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The Incidence and Progression of Age-Related Macular Degeneration over 15 Years

The Blue Mountains Eye Study

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Purpose: To assess the 15-year incidence and progression of age-related macular degeneration (AMD) in an older Australian population.

Design: Population-based cohort study.

Participants: Blue Mountains Eye Study (BMES) participants (n = 3654) aged 49+ years were examined during 1992−1994. Of these, 2334 (75.8% of survivors) were reexamined after 5 years (1997−1999), 1952 (76.7% of survivors) after 10 years (2002−2004), and 1149 (56.1% of survivors) after 15 years (2007−2010).

Methods: Color retinal photographs were taken, and comprehensive questionnaires were administered at each visit and DNA was genotyped. Retinal photographic grading was performed by the same graders following the Wisconsin AMD grading protocol. Side-by-side comparisons were used to confirm newly developed AMD lesions. Incidence was estimated using Kaplan−Meier estimates. Associations of AMD incidence with age, sex, smoking status, presence of the *complement factor H (CFH)-rs1061170* and *age-related maculopathy susceptibility 2 (ARMS2)-rs10490924* polymorphisms, and fish consumption were analyzed using discrete logistic regression models. Generalized estimation equation models were used to assess the risk of incident late AMD associated with baseline AMD lesion characteristics.

Main Outcome Measures: The 15-year incidence and progression of AMD, and associated factors.

Results: The 15-year incidence was 22.7% for early AMD and 6.8% for late AMD. After adjusting for competing risks, early and late AMD incidence were 15.1% and 4.1%, respectively. Age was strongly associated with early and late AMD incidence (both $P < 0.0001$). After age standardization to the Beaver Dam Eye Study (BDES) population, early and late AMD incidence in the BMES were 13.1% and 3.3%, respectively. Female sex and the presence of both risk alleles of *CFH-rs1061170* or *ARMS2-rs10490924* were independently associated with early AMD incidence, whereas current smoking and presence of ≥1 risk allele of *CFH-rs1061170* or *ARMS2-rs10490924* were associated with late AMD incidence. Fish consumption was inversely associated with late but not early AMD incidence. Severity of early AMD lesion characteristics was a strong predictor of progression to late AMD.

Conclusions: We documented the 15-year incidence of early and late AMD in an older Australian population that were comparable to BDES observations. Risk of progression to late AMD was strongly associated with severity of early AMD lesions. *Ophthalmology 2015;■:1−8 © 2015 by the American Academy of Ophthalmology.*

Age-related macular degeneration (AMD) continues to be one of the leading causes of blindness and visual impairment in older populations despite recent advances in treatments.[1−4] The incidence and progression of early and late-stage AMD over 5 and 10 years have been reported in a number of large population-based studies in the United States, Europe, Asia, and Australia over the past 2 decades.[2,5−10] Greater severity of early AMD lesions, including increased drusen area, presence of pigmentary abnormalities, and location of lesions close to the fovea, was shown to be associated with greater risk of progression to late AMD.[6,7,10,11] The relationship between demographic and lifestyle risk factors, including older age, sex, and smoking status, with the incidence and progression of AMD was also shown in some of these populations.[12]

However, data on the incidence of AMD over the long-term (>10 years) are limited. The Copenhagen City Eye Study and the Beaver Dam Eye Study (BDES) are the only population-based studies thus far to report 14- and 15-year AMD incidence, respectively.[11,13] In this report, we aimed to build on the previous 5- and 10-year AMD incidence findings to describe the 15-year incidence of early and late AMD and its component lesions in an older Australian population (the Blue Mountains Eye Study [BMES]) and to assess risk factors and baseline early AMD lesions characteristics associated with the risk of progression to late AMD over the longer term.

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Methods

Study Population

The BMES is a population-based study of vision and eye disease in persons aged 49 years and older residing in the Blue Mountains region, west of Sydney Australia. The study recruited 3654 participants (82.4% of those eligible) during baseline examinations (1992−1994, BMES I). Of these, 2334 participants (75.8% of survivors; 575 deceased) attended 5-year follow-up examinations (1997−1999, BMES II); 10-year examinations were attended by 1952 participants (76.7% of survivors; a further 535 died; 2002−2004, BMES III). The final 15-year follow up examinations were attended by 1149 participants (56.1% of survivors; a further 496 died; 2007−2009, BMES IV). The mean (median, minimum, and maximum) follow-up period was 5.1 years (4.9, 3.4, and 7.8, respectively) for the 2334 BMES II participants; 10.5 years (10.4, 8.9, and 12.9, respectively) for the 1952 BMES III participants; and 15.6 years (15.5, 13.6, and 17.7, respectively) for the 1149 BMES IV participants. All 4 examinations were approved by the University of Sydney and Western Sydney Area Health Service Human Research Ethics Committees and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants at each visit.

Procedures

A comprehensive questionnaire was administered, and eye examinations were performed at each visit, as previously described.[10,14] Briefly, 30° stereoscopic retinal fundus photographs of the macula and other retinal fields of both eyes were obtained using a Zeiss FF3 fundus camera (Carl Zeiss, Oberkochen, Germany) and Kodachrome 25 slide film (Kodak) at BMES I, II, and III examinations. At the BMES IV examination, because of the unavailability of Kodachrome, 40° digital photographs were obtained with a Canon CF-60 DSi fundus camera with a DS Mark II body (Canon Inc., Tokyo, Japan). Photographs were obtained for both eyes in 98%, 98%, 85%, and 92% at the baseline, 5-, 10-, and 15-year examinations, respectively, and for at least 1 eye in 99%, 99%, 87%, and 92% at the baseline, 5-, 10-, and 15-year examinations, respectively. Diet was assessed from a self-administered food frequency questionnaire completed by participants at each examination. Blood samples were collected from participants at the BMES II and III examinations, and DNA extraction and genotyping were performed in >80% of these BMES participants.

Photographic Grading

Retinal photographic grading was performed by 2 senior graders and closely followed the Wisconsin Age-Related Maculopathy Grading System protocol.[15] As previously described, film fundus photographs were initially graded in a masked manner, and side-by-side grading between BMES I and II, and BMES I and III was performed subsequently for participants with AMD lesions identified after each follow-up examination.[9,14] Inter- and intra-grader reliability showed good agreement for AMD grading, with quadratic weighted kappa values ranging from 0.64−0.93 and 0.54−0.94, respectively.[14] Adjudication was provided by a senior retinal specialist (P.M.) if needed. The BMES IV digital retinal photographs were graded in the same masked manner using the grading software DH Client (Digital Healthcare: Image Management Systems, www.digital-healthcare.com, Cambridge, UK). Consensus on BMES incident late AMD cases was provided by lead investigators of the Three Continent AMD Consortium.[16]

Late AMD was defined as the presence of neovascular AMD, indicated by retinal pigment epithelial or neurosensory subretinal detachment, retinal or subretinal hemorrhage, subretinal fibrosis or old atrophic disciform scars, or photocoagulation scars with a history of neovascular AMD, or the presence of pure geographic atrophy (GA) within the macula, as described in the International Age-Related Maculopathy Classification.[17] Early AMD was defined as the presence of large (≥125 μm in diameter) indistinct soft drusen, reticular drusen, or the copresence of large distinct soft drusen and retinal pigmentary abnormalities (hyperpigmentation or depigmentation of retinal pigment epithelial cells), within the macula, in the absence of any late AMD lesions. The maximal diameter of individual drusen and collective macular areas involved by drusen and pigmentary abnormalities within the eye was estimated as specified in the Wisconsin Age-Related Maculopathy Grading System, using circles with diameters of 63 μm, 125 μm, 250 μm, 350 μm, and 644 μm, 0.5 or 1 disc area.[15]

Definition of Age-Related Macular Degeneration Incidence in the First Eye

Incident late AMD in the first eye was defined as the appearance of neovascular AMD or GA in either eye at any follow-up examination when the lesion was not present in either eye at baseline. For participants at risk of incident neovascular AMD, cases with this lesion at baseline were excluded but cases with GA at baseline were not excluded. Participants with GA or neovascular AMD at baseline and with neovascular AMD at follow-up were excluded from those at risk of incident GA. If GA was secondary to neovascular AMD or laser treatment of neovascular AMD, it was not considered as incident GA.

The BMES participants who developed late AMD during the follow-up period were all seen by the principal investigator of the BMES (PM) for confirmation and were treated and followed at the Eye Clinic, Westmead Hospital. These participants also were labeled using BMES identification numbers in their patient records and were included as incident late AMD cases.

Incident early AMD was defined as the appearance of indistinct soft or reticular drusen, or the co-presence of distinct soft drusen and retinal pigmentary abnormalities in either eye, at any follow-up examination where no late or early AMD was present in either eye at baseline. Participants with distinct soft drusen or retinal pigmentary abnormalities alone at baseline who later developed complementary lesions that comprised a diagnosis of early AMD were included as incident early AMD cases. Incidence of indistinct soft or reticular drusen was defined as the appearance of these lesions in either eye at follow-up visits, where none were present at baseline, and excluding late AMD, regardless of the presence of retinal pigmentary abnormalities. Incidence of retinal pigmentary abnormalities was defined as the appearance of these abnormalities in either eye at follow-up visits in participants with no pigment abnormalities at baseline and no late AMD at any follow-up visits.

Other Study Outcomes

The incidence of early and late AMD in the second eye of participants with unilateral early or late AMD at baseline and the progression from early AMD to late AMD in at least 1 eye over 15 years were assessed among persons with AMD in 1 or both eyes at baseline.

Genotyping

Genotyping was performed on the BMES cohort and the BMES Extension Survey (1999−2000) samples using an Illumina Human 670-Quad custom array version 1 (Illumina Inc., San Diego, CA) with stringent quality-control testing using PLINK (Purcell S. PLINK version 1.07. Available at: http://pngu.mgh.harvard.edu/purcell/plink/,