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Ocular Risk Factors for Age-related Macular Degeneration: The Los Angeles Latino Eye Study (LALES)

Samantha Fraser-Bell, FRANZCO, MPH[1,2], **Farzana Choudhury, MBBS, MPH**[1], **Ronald Klein, MD, MPH**[3], **Stanley Azen, PhD**[1,4], and **Rohit Varma, MD, MPH**[1,4] **on behalf of the Los Angeles Latino Eye Study Group4**

[1] Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA

[2] Department of Ophthalmology, University of Sydney, NSW, Australia

[3] Department of Ophthalmology and Visual Sciences, University of Wisconsin School of Medicine and Public Health, Madison, WI

[4] Doheny Eye Institute and Department of Ophthalmology, Keck School of Medicine, University of Southern California, Los Angeles, CA

Abstract

Purpose—To assess the association of ocular factors and age-related macular degeneration (AMD) in Latinos.

Design—Population-based, cross-sectional study of 6357 self-identified Latinos aged 40 years and older.

Methods—Ophthalmic examination included subjective refraction, measurement of axial length, evaluation of iris color, Lens Opacities Classification System II (LOCS II) grading of cataracts, and stereoscopic macular photographs for AMD lesions. Generalized estimating equation analysis incorporated data from both eyes to estimate odds ratios adjusted for covariates.

Results—After controlling for confounders (age, gender and smoking), prior cataract surgery was associated with advanced AMD (OR: 2.8, 95% CI 1.0, 7.8), increased retinal pigment (OR: 1.6, 95% CI 1.0, 1.5) and retinal pigment epithelial depigmentation (OR: 2.2, 95% CI 1.1, 4.4). The presence of any lens opacity was associated with soft drusen (OR: 1.2; 95% CI 1.0, 1.5). Longer axial length (per mm) was associated with a decreased odds of soft drusen, increased retinal pigment, and geographic atrophy (GA) (ORs: 0.8 [95% CI 0.7, 0.9], 0.8 [95% CI 0.7, 0.9], 0.7 [95% CI 0.5, 0.9], respectively. Myopia was inversely associated with soft drusen (OR: 0.8; 95% CI 0.7, 1.0). Lighter colored irises were associated with GA (OR: 5.0; 95% CI 1.0, 25.3).

Correspondence and reprint requests to: Rohit Varma MD, MPH, Doheny Eye Institute, Suite 4900, 1450 San Pablo Street, Los Angeles, CA 90033. Phone: (323) 442-6411; FAX: (323) 446-6412; rvarma@usc.edu.

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Statement about Conformity: The study protocol was approved by the Institutional Review Board (IRB)/Ethics Committee at the University of Southern California and all study procedures adhered to the recommendations of the Declaration of Helsinki. Written consent was obtained from all participants.

Conclusions—Cross-sectional associations of ocular factors such as cataract, cataract surgery, and refractive errors with early AMD lesions found in Latinos were consistent with those in whites. Additionally, prior cataract surgery was associated with advanced AMD.

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness and visual impairment in the US and other industrialized countries[1–3]. Previous population-based studies among Caucasians have identified possible associations of various ocular factors with AMD. These include hyperopia with both early[4;5] and advanced AMD[4], cataracts with early AMD[6], and iris color with both early and advanced AMD[7]. Pooled data from the Blue Mountains and Beaver Dam Eye studies found an association between cataract surgery and advanced AMD[8] as too did pooled data from the Salisbury Eye evaluation Survey, Proyecto VER and the Baltimore Eye Survey[9].. This paper aims to examine the association of various ocular risk factors with early and advanced AMD lesions among Latinos, primarily Mexican Americans living in La Puente, California.

Methods

The Los Angeles Latino Eye Study (LALES) is a population-based, cross-sectional study of adult Latinos aged 40 years and older, living in six census tracts in the city of La Puente, California. This city was chosen because of its large, stable Latino population and its similar socioeconomic demographic profile to that of Latinos in the U.S[10]. The survey design and methods have been reported in detail elsewhere[10;11]. Briefly, after written, informed consent was obtained, a detailed in-home interview was conducted to determine demographic factors, ocular and medical histories, various risk factors, and access to medical and ocular care. Trained ophthalmologists and technicians used standardized protocols in performing a comprehensive ocular examination, which included 30° stereoscopic color fundus photographs of Diabetic Retinopathy Study fields one, two and a modified field three on all participants[12;13]

Iris color was graded as blue, grey, hazel, or brown using The Iris Color Classification System, 1990[14]. Lenses were examined at the slit lamp under maximum dilation with tropicamide 1% and phenylephrine 2.5%. The Lens Opacities Classification System II (LOCS II) [15] was used to categorize lens opacities into five nuclear, five posterior subcapsular (PSC), and seven cortical grades of increasing severity, according to photographic standards[15] Lens opacities were considered to be present if of a LOCS II grade of 2 or more were present. Mixed cataract was defined as the presence of more than one type of lens opacity (nuclear, PSC or cortical) with a LOCS score of >=2 in any area. Reproducibility of LOCS II grading was measured by proportionally weighted kappa statistics for agreement by an independent replicate on 50 participants every 5 to 6 months. Results showed good intergrader agreement for all opacity types (weighted kappa =0.7–0.8).

Visual acuity for each LALES participant was measured for each eye[16] Automated refraction was performed (using the Humphrey Autorefractor Model 599, Carl Zeiss Meditec, Dublin, Calif.), followed by subjective refraction using standardized protocols. Spherical refractive error was measured to the closest 0.25 diopters (D). Cylinder power was measured to the closest 0.25D. The spherical equivalent (SE; sphere plus half cylinder) was used in all analyses as the measure of refractive error. Axial length was estimated using the average of three measurements obtained using an A-scan ultrasound (Ultrasonic A-SCAN pachymeter, Exton, PA).

A modified Wisconsin Age-related Maculopathy Grading System[12] was used to grade individual age-related macular degeneration lesions by masked graders at the Wisconsin Ocular Epidemiology Grading Center. A more detailed description about all grading

procedures and definitions has been presented elsewhere.[11] Early AMD was defined as the absence of signs of advanced AMD and the presence of 1) soft indistinct or reticular drusen or 2) hard distinct or soft distinct drusen with pigmentary abnormalities (RPE depigmentation or increased retinal pigment). Advanced AMD was defined as the presence of 1) geographic atrophy or 2) exudative AMD. Signs of exudative AMD were retinal pigment epithelial detachment or serous detachment of the sensory retina, subretinal or sub-RPE hemorrhages, and subretinal fibrous scars. Geographic atrophy was defined as a circular discrete area (of at least 175μm in diameter) of retinal depigmentation with visible choroidal vessels, in the absence of exudative AMD.

Data and statistical analyses

Data were entered into an automated database using Microsoft Access-98, with internal automated quality control checks. The Statistical Analysis System (version 8; SAS Institute Inc, Cary, NC) was used for tabulations and statistical analyses. All odds ratios were age- and sex-adjusted and all confidence interval presented are 95%. Intergrader and intragrader agreement was assessed using the quadratic weighted kappa statistic on a random subset of 30 eyes. There was moderate to excellent inter- and intraobserver agreement (κ= 0.8–1.0 for early AMD, exudative AMD and geographic atrophy and κ=0.4–0.9 for individual early AMD lesions). Logistic regression was performed using each AMD lesion as a dependent variable. GEE analyses were performed to assess associations of ocular variables with AMD.

Results

Of the 7789 eligible self-identified Latinos, 6870 individuals (88%) completed an in-home interview and 6357 (82%) participated in a clinical examination. A total of 5875 participants with complete clinical examination, biometry, and refractive status were included in the analyses. The mean age of participants was 54.6 years (SD± 10.7) and 58.4 % were female. Cataract was present in 986 (16.8%) participants and 193 or 3.3% had previously had cataract surgery. (Table 1) After adjusting for age, sex and history of smoking, there was a statistically significant association of any of the 3 types of lens opacity combined with soft indistinct drusen. Prior cataract surgery increased the odds of increased retinal pigment, RPE depigmentation and advanced AMD. (Table 2)

Table 3 presents the odds of having early and advanced AMD by refractive error and axial length after adjusting for age, sex and history of smoking. Myopia was protective for soft drusen, but not advanced AMD. Similarly, there was a protective association of longer axial length per 1mm with soft indistinct drusen and increased retinal pigment and GA.

Iris color stratified by AMD status is presented in Table 1 and odds ratios for AMD shown in table 3. Lighter colored irides were associated with fivefold higher odds of GA after adjusting for age, sex and history of smoking. Although the odds of any advanced AMD was also increased, this was not statistically significant (OR: 2.4, 95%CI: 1.0, 5.8), p=0.07.

Discussion

This report presents the association of ocular factors and AMD lesions using data from the Los Angeles Latino Eye Study. Strengths of the study were its size and the use of standardized protocols to determine ocular risk factors and AMD and its components. Associations between prior cataract extraction and early and advanced AMD, nuclear sclerotic cataract and soft drusen, light iris color and geographic atrophy were found. Longer axial length was negatively associated with early AMD lesions and geographic atrophy.

The relationship between cataract, cataract surgery and AMD has been investigated in many previous epidemiologic studies with inconsistent findings[8;9;17–19]. Cataract and AMD may share one or more risk factors, or each may serve as a biomarker of ageing. We found a significant association of nuclear sclerotic cataract and soft drusen but not advanced AMD. Similarly, the Beaver Dam Eye Study reported an association between nuclear sclerosis and early AMD (OR 1.96; 95% CI 1.3–3.0), but not with advanced AMD[6].

Cataract surgery prior to entry into the LALES was associated with three times increased risk of advanced AMD, doubled the risk of decreased retinal pigment and increased the risk of increased retinal pigment. These findings are consistent with pooled findings from other prevalent studies that included the Salisbury Eye evaluation Survey, Proyecto VER and the Baltimore Eye Survey[9].

Findings from many prospective studies have reported similar associations. Cataract surgery was associated with long term incidence of advanced AMD in the Beaver Dam Eye Study (BDES) [18] and in pooled findings from the BDES and BMES[8]. It is not known what the AMD status of these eyes were prior to cataract surgery, and whether they had earlier surgery due to increased symptoms from early AMD as well as cataract, or whether inflammation related to the surgery was the cause of the incident advanced AMD and early AMD lesions. Recently, the Rotterdam Eye study reported an association of cataract surgery with incident geographic atrophy (OR, 3.44; 95% CI, 1.68–7.08) after adjustment for co-variates. There was no significant association of cataract surgery with exudative AMD in that cohort[20]. However, more recently, The Age Related Eye Disease Study (AREDS), a prospective study of 4757 participants aged 55 to 80 years enrolled from 1992 to 1998 from retinal clinics in the US did not find an association between cataract surgery and progression to advanced AMD.

Although our positive findings of an association of AMD with cataract and cataract surgery are in agreement with a number of cross-sectional and longitudinal studies among non Hispanic Whites, the relationship between cataract and AMD is still not clear.

In LALES, myopia was associated with decreased odds of soft drusen and longer axial length was associated with decreased odds of geographic atrophy. There was no association of hyperopia with AMD. This lack of an association with hyperopia is consistent with findings from the BDES but inconsistent with several case-controlled and cross-sectional studies which have found an association between AMD and hyperopia[22–24] Further, epidemiological studies, including the BMES and Rotterdam Eye Study found an association between hyperopia and early AMD[4;5]. In the Rotterdam Eye Study, each diopter of hyperopia increased the risk of early AMD prevalence (OR: 1.09 (95% CI: 1.04–1.14)) and advanced AMD (OR: 1.09 (95% CI: 1.00–1.19))[4] and in the Blue Mountains Eye Study, each diopter towards hyperopia also increased the risk of early AMD (OR: 1.1; 95% CI: 1.0–1.2) and moderate to high hyperopia doubled the risk of early AMD (OR, 2.0; CI, 1.2–3.4)[5]. Results from the Beijing eye study also found hyperopia to be statistically significantly associated with early AMD[38]. One of the postulated mechanisms for how hyperopia results in AMD is that eyes with hyperopia are thought to have increased scleral rigidity due to a shorter axial length resulting in an increased choroidal vascular resistance and impaired retinal pigment epithelial function[4]. This supports a paper by Friedenwald who reported that the coefficient of scleral rigidity was inversely proportional to axial length, directly proportional to age and could be considered as an ‘index of senescence’[25]. In LALES, although, we found no association with hyperopia, our finding of a protective effect of both myopia and longer axial length for soft drusen is consistent with this.

Age related macular degeneration appears to be less prevalent in pigmented races[26–30]. A number of studies have reported an association of advanced AMD in eyes with blue or lighter colors compared with dark brown irides[7;23;31–33]. We found a fivefold increased risk of geographic atrophy in persons with lighter colored irides. Although the risk of any advanced AMD in persons with light colored irides was doubled, this was only of borderline significance. It has been postulated that the lower risk of age related macular degeneration among participants with darker irides may be that those persons also have more melanin in their choroid and retina and melanin may act as a free radical scavenger and thus provide protection from light-induced oxidative damage to the retina[34]. An alternative explanation for this finding may be an underlying genetic factor correlated with light iris color. However, other studies have not found any significant association of iris color with AMD[22;35–37]. The reasons for this disparity are not evident.

Strengths, Limitations and Conclusion

An important limitation of our study is the small number of participants with advanced AMD in our cohort, which led to reduced statistical power to detect significant associations. We also cannot exclude chance findings. Also, when comparing our findings with those from other studies, caution should be exercised because the methods used in collecting and analyzing these risk factors may be different. However, the presence of a relationship, even with differing definitions, in different studies and in different racial/ethnic groups may suggest similar biologic mechanisms for the presence of various types of AMD and various AMD lesions.

The major strength of this study was the fact that it is the largest population based ocular epidemiology study among the largest ethnic minority group of the United States. The Latino population has unique demographic, socioeconomic, as well as ocular health characteristics that influence the development of eye disease and the subsequent impact on quality of life. However, there is very limited data on risk factors of AMD in this population. So, we believe, this study adds to our understanding of different ocular risk factor among this fastest growing ethnic group of USA.

In summary, we found a number of cross-sectional associations including one between prior cataract extraction and advanced AMD, consistent with findings in non Hispanic whites. The relationship of these risk factors to incident early and advanced AMD in Latinos are required to further establish these relationships among persons of different ethnicities.

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Table 1

Frequency Distribution of lens opacities, cataract surgery, refractive error and iris color in Latinos with and without specific age-related macular degeneration lesions in the the Los Angeles Latino Eye Study

	No AMD (N=10681)		Early AMD (N=664)		Soft Indistinct Drusen (N=421)		Increased Retinal Pigment (N=381)		RPE* Depigmentation (N=153)		Any Advanced AMD (N=36)		Geographic Atrophy (N=13)		Exudative AMD (N=23)	
Characteristic	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Cataract																
Any cataract	1394	13.1	127	19.1	105	26.8	65	17.1	27	17.6	13	36.1	5	38.5	8	34.8
Nuclear sclerosis	617	5.8	68	10.2	58	14.8	37	9.7	17	11.1	13	36.1	5	38.5	8	34.8
Posterior subcapsular	141	1.3	17	2.6	15	2.3	9	2.4	1	0.7	3	8.3	0	0.0	3	13.0
Cortical cataract	1018	9.5	92	13.9	74	18.9	49	12.9	20	13.1	7	19.4	1	7.7	6	26.1
Mixed	350	3.3	46	6.9	40	10.2	28	7.3	11	7.2	8	22.2	1	7.7	7	30.4
Cataract surgery	216	2.0	43	6.5	39	9.3	25	6.6	14	9.2	11	30.6	4	30.8	7	30.4
Refractive error																
emetropia (−0.5 to 0.5)	5163	48.3	261	39.3	154	37.1	151	39.6	63	41.2	7	19.4	3	23.1	4	17.4
hyperopia mild (+0.5 to +3)	3004	28.1	230	34.6	138	5.1	141	37.0	44	28.8	19	52.8	7	53.8	12	52.2
hyperopia mod/high (>+3)	389	3.6	31	4.7	21	33.3	15	3.9	9	5.9	2	5.6	0	0.0	2	8.7
myopia mild (−0.5 to −3)	1714	16.0	120	18.1	85	20.5	59	15.5	30	19.6	6	16.7	3	23.1	3	13.0
myopia mod/high (<−3)	379	3.5	15	2.3	17	4.1	10	2.6	4	2.6	0	0.0	0	0.0	0	0.0
Iris color																
lighter (gray/blue/green)	3715	34.7	207	31.1	135	32.4	127	33.3	57	37.3	21	58.3	10	77	11	47.8
tan/brown	6952	65.1	451	67.9	282	67.6	249	65.4	93	60.8	13	36.1	3	23.1	10	43.5

Note: N is number of eyes.

*Retinal Pigment Epithelium

Table 2

Odds ratios for the association between lens opacities, cataract surgery and type of age-related macular degeneration (AMD) lesions in participants in the Los Angeles Latino Eye Study

	Soft Indistinct Drusen	Increased Retinal Pigment	RPE** Depigmentation	Any Advanced AMD	Geographic Atrophy	Exudative AMD
Characteristic	**OR (95%CI)***	**OR (95%CI)***	**OR (95%CI)***	**OR (95%CI)***	**OR (95%CI)***	**OR (95%CI)***
Cataract						
Absent	1	1	1	1	1	1
Present	**1.2(1.0, 1.5)**	0.8 (0.5, 1.0)	0.8 (0.5, 1.4)	0.5 (0.2, 1.1)	0.8 (0.2, 3.5)	0.7 (0.2, 1.7)
Nuclear sclerosis						
Absent	1	1	1	1	1	1
Present	1.2 (0.95, 1.6)	1.0 (0.6, 1.3)	1.3 (0.7, 2.4)	1.9 (0.7, 4.9)	2.2 (0.5, 10.2)	1.7 (0.6, 4.5)
Posterior subcapsular						
Absent	1	1	1	1	1	1
Present	0.9 (0.6, 1.5)	1.1 (0.5, 2.5)	0.3 (0.0, 2.2)	1.5 (0.5, 4.7)	0.3 (0.0, 3.8)	2.7 (0.8, 9.4)
Cortical						
Absent	1	1	1	1	1	1
Present	1.1(0.9, 1.4)	0.9 (0.6, 1.3)	0.9 (0.5, 1.7)	0.5 (0.2, 1.6)	0.2 (0.0, 1.8)	0.9 (0.3, 2.6)
Mixed						
Absent	1	1	1	1	1	1
Present	1.0 (0.8, 1.5)	1.4 (0.9, 2.3)	1.5 (0.7, 3.3)	1.3 (0.4, 4.6)	0.3 (0.0, 4.3)	**2.8 (0.92, 8.5)**
Cataract surgery						
None	1	1	1	1	1	1
Yes	1.0 (0.7, 1.4)	**1.6 (1.0, 2.6)**	**2.2 (1.1, 4.4)**	**2.8 (1.0, 7.8)**	2.6 (0.4, 14.7)	2.8 (0.8, 9.6)

*Odds ratios adjusted for age, sex and smoking. Odds ratios in bold are statistically significant.

**Retinal Pigment Epithelium

Table 3

Odds ratios for the association between Refractive Error, Axial Length, Iris Color and type of age-related macular degeneration (AMD) lesions in participants in the Los Angeles Latino Eye Study

	Soft Indistinct Drusen	Increased Retinal Pigment	RPE** Depigmentation	Any Advanced AMD	Geographic Atrophy	Exudative AMD
Characteristic	**OR (95%CI)***	**OR (95%CI)***	**OR (95%CI)***	**OR (95%CI)***	**OR (95%CI)***	**OR (95%CI)***
Refractive error						
Emetropia	1	1	1	1	1	1
Hyperopia	0.9 (0.8, 1.1)	1.1 (0.8, 1.4)	0.9 (0.6, 1.3)	1.0 (0.4, 2.4)	0.9 (0.2, 3.5)	1.1 (0.4, 3.4)
Myopia	**0.8 (0.7, 1.0)**	0.9 (0.7, 1.2)	1.1 (0.7, 1.7)	0.6 (0.1, 1.9)	0.6 (0.1, 3.3)	0.4 (0.1, 2.7)
Axial length (per mm)	**0.8 (0.7, 0.9)**	**0.8 (0.7, 0.9)**	0.9 (0.7, 1.0)	0.9(0.6, 1.3)	**0.7 (0.5, 0.9)**	0.9 (0.6, 1.5)
Iris color						
Tan/brown	1	1	1	1	1	1
Other colors	0.8 (0.7, 1.0)	0.8 (0.6, 1.0)	1.0 (0.7, 1.5)	2.2 (0.9, 5.3)	**5.0 (1.0, 25.3)**	1.4 (0.5, 3.8)

* Odds ratios adjusted for age, sex and smoking. Odds ratios in bold are statistically significant.

** Retinal Pigment Epithelium