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Risk Factors Associated with Age-Related Nuclear and Cortical Cataract:

A Case-control Study in the Age-Related Eye Disease Study, AREDS Report No. 5

Age-Related Eye Disease Study Research Group

Abstract

Objective: To investigate possible risk factors for age-related nuclear and cortical cataracts in participants in the Age-Related Eye Disease Study (AREDS).

Design: Case-control study.

Participants: Of the 4757 persons enrolled in AREDS, 4477 age 60 to 80 years are included in the study.

Main Outcome Measures: Slit-lamp lens photographs were used to classify participants into one of three nuclear opacity groups (moderate nuclear, mild nuclear, and controls), ignoring cortical opacities. Retroillumination lens photographs were used to classify participants into one of three cortical opacity groups (moderate cortical, mild cortical, and controls), ignoring nuclear opacities.

Results: Persons with moderate nuclear opacities were more likely to be female, nonwhite, and smokers and to have large drusen. Moderate nuclear opacities were less common in persons with higher educational status, a history of diabetes, and among those taking nonsteroidal antiinflammatory drugs. Moderate cortical opacities were associated with dark iris color, large drusen, weight change, and, at a borderline level of significance, higher levels of sunlight exposure and use of thyroid hormones. Moderate cortical opacities were less common in persons with higher educational status.

Conclusion: Consistent findings have now been reported across many studies for gender, educational status, sunlight exposure, and smoking. Our findings that use of nonsteroidal antiinflammatory drugs is inversely associated with nuclear cataract and that dark iris color and use of thyroid hormones may increase cortical cataract risk are less well substantiated and require further investigation. *Ophthalmology 2001;108:1400-1408*

Visual impairment and blindness from cataract is an important public health problem throughout the world. Age-related cataract accounts for about half of the 32 million cases of blindness worldwide.[1] Most persons with severe impairment from cataract are in the developing countries of Asia and Africa, where barriers to cataract surgery are greatest. In developed countries, where cataract surgery is widely available, cataracts are a less frequent cause of blindness but a common cause of visual impairment. In the population-based Baltimore Eye Survey[2] and the Salisbury Eye Evaluation Project,[3] cataracts were the leading cause of visual impairment (best-corrected visual acuity in the better eye of worse than 20/40 but better than 20/200) among older adults. In both studies, rates of visual impairment from

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Writing team is in the Appendix. Full list of the AREDS Research Group is in Am J Ophthalmol 2001;131:167-175.

cataract were higher in African Americans than in whites. Although surgical treatment for cataract is effective, the cost of the large number of procedures done each year is high. In the United States, cataract surgery is the most frequently performed surgical procedure in the Medicare program, with approximately 1.35 million cataract operations done each year at a cost of approximately $3.4 billion.[4] The identification of modifiable risk factors or interventions that affect the development of cataract could have a large economic impact and reduce rates of blindness and visual impairment throughout the world.

The Age-Related Eye Disease Study (AREDS) is an ongoing multicenter study of the natural history of cataract and age-related macular degeneration (AMD).[5] The study includes a randomized clinical trial that will evaluate the effect of high doses of selected nutritional supplements on the incidence and progression of the two conditions. AREDS has also been designed, in part, to search for clues about the cause of cataract and possible strategies for intervention. Participants whose lens status ranged from no opacities to moderately severe opacities were entered into this longitudinal study. Data were collected at entry on a wide range of possible risk factors for cataract, including those suggested by earlier laboratory and clinical studies: educational status,[6-9] smoking,[7,9-12] diabetes,[7,9,13-15] sunlight exposure,[6,9,16-20] body mass index,[21-23] drug use,[7,9,20] estrogen replacement therapy,[24-26] and dietary intake of various micronutrients.[27,28] This report is an exploration of the relationship between baseline lens status and prior or concurrent potential nonnutritional risk factors. The role of nutritional intake will be examined in a subsequent report.

Material and Methods

Study Population

Details of the AREDS study design have been published elsewhere[5] and are briefly described here. A total of 4757 persons, 55 to 80 years of age at the time of enrollment, were entered into the study at 11 eye care centers from 1992 to 1998. The ocular eligibility requirements were largely determined by the AMD component of AREDS. Persons in four AMD categories were enrolled, with macular status ranging from essentially no macular pathology in either eye (category 1) to advanced AMD or lesions of AMD with visual acuity less than 20/30 in only one eye (category 4). Except for the requirements that all participants have at least one eye with a visual acuity of 20/30 or better and that the media be sufficiently clear to classify AMD status with fundus photographs, lens opacity status was not specifically considered in selecting participants. However, the effect of eligibility requirements may have been to exclude persons with more extensive opacities from enrollment. The large sample size requirement for the AMD component of the study and the expected high prevalence of lens opacities in the targeted age group made it likely that a diverse array of age-related lens opacities of mild to moderate severity would be present in the cohort. Additional exclusions included persons with more than minimal diabetic retinopathy, previous ocular surgery (except cataract surgery and unilateral photocoagulation for neovascular AMD), and eye diseases that could complicate assessing the progression of lens opacities or AMD (e.g., optic atrophy, acute uveitis). Finally, persons with illnesses and disorders that made long-term follow-up unlikely were not eligible.

The 11 AREDS clinics recruited participants from sources that were the most productive for each clinic. Sources of participants included medical records of patients being seen at the clinic; referring physicians; patient lists from hospitals and health maintenance organizations; screenings at malls, fairs, senior centers, and other gathering places; public advertisements (radio, TV, newspapers, flyers); friends and family of participants and of clinical center staff.

The AREDS protocol was approved by each center's institutional review board before initiation of the study, and informed consent was obtained from all participants before enrollment. The present analysis of 4477 participants excludes all 110 persons age 55 to 59 among whom

cataract prevalence was low and who were all in AMD categories 3 and 4. Also excluded were 128 persons with bilateral aphakia or pseudophakia and 42 persons missing photographs for both eyes or whose single phakic eye had lens opacity of severity less than mild. The phakic eye was used to classify lens status in the remaining participants with unilateral pseudophakia.

Procedures

An eye examination, a limited physical examination, and a detailed questionnaire were administered at the baseline visits and provided data on possible risk factors for lens opacities. Data from the general physical and ophthalmic examinations included height, weight, blood pressure, manifest refraction, best-corrected visual acuity, intraocular pressure, slit-lamp biomicroscopy, and ophthalmoscopy. The questionnaire provided demographic information, history of smoking, medical history, history of specific prescription drug and nonprescription medication use, and history of vitamin and mineral use. A questionnaire on sunlight exposure was implemented in 1996. Stereoscopic color fundus photographs of the macula were also obtained.

Specially modified Topcon slit-lamp cameras and Neitz retroillumination cameras were used to take color photographs of the lenses of participants at baseline.[29] The lens photographs were evaluated at a central reading center by trained and certified examiners. The Age-Related Eye Disease System for Classifying Cataracts,[30] an extension of the Wisconsin System for Classifying Cataracts from Photographs,[29] was used to assess the presence and severity of nuclear, cortical, and posterior subcapsular lens opacities. The extent of cortical and posterior subcapsular (PSC) opacities was graded by estimating the area of lens involvement in sectors of a grid overlay on the retroillumination photographs. The individual subfield percentages were combined to estimate an overall percentage of involvement within the central 5 mm of the lens and, for cortical opacities, within the full visible lens. Nuclear opacity grades ranged from 0.9 to 6.1 using cut-points set by a series of standard photographs with increasingly severe nuclear sclerosis.[30] PSC opacities are ignored in this report, because they were uncommon in the cohort (only 2.5% of persons had PSC > 5% of the central 5 mm in at least one eye) and, when seen, often occurred with nuclear or cortical opacities.

Case-Control Design

Possible risk factors for nuclear opacity and cortical opacity were considered in separate analyses.

Nuclear Opacity. Participants were classified into one of three nuclear opacity groups, ignoring cortical opacity.

Group 1: Moderate nuclear: Nuclear grade ≥ 4 in at least one eye.

Group 2: Mild nuclear: Nuclear grade < 4 in each eye and > 2 in at least one eye.

Group 3: Controls: Nuclear grade ≤ 2 in each eye.

Cortical Opacity. Participants were classified into one of three cortical opacity groups, ignoring nuclear opacity. Percent cortical is of the full visible lens. Pupil dilatation of at least 6 mm was achieved in 97% of the eyes photographed.

Group 1: Moderate cortical: Cortical > 5% in at least one eye.

Group 2: Mild cortical: Cortical $\leq 5\%$ in each eye and > 0% in at least one eye.

Group 3: Controls: Cortical = 0% in each eye.

We evaluated risk factors for each lens opacity case group by comparing it with the control group. The baseline risk factor variables can be divided into four classes: demographic, medical history, use of medication, and ophthalmic. For analysis, continuous variables were categorized into three groups by the first and fourth quintiles, except for age in years, which has categories 60 to 65, 66 to 70, and 71 to 80.

Demographic. Age, race, gender, education, smoking status (current cigarette smoker, past smoker, never smoked), body mass index (BMI), weight change since age 20, and sunlight exposure (adult lifetime average annual ocular ultraviolet (UV)-B exposure: a function of regional ambient UV-B, hours spent outdoors from April through September, outdoor time spent over water, use ofocular protection-brimmed hat, sunglasses, and prescription spectacles; adapted from McCarty et al).[31]

Medical History. Presence of hypertension (systolic ≥ 160 mmHg, diastolic ≥ 90 mmHg, or taking medication for hypertension), angina, diabetes (under treatment for diabetes), skin cancer (melanoma, basal or squamous cell), and arthritis were noted.

Use of Oral Medication (current use with 5 or more lifetime years of regular use by at least 5% of participants). Diuretics, aspirin, antacids, hydrochlorothiazide, nonsteroidal antiinflammatory drugs, thyroid hormones, β-blockers, and, for women only, estrogen or progestogen use were noted.

Ocular: Iris Color and Refractive Error. Iris color was graded in each eye compared with standards on a scale from 1 (light or blue) to 4 (dark or brown); a person was "light" if both eyes were code 1, "dark" if both eyes were code 4, "mixed" otherwise. A person was "myopic" if both eyes were myopic by -1.0 diopters spherical equivalent refractive error or more; "hyperopic" if both eyes had +1.0 diopters spherical equivalent refractive error or more; else "other," which includes emmetropes and mixed cases. The refractive error of the phakic eye was used to classify the refractive status of participants with unilateral pseudophakia. A person was assigned to one of five AMD categories according to the age-related macular condition of the more severely affected eye: no or few small drusen, intermediate drusen, large drusen, geographic atrophy, neovascular maculopathy.[32]

Statistical Modeling and Analyses

Risk factors were identified separately for nuclear and cortical cataract in a three-stage process using polychotomous logistic regression (SAS procedure CATMOD). Age and gender were included in all models. In this procedure, the two levels of severity of each type of lens opacity are compared simultaneously with the control group. In *stage 1*, each risk factor was included separately in a "univariable" analysis. Variables identified as significant ($P < 0.2$) for at least one case group were retained for further analysis. Three-level categorical variables were retained if the high versus low (top 20% versus bottom 20%) comparison was significant. The five-level variable AMD was retained if any comparison with the mildest level (no or few drusen) was significant.

In *stage 2*, all variables retained from stage 1 from any of the regressions were entered as a group into a single multivariable polychotomous model. In *stage 3*, model simplification consistent with chi-square tests of change in deviance was performed. This simplification consisted of identifying nominally nonsignificant ($P > 0.1$) coefficients from stage 2 and replacing them by structural zeros. Variables not significant for any case group were excluded from the model. Model simplification continued until all variables included were significant at $P < 0.1$, and the reduced model yielded a nonsignificant ($P > 0.05$) worsening of fit according to the likelihood ratio criterion. The significance of estrogen replacement therapy was evaluated by including it in the final model restricted to women.

Prevalence odds ratios (ORs) that describe the association between presence of disease and the risk factors were computed for each case group relative to the controls.

Results

The demographic characteristics of the 4477 participants who were included in the analyses are shown in Table 1 by type and severity of lens opacity. For nuclear opacity, the number of participants classified with moderate or with mild opacity or as controls is 615, 2044, and 1818, respectively. For cortical opacity, the number of participants classified with moderate or with mild opacity, or as controls is 1068, 2601, and 808, respectively.

Age-gender adjusted prevalence ORs for each risk factor by lens opacity category from the stage 1 univariable analyses are given in Table 2. ORs significant at $P< 0.2$ are in boldface.

The fit of the stage 3 reduced polychotomous multivariable logistic regression model was acceptable (i.e., not significantly worsened as assessed by change in deviance; nuclear opacity model, $P = 0.64$; cortical opacity model, $P = 0.74$). Estimated odds ratios and significant associations ($P \leq 0.05$) from the stage 3 final models are given in Table 3.

Significant Associations with Prevalent Cataract

Nuclear Cataract. We found the presence of moderate nuclear opacity is significantly associated with increasing age (> age 70 versus ≤ age 65, OR = 12.7), nonwhite race (OR = 2.09), current smoking (OR = 1.96), female gender (OR = 1.77), and large drusen (OR = 1.29). Persons at lower risk for moderate nuclear opacity are those with higher education (OR = 0.64), with diabetes (OR = 0.68), and those taking nonsteroidal antiinflammatory drugs (OR = 0.65). Similar associations are found with mild nuclear opacity, except for diabetes. ORs for dark iris color were similar for moderate (OR = 1.44) and mild (OR = 1.38) nuclear cataract, but the finding was significant only for the more prevalent mild type. Associations with myopia are in opposite directions for the two levels of nuclear cataract, inverse for mild nuclear opacity (OR = 0.78) and direct, at a borderline level of significance, for moderate nuclear opacities (OR = 1.31).

Cortical Cataract. The presence of moderate cortical opacity is associated with increasing age (> age 70 versus ≤ age 65, OR = 5.96), dark iris color (OR = 3.85), weight change (OR = 1.49), large drusen (OR = 1.38), and, at a borderline level of significance, higher levels of sunlight exposure (OR = 1.33) and use of thyroid hormones (OR = 1.46). Persons with higher education are at lower risk of moderate cortical cataract (OR = 0.74). Associations with age (OR = 2.04), dark iris color (OR = 3.13), large drusen (OR = 1.34), sunlight exposure (OR = 1.34), and use of thyroid medications (OR = 1.52) are also found with mild cortical opacity. For mild cortical opacities the odds ratios for sunlight exposure and use of thyroid hormones are similar to those for moderate cortical opacities and are significant at the 0.05 level. In addition, there is a decreased risk of mild cortical opacities in persons who are nonwhite (OR = 0.47), and an increased risk for persons with intermediate size drusen (OR = 1.26).

Discussion

We have used data collected at baseline in AREDS to identify possible risk factors for age-related nuclear and cortical cataract. Associations were noted for many factors that have previously been reported as possible risk factors for cataract.

Associated Risk Factors

As expected, the odds ratio for age was large. The age effect was more marked for nuclear than cortical cataracts. For example, for moderate nuclear cataract the OR for persons over age 70

compared with persons under age 66 was 12.7. The corresponding OR for moderate cortical cataract was 5.96. It remains a challenge for epidemiologic and laboratory studies to explain the rapid and large increase in cataract risk with advancing age. Studies of genetic factors that affect aging, and the interaction of such factors with environmental insults, may help explain the strong influence of age on cataract risk.

The cumulative evidence from many studies suggests a slight excess risk of cataract for women.[6,7,20,33-36] In AREDS the excess risk was only for nuclear cataract. Clinic-based case-control studies[7,33] and a general population survey[36] have reported a statistically significant excess risk of cortical opacities for women. However, three population-based surveys[20,34,35] found a higher prevalence of both cortical and nuclear opacities in women. Although the finding of an excess risk of cataract for women seems consistent across studies, it is less clear whether this pertains to all cataract types or only some types. Hormonal influences or differential environmental exposures for men and women may explain the small, but apparently real, gender difference in cataract risk.

We found a higher risk of nuclear cataracts in nonwhites, who in AREDS are mostly African Americans. No association was noted between race and moderate cortical opacities. The finding that nonwhites were at decreased risk of mild cortical opacities was unexpected and perhaps spurious. Three population-based studies[6,35,37] have reported an increased risk of cortical cataract in blacks. Compared with whites, participants of African descent in the Barbados Eye Study had a higher overall prevalence of lens opacities and cortical opacities. Black race was also associated with cortical opacities in the Lens Opacities Case-Control Study.[7] Racial differences in cataract risk may be related to genetic factors or differences in exposures to cataract risk factors. The apparent greater risk of cataract in blacks, although not the major explanation, may contribute to the much higher rates of blindness caused by unoperated cataracts in blacks compared with whites.[38]

The association between educational achievement and cataract has been one of the most consistently reported observations in epidemiologic studies of cataract.[6-9] In our study, as in other studies, the relationship persists even after adjustment for potential confounders, factors such as smoking, alcohol use, and diabetes, which have been associated with both educational status and cataract. These results suggest that there are unknown confounding factors associated with both educational level and lens opacity severity. Identification of these factors could lead to the development of interventions designed to reduce the risk of development of lens opacities.

There is a growing consensus that smoking increases the risk of nuclear cataract; no association has been reported for cortical cataract.[7,9-12] In AREDS the ORs for nuclear cataract associated with current smoking were 1.96 and 1.44 for moderate and mild nuclear opacities, respectively. No association was noted for cortical cataracts. Associations between cigarette smoking and nuclear cataract have been reported in case-control,[7] cross-sectional,[20,39,40] and prospective studies of lens opacities,[12,41] as well as in studies of incident cataracts[42] and extracted cataracts.[43] The consistency of this finding across studies and in diverse populations, combined with reports of a dose-response relationship,[10,41] suggests that smoking is one of the relatively few known modifiable factors associated with cataract. Suggested mechanisms by which smoking might damage the lens include an increase in oxidative stress caused by a lowering of circulating nutrients with antioxidant capabilities[42,43] or lens damage from by-products of smoke, such as cadmium[44] or isocyanate.[45]

Ecologic studies have reported a higher prevalence of cataract in areas of greater sunlight and/or UV light exposure.[6,9,18] Data from the first Health and Nutrition Examination Survey showed a higher prevalence of cataract, in particular cortical cataract, in areas with higher UV

light exposure.[6] Subsequent studies that have attempted to quantify individual cumulative lifetime exposure to UV-B radiation have provided evidence in support of the UV light/cataract hypothesis.[16,17,19] In a study of Chesapeake watermen that estimated individual annual exposure to UV-B radiation after age 15, men in the upper 25% of exposure had a more than threefold increase in risk of cortical cataract compared with men in the lowest 25%.[16] In AREDS, where we used an instrument similar to that in the Chesapeake watermen study to quantify individual exposure, we found a higher risk of cortical cataract in persons with higher lifetime average annual ocular UV-B exposure, although the finding for moderate cortical opacities was at a borderline level of significance. Differences in significance levels for mild and moderate cortical opacities may have resulted from the smaller number of participants with moderate opacities and the resultant decrease in statistical power. Although the totality of evidence from epidemio-logic studies suggests that cortical cataract is associated with UV light exposure, the relative contribution of such exposure to overall risk of visually significant cataract in the general population remains unclear.

We examined the relationship between cataract and those medications that were being used by at least 5% of the participants at baseline. Risk of cataract was assessed for 5 or more years of use compared with less or no use of the medication. Use of nonsteroidal antiinflammatory drugs (e.g., aspirin, ibuprofen, naproxen, piroxicam) was associated with a decreased risk of nuclear cataract. No associations were noted when aspirin use was examined separately. Our data do not permit us to examine whether the findings for the antiinflammatory drugs reflect a possible protective effect of the drugs or of the underlying conditions being treated with the drugs. We found no association between cataract and self-reported arthritis, a condition that is commonly treated with nonsteroidal analgesics. However, the finding for arthritis could be biased by unreliable self-reporting of the diagnosis of arthritis. A protective effect for aspirin-like analgesics was previously reported in a case-control study that included persons scheduled for cataract surgery as cases.[46] However, in a large prospective study of women, there was no evidence of a beneficial effect of nonsteroidal analgesics on rates of cataract extraction.[21] A possible protective effect for aspirin itself has been suggested by Cotlier.[47] Data from The Physicians' Health Study, a randomized trial of aspirin and β-carotene among U.S. male physicians, tended to exclude a large benefit from 5 years of low-dose aspirin therapy on cataract development and extraction, but data from that study were compatible with a modest benefit on cataract extraction with this duration of aspirin treatment.[48] Most other studies have noted no beneficial effect of aspirin on cataract.[7,9,33,49-51]

Users of thyroid hormones seemed to be at greater risk of cortical cataract in AREDS. We could not determine whether this finding is explained by an association with the underlying diseases being treated or the drugs themselves. Further substantiation is needed before concluding that use of thyroid hormones increases the risk of cataract.

Persons who had gained 53 or more pounds compared with those who had gained 10 or fewer pounds since age 20 were at increased risk of moderate cortical cataract. Higher body mass index (BMI: mass index = weight in kilograms divided by the square of height in meters) was associated with moderate cortical cataract in the AREDS age-gender adjusted analyses but not in the fully adjusted model. Epidemiologic studies that have examined the relationship between weight-related variables such as BMI and risk of specific cataract types have not produced consistent results.[7,21-23,52-54] Prospectively collected data from the Framingham Heart and Eye Studies reported an increased risk of cortical cataract with higher average BMI and increasing BMI over time, but no association with fluctuations in BMI.[23] The Salisbury Eye Evaluation Project also found that the risk of cortical opacification was greater in persons with higher BMIs.[54] Studies of nuclear opacities have produced mixed results, with some[7,54] reporting a decreased risk of nuclear opacification with higher BMI levels and another[22] reporting an increased risk of nuclear cataracts and cataract extraction with higher BMI levels.

No association between BMI and risk of cataract surgery was noted in the Beaver Dam Eye Study.[53] The inconsistency of findings across studies makes it difficult to evaluate the relationship between weight-related characteristics and risk of cataract.

We found that darker iris color was associated with cortical cataract and mild nuclear cataract. Other studies have noted associations between darker iris color and nuclear cataract,[20,33] but a biologic explanation for this finding has not been identified.

In what was probably a spurious finding, myopia was inversely associated with mild nuclear cataract. The finding of a direct association between myopia and moderate nuclear cataract, although at a borderline level of significance, was more expected. The myopic shift that is often seen clinically as nuclear cataract develops is the likely explanation for the latter finding.

In AREDS, statistically significant associations were found for cortical cataract and more advanced forms of drusen (large drusen or extensive intermediate size drusen). This finding must be interpreted cautiously because of the possibility of selection bias. For entry into AREDS, patients with no or minimal maculopathy (no drusen, small drusen, or intermediate drusen) were required to have media that were sufficiently clear to discern potential small (<63μm in diameter), punctate, or hard drusen on photographs. For patients with more advanced macular changes, such as large drusen or advanced AMD, the media had to be only sufficiently clear to discern these more advanced lesions on photographs. Thus, the eligibility criteria could have led to the selective enrollment of patients with both more severe lens opacities and more advanced AMD. It should be noted, however, that an association was noted only for cortical cataract and intermediate or large drusen but not for the most advanced forms of AMD— geographic atrophy and neovascular AMD. Results from other studies have not been consistent, and comparisons across studies are complicated by differing definitions of macular degeneration and cataract. Cross-sectional data from the Beaver Dam study found an association between "early age-related maculopathy" and nuclear cataract, but prospective data from that study reported no relationship between nuclear opacities and either "early" or "late" AMD.[55] In a study of Chesapeake Bay watermen, there was significantly greater risk of AMD in the presence of nuclear opacities,[56] and in the National Health and Nutrition Examination Survey there was an increased frequency of AMD in the presence of nuclear or cortical opacities.[57] However, the Blue Mountains Eye Study reported no associations between cataract types and age-related maculopathy.[58] On the basis of the data accumulated to date, it is not clear whether eyes with AMD are at greater risk of cataract.

Nonsignificant Factors

Some risk factors that have previously been reported were not significantly associated with cataract in our fully adjusted model.

Diabetes has been one of the more consistently reported risk factors for cataract, particularly among persons less than age 70.[7,9,13] Most studies have reported an excess risk of cortical[7] and PSC cataracts[6,7,14] in persons with diabetes. We found no association between diabetes and cortical cataract and were unable to study the relationship with PSC cataracts, because too few participants in AREDS had this form of cataract. Like the Lens Opacities Case-Control Study, we observed an inverse association between diabetes and nuclear cataract.[7] It is possible that our ability to examine the relationship between diabetes and cataract may have been hampered by the eligibility criteria of AREDS, which called for the exclusion of persons with diabetes with more than minimal diabetic retinopathy. To the extent that increasing diabetic retinopathy is positively associated with cataract risk, those persons at the highest risk for cataract may have been systematically excluded, biasing the findings. Also, the older age of the cohort (median age, 69 years) may have restricted our evaluation of diabetes as a risk factor, because, when found, the diabetes/cataract association has been generally noted in persons less

than age 70.[13] The increased prevalence of cataract in postmenopausal women compared with men has suggested a possible relationship between estrogen and the development of cataract. In our study, women who were current users of estrogen replacement therapy and who had more than 5 lifetime years of regular use of such medication were significantly less likely to have nuclear and cortical opacities in the age-gender adjusted model but not in the fully adjusted model. In additional analyses (not shown), when we changed the definition of estrogen use to "ever" versus "never" use, the ORs were little changed in the full model, but the finding was then significantly protective for both moderate and mild nuclear cataract (OR = 0.71 and 0.82, respectively). Three earlier studies have noted an association between postmenopausal estrogen use and lens opacities. Two of the studies have suggested a protective effect for nuclear sclerosis.[24,26] The third reported reduced risk of cortical opacities among estrogen users older than age 65 years.[25] The cumulative evidence from the several studies that have examined the effect of estrogen use raises the possibility that reduction in the risk of cataract may be an additional benefit of post-menopausal estrogen use.

Many of the findings in AREDS reinforce results from earlier studies. Similarity of findings for gender, educational status, sunlight exposure, and smoking across studies with different selection criteria, definitions of cataract, methods of ascertaining risk factor data, and analytic approaches makes it more likely that reported associations are real.

Appendix

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Table 1.

Characteristics of Cataract and Control Participants

	Nuclear*				Cortical†			
	Moderate n = 615	Mild 2044	Controls 1818	Total 4477	Moderate 1068	Mild 2601	Controls 808	Total 4477
	%	%	%	N	%	%	%	N
Age (yrs)								
60-65	10	23	40	1250	14	29	41	1252
66-70	26	34	38	1551	34	35	34	1552
71-80	64	43	22	1676	51	36	25	1673
Race								
Other	5	5	3	199	7	3	4	201
White	95	95	97	4278	93	97	96	4276
Gender								
Female	63	58	51	2502	58	55	55	2496
Male	37	42	49	1975	42	45	45	1981
Education‡								
No college	40	39	29	1585	42	34	32	1587
Some college	31	30	30	1343	30	29	29	1343
	29	31	41	1546	28	36	40	1544
College graduate								
Smoking status								
Never smoked	43	44	46	1994	46	44	45	1998
Former smoker	47	48	48	2143	47	49	46	2139
Current smoker	10	8	6	340	7	8	9	340
Diabetes								
No	94	92	92	4128	91	93	92	4128
Yes	6	8	8	349	9	7	8	349

*Nuclear—moderate: nuclear grade ≥ 4 in at least one eye. Mild: nuclear < 4 in both eyes and > 2 in at least one eye. Control: nuclear ≤ 2 in both eyes.

†Cortical—Moderate: cortical grade > 5% in at least one eye. Mild: cortical ≥ 5% in both eyes and > 0% in at least one eye. Control: cortical = 0% in both eyes.

‡Three persons with unknown educational achievement.

Table 2.

Age- and Gender-adjusted Associations (Odds Ratios) between Prevalence of Lens Opacity and Baseline Risk Factors

Risk Factor	Exposure			Nuclear		Cortical	
	A	vs.	B	Moderate (n=5 615)	Mild (n=5 2044)	Moderate (n=5 1068)	Mild (n=5 2601)
Age	71-80		60-65	12.5	3.40	6.05	2.03
Gender	Female		Male	1.85	1.43	1.22	1.02
Race	Other		White	2.30	2.14	2.18	0.81
Education	College graduate		High school or less	0.61	0.62	0.60	0.87
Smoking status	Current		Never	1.99	1.49	0.78	0.89
BMI*	Top 20%		Bottom 20%	1.05	1.12	1.40	0.93
Weight change†	Top 20%		Bottom 20%	1.00	1.16	1.51	0.89
Sunlight exposure‡	Top 20%		Bottom 20%	0.94	0.92	1.28	1.31
Hypertension	Present		Absent	0.99	1.08	1.12	0.89
Angina	Present		Absent	1.04	1.06	1.13	1.00
Diabetes	Present		Absent	0.72	1.05	1.28	0.95
Skin cancer	Present		Absent	0.88	0.81	0.68	0.87
Arthritis	Present		Absent	0.92	0.95	1.05	1.00
Diuretics	Present		Absent	0.95	1.14	1.17	1.02
Aspirin	Present		Absent	0.92	0.92	1.17	1.08
Antacids use	Present		Absent	1.05	1.14	0.68	0.85
Hydrochlorothiazide use	Present		Absent	0.98	1.24	1.22	1.06
Antiinflammatory drugs	Present		Absent	0.68	0.82	1.15	1.09
Thyroid hormones	Present		Absent	0.70	0.89	1.45	1.52
β-blocker use	Present		Absent	1.09	1.11	1.51	1.13
Hormone use♀	Present		Absent	0.69	0.78	0.75	1.14
Iris color	Dark		Light	1.87	1.65	3.64	2.11
Refractive error	Myopic		Hyperopic	1.19	0.72	0.88	0.85
AMD category	Intermediate drusen		Control	0.99	1.02	1.03	1.18
	Large drusen		Control	1.35	1.09	1.38	1.33
	Geographic atrophy		Control	1.52	1.26	0.95	1.38
	Neovascular		Control	1.36	1.02	1.39	1.14

Associations are prevalence odds ratios comparing each cataract category with its control group, age- and gender-adjusted from Stage 1 polychotomous logistic regression.

Odds ratio >1 implies persons with exposure A show increased risk of disease compared with exposure B.

Odds ratios in boldface are nominally significant (P< 0.2).

*Body mass index: top, ≥ 31, bottom,≤ 23.6.

†Weight change: top, ≥ 53; bottom, ≤ 10 pounds since age 20.

‡Sunlight exposure: top, ≥ 1.65; bottom, ≤ 0.22, adult lifetime average annual ocular ultraviolet-B exposure (1.0= ocular exposure from model is equivalent to 1 hour/day outdoors in temperate months in typical U.S. region, not over water, and not wearing hat, glasses or sunglasses[31])

Table 3.

Polychotomous Multivariable Associations (Odds Ratios) between Prevalence of Cataract and Baseline Risk Factors

Risk Factor	Lens Opacity Type			
	Nuclear		Cortical	
	Moderate	Mild	Moderate	Mild
Variables with 3 levels: top vs. bottom				
Age*	12.7(9.32, 17.3)†	3.39(2.86, 4.03)†	5.96(4.57, 7.78)†	2.04(1.64, 2.50)†
Education	0.64(0.50, 0.81)†	0.65(0.55, 0.76)†	0.74(0.62, 0.88)†	—
Refractive error‡	1.31(0.98, 1.77)	0.78(0.64, 0.95)§		
Iris color	1.44(0.94, 2.23)	1.38(1.07, 1.79)§	3.85(2.59, 5.73)†	3.13(2.16, 4.54)†
Smoking status	1.96(1.35, 2.83)†	1.44(1.10, 1.89)†		
Sunlight exposure	—	—	1.33 (0.98, 1.82)	1.34(1.03, 1.74)§
Weight change			1.49(1.18, 1.88)†	—
Binary variables: present vs. absent				
Gender (Female= present)	1.77(1.44, 2.19)†	1.35(1.18, 1.55)†	1.12 (0.92, 1.38)	0.98 (0.83, 1.16)
Race (Other 5 present)	2.09(1.21, 3.59)†	1.62(1.11, 2.37)§	—	0.47(0.33, 0.66)†
Diabetes	0.68(0.47, 0.98)§	—		
Antiinflammatory drugs	0.65(0.48, 0.89)†	0.81(0.66, 0.99)§		
β–blocker use			1.30 (0.97, 1.75)	—
Thyroid hormones			1.46 (0.97, 2.19)	1.52(1.06, 2.18)§
Hypertension	—	—	—	0.88 (0.78,1.00)
Multinomial variable: each category vs. control				
Intermediate drusen	0.99(0.74, 1.32)	—	1.05 (0.79, 1.39)	1.26(1.01, 1.58)§
Large drusen	1.29(1.01, 1.66)§	—	1.38(1.07, 1.78)§	1.34(1.08, 1.66)†
Geographic atrophy	1.23(0.70, 2.13)	—	0.97 (0.48, 1.93)	1.47 (0.83, 2.59)
Neovascular	1.33(0.98, 1.78)	—	1.32 (0.96, 1.83)	1.10 (0.86, 1.51)

Odds ratios (95% confidence intervals) from Stage 3 model, comparing each cataract category with controls. Coefficients are estimated only for those cataract–variable combinations with significant coefficients in Stage 2; nonsignificant coefficients are modeled by structural zeros (indicated by –).

* Age groups: 60–65, 66–70, 71–80 years.

† $P \leq 0.01$.

‡ Myopia vs. hyperopia.

§ $P \leq 0.05$.