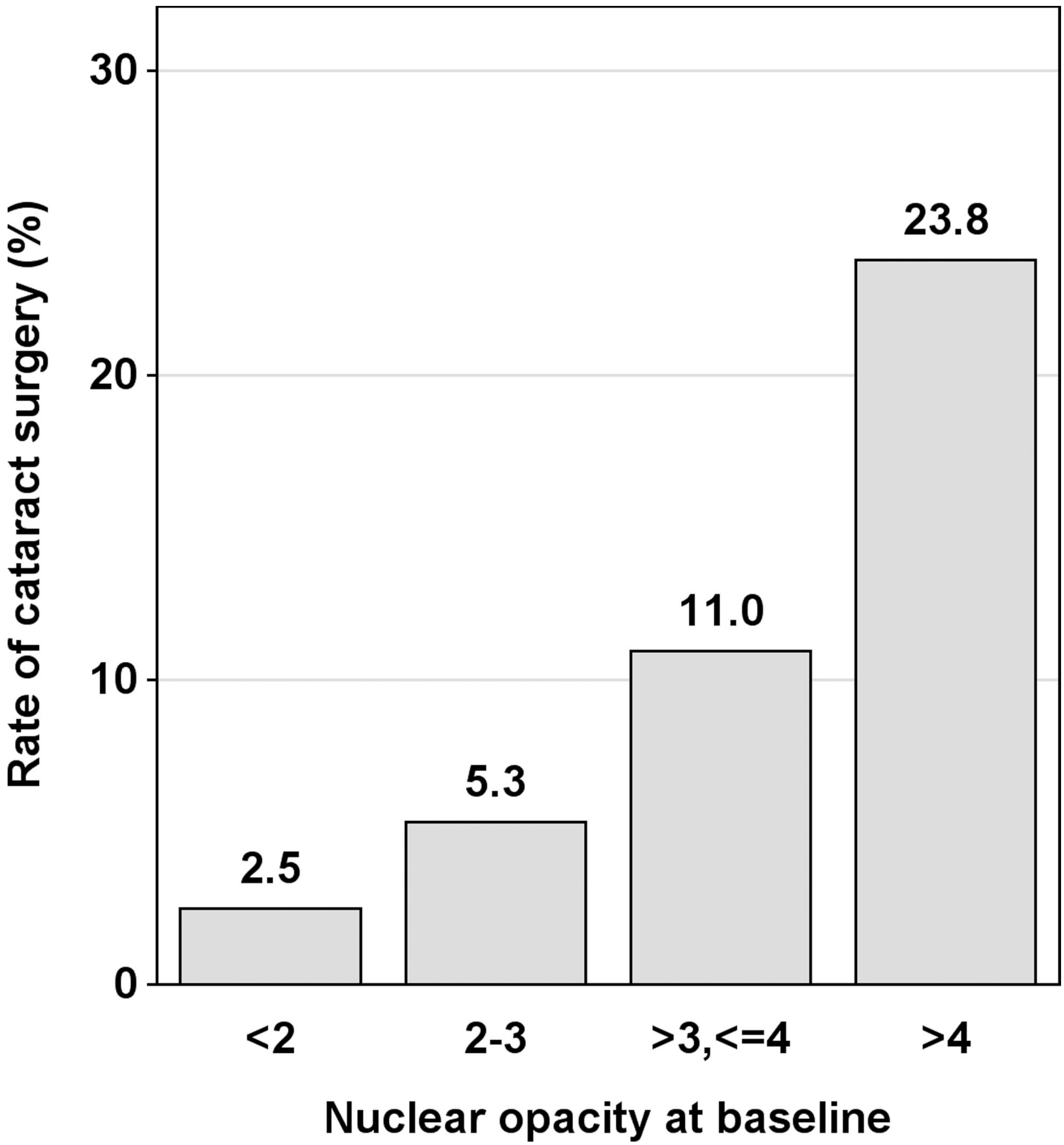
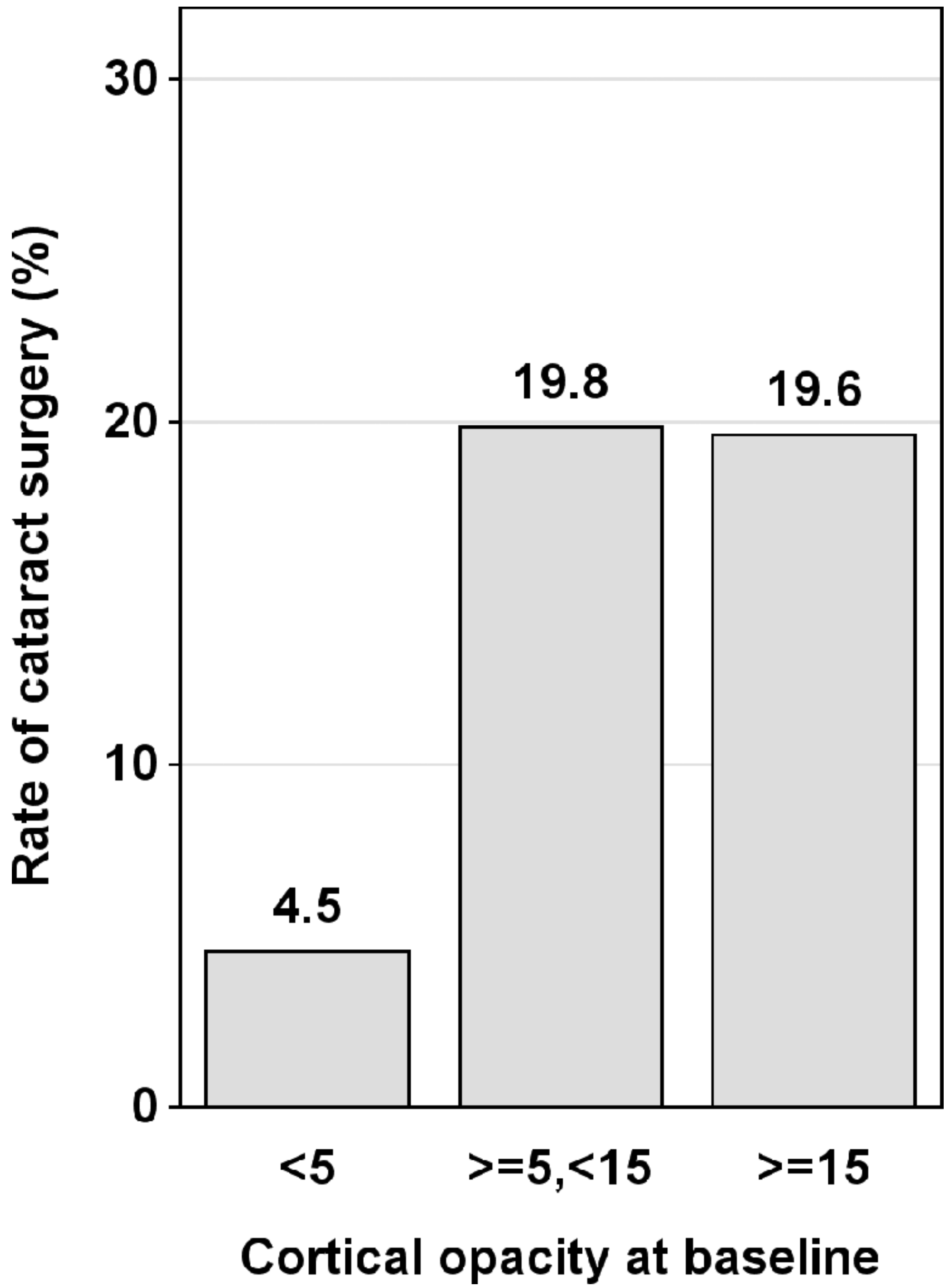


Figure 3.
Distribution of two-year changes, both the median and mean, in severity of the nuclear cataract.


Rate of cataract surgery (%)
30
20
10
0
2.5
5.3
11.0
23.8
<2
2-3
>3,<=4
>4
Nuclear opacity at baseline


Rate of cataract surgery (%)
30
20
10
0
4.5
19.8
19.6
<5
>=5,<15
>=15
Cortical opacity at baseline

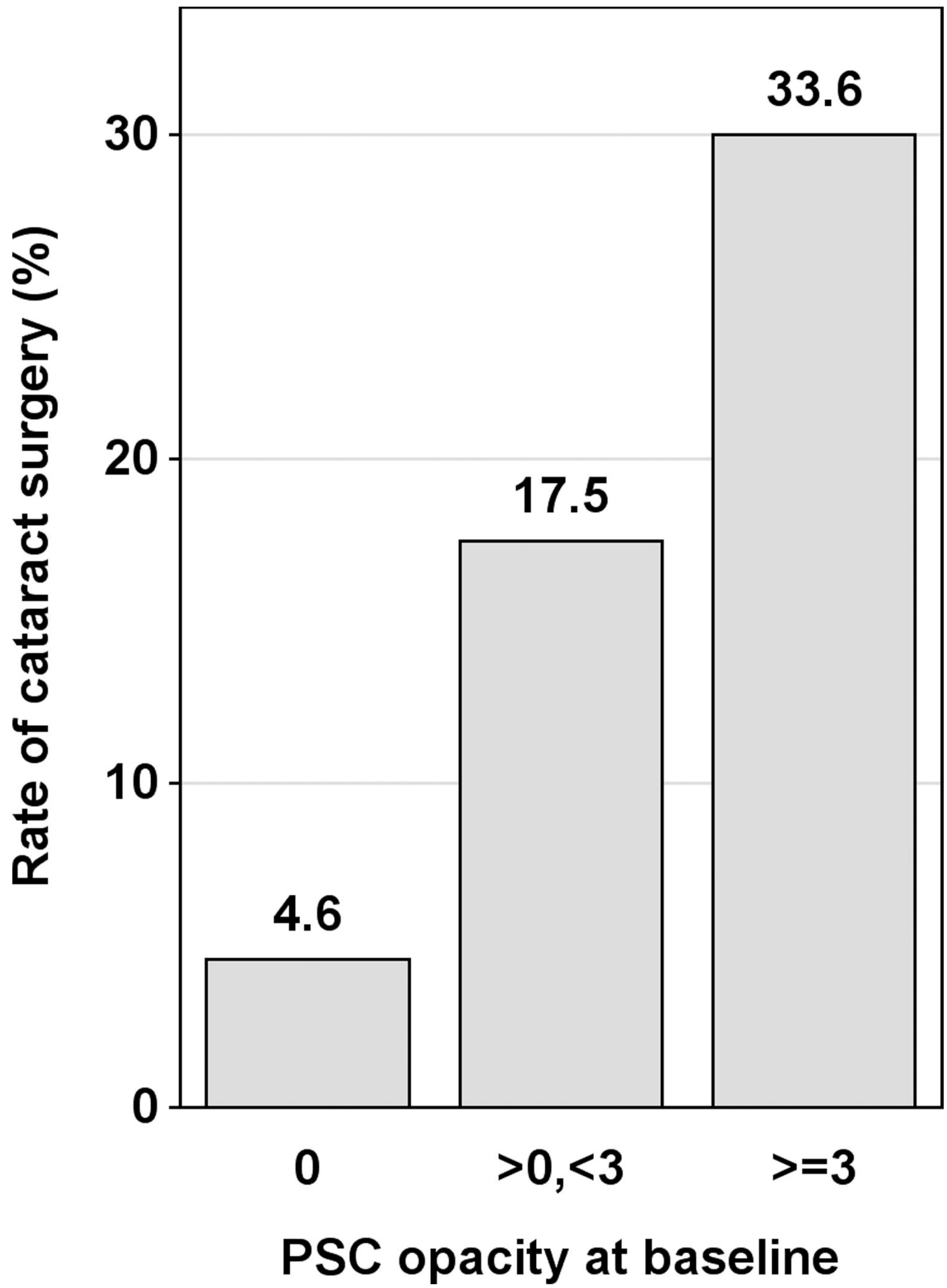


Figure 4.
Rates of progression to cataract surgery at 5 and 10 years for different levels of cataract severity at baseline for the 3 cataract type: (a) nuclear cataract, (b) cortical cataract, (c) posterior subcapsular cataract.

Table 1

Baseline characteristics of participants enrolled in the Age-Related Eye Disease Study (AREDS) included in the analyses of lens progression

Characteristics of Participants	N = 3466
Age (mean, standard deviation)	68.8 (4.9)
Male	1537 (44.3)
Smoking	
Never	1622 (46.8)
Former	1625 (46.9)
Current	219 (6.3)
Diabetes	275 (7.9)
AMD category	
1	1003 (28.9)
2	940 (27.1)
3	1170 (33.8)
4	353 (10.2)

Values are expressed as number (%) of participants unless otherwise indicated. Values are for participants included in the analysis of cataract surgery by five years for nuclear cataract. Participants included in the analyses of cataract surgery by five years for cortical (N=3478) and PSC cataracts (N=3471) have similar baseline characteristics, as do the patients included in the analyses of visual acuity loss.

AREDS AMD categories: 1. None or few small drusen, 2. Small or medium sized drusen 3. Extensive medium sized drusen or large drusen, 4. Late AMD in one eye

Table 2

Number of participants included in the analyses and the number of eyes that experienced the outcome of cataract surgery or 2 or more lines of visual acuity loss in the 6 separate analyses of 3 cataract types.

	Nuclear Cataract	Cortical Cataract	PSC Cataract
Cataract surgery (number included/ number affected with cataract surgery)	3466/336	3478/339	3471/339
≥ **2-line visual acuity loss** (number included/number affected with vision loss)	3419/663	3429/663	3424/663

The two primary endpoints, progression to cataract surgery and two-line or greater loss of visual acuity by 5 years, were evaluated based on a change in opacity grade by year 2 for the three types of cataract (nuclear, cortical, and PSC).

Table 3

Baseline lens opacity grades, and two year changes in grade by cataract surgery and visual acuity loss analyses at year five.

	Cataract surgery analysis	≥2-line visual acuity loss analysis
	N (%)	N (%)
Nuclear	6054 (100)	5970 (100)
Baseline opacity grade		
≤2	3411 (56.3)	3381 (56.6)
>2,≤3	1651 (27.3)	1626 (27.2)
>3,<4	554 (9.2)	540 (9.0)
≥4	438 (7.2)	423 (7.1)
Change in grade by year 2		
<1	5133 (84.8)	5070 (84.9)
≥1	921 (15.2)	900 (15.1)
Concurrent lens opacities by year 5		
Moderate cortical	1191 (19.7)	1636 (27.4)
Moderate PSC (central 5mm)	325 (5.4)	590 (9.9)
Cataract surgery in fellow eye	376 (6.2)	–
Cortical (central 5mm)	6082 (1000)	5995 (100)
Baseline opacity grade (%)		
0	3980 (65.4)	3935 (65.6)
>0, ≤5	1697 (27.9)	1666 (27.8)
>5, ≤10	161 (2.6)	154 (2.6)
>10	244 (4.0)	240 (4.0)
Change in grade by year 2		
<5	5826 (95.8)	5752 (95.9)
≥5	256 (4.2)	243 (4.1)
Concurrent lens opacities by year 5		
Moderate nuclear	1150 (18.9)	1742 (29.1)
Moderate PSC (central 5mm)	323 (5.3)	586 (9.8)
Cataract surgery in fellow eye	378 (6.2)	–
PSC (central 5mm)	6069 (100)	5984 (100)
Baseline opacity grade (%)		
0	5733 (94.5)	5665 (94.7)
>0	336 (5.5)	319 (5.3)
Change in grade by year 2		
<5	5987 (98.6)	5914 (98.8)
≥5	82 (1.4)	70 (1.2)
Concurrent lens opacities by year 5		
Moderate nuclear	1145 (18.9)	1739 (29.1)

	Cataract surgery analysis	≥2-line visual acuity loss analysis
	N (%)	**N (%)**
Moderate cortical	1201 (19.8)	1644 (27.5)
Cataract surgery in fellow eye	377 (6.2)	–

The values represent the number of eyes (N) within each category as well as the percentage of the total number of eyes for each analysis (%).

Table 4

Hazards Ratios (HR) of cataract surgery and loss of visual acuity at 5 years based on lens opacity changes at 2 years.

	Level	Cataract surgery analysis		≥2-line visual acuity loss analysis	
		HR (95%CL)	P	HR (95%CL)	P
Nuclear					
Change in grade (ref: <1)	≥1	2.77 (2.07, 3.70)	<.001	1.83 (1.49, 2.25)	<.001
Age		1.07 (1.04, 1.10)	<.001	1.05 (1.03, 1.07)	<.001
Male		0.97 (0.75, 1.25)	0.794	0.90 (0.76, 1.08)	0.253
Smoking	Former	1.12 (0.86, 1.46)	0.388	1.08 (0.90, 1.29)	0.403
	Current	1.19 (0.75, 1.89)	0.470	1.24 (0.87, 1.76)	0.237
Diabetes		1.69 (1.13, 2.52)	0.010	1.04 (0.76, 1.41)	0.805
Baseline grade (ref: ≤2)	>2,≤3	1.79 (1.29, 2.49)	<.001	1.41 (1.16, 1.72)	<.001
	>3,<4	3.75 (2.55, 5.51)	<.001	2.37 (1.82, 3.09)	<.001
	≥4	8.09 (5.52,11.85)	<.001	3.17 (2.40, 4.18)	<.001
Concurrent cortical		1.74 (1.34, 2.26)	<.001	1.19 (1.00, 1.43)	0.049
Concurrent PSC (central 5mm)		4.66 (3.49, 6.22)	<.001	1.98 (1.60, 2.45)	<.001
AMD Category	2	–	–	0.77 (0.62, 0.95)	0.014
	3	–	–	0.66 (0.54, 0.81)	<.001
	4	–	–	0.48 (0.34, 0.70)	<.001
Cortical (central 5mm)					
Change in grade (ref: <5)	≥5	1.91 (1.27, 2.87)	0.002	1.13 (0.78, 1.65)	0.519
Age		1.07 (1.04, 1.10)	<.001	1.05 (1.03, 1.07)	<.001
Male		1.01 (0.78, 1.31)	0.949	0.89 (0.75, 1.06)	0.206
Smoking	Former	1.08 (0.83, 1.41)	0.562	1.07 (0.90, 1.28)	0.431
	Current	1.24 (0.76, 2.02)	0.392	1.26 (0.88, 1.80)	0.211
Diabetes		1.49 (0.93, 2.37)	0.095	1.01 (0.74, 1.38)	0.932
Baseline grade (ref: 0)	>0,≤5	1.39 (1.05, 1.83)	0.021	1.30 (1.09, 1.55)	0.003
	>5, ≤10	3.52 (2.29, 5.41)	<.001	1.92 (1.26, 2.94)	0.003
	>10	2.35 (1.45, 3.81)	<.001	1.53 (1.03, 2.26)	0.034
Concurrent nuclear		3.12 (2.38, 4.11)	<.001	2.12 (1.78, 2.53)	<.001

	Level	Cataract surgery analysis		≥2-line visual acuity loss analysis	
		HR (95%CL)	P	HR (95%CL)	P
Concurrent PSC (central 5mm)		4.30 (3.18, 5.82)	<.001	1.95 (1.58, 2.40)	<.001
AMD Category	2	–	–	0.78 (0.63, 0.96)	0.019
	3	–	–	0.68 (0.55, 0.83)	<.001
	4	–	–	0.44 (0.31, 0.64)	<.001
PSC (central 5mm)					
Change in grade (ref: <5)	≥5	8.26 (5.55,12.29)	<.001	3.05 (1.79, 5.19)	<.001
Age		1.08 (1.05, 1.11)	<.001	1.06 (1.04, 1.08)	<.001
Male		0.91 (0.71, 1.18)	0.492	0.92 (0.77, 1.09)	0.336
Smoking	Former	1.17 (0.90, 1.52)	0.253	1.08 (0.90, 1.28)	0.405
	Current	1.18 (0.73, 1.90)	0.495	1.24 (0.87, 1.78)	0.233
Diabetes		1.46 (0.94, 2.28)	0.093	1.02 (0.75, 1.39)	0.876
Baseline grade (ref: 0)	>0	2.63 (1.89, 3.66)	<.001	1.56 (1.14, 2.12)	0.005
Concurrent nuclear		3.54 (2.73, 4.60)	<.001	2.19 (1.84, 2.61)	<.001
Concurrent cortical		1.99 (1.53, 2.60)	<.001	1.26 (1.06, 1.51)	0.010
AMD Category	2	–	–	0.78 (0.63, 0.97)	0.023
	3	–	–	0.67 (0.55, 0.83)	<.001
	4	–	–	0.45 (0.31, 0.65)	<.001

Values are the result of Cox proportional hazard regression and take into account the correlation between eyes using the Wei-Lin-Weissfeld (WLW) method. The highlighted cells represent the HRs of the two primary endpoints, cataract surgery and 2-line or greater visual acuity loss based on the primary variable, change in lens opacity grade using the AREDS System for Classifying Cataracts by year two for the three cataract types. Baseline covariates included in the analyses were age as a continuous variable; gender (female gender is the reference group); both a former and current smoking history as reported by the patient; a medical history of diabetes mellitus type II; baseline AMD severity as measured using the AREDS categorization system [2]; baseline lens opacity grade; and the presence of multiple cataract types.

Table 5

Concordance Probability Estimates (standard error) for cataract surgery and 2-line or greater visual acuity loss analyses by five years for the three cataract types.

Opacity Type	Cataract surgery analysis	≥2-line visual acuity loss analysis
Opacity Type		
Nuclear	0.73 (0.012)	0.65 (0.011)
Cortical (central 5mm)	0.70 (0.012)	0.65 (0.011)
PSC (central 5mm)	0.71 (0.012)	0.64 (0.011)

These values were calculated with the SAS program from Gönnen and Heller. The CPE's for all the analyses are greater than 0.5 (SE≤0.1) and indicate that the adjusted Cox proportional hazard regression models have modest predictive power.