CLINICAL SCIENCE

Risk factors for age related maculopathy in a Japanese population: the Hisayama study

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Aims: To examine the risk factors for age related maculopathy (ARM) in a sample Japanese population.

Methods: In 1998, a cross sectional community survey was conducted among residents of Hisayama. A total of 596 men and 886 women living in Hisayama, Japan, aged 50 years or older consented to participate in the study. Each participant underwent a comprehensive examination that included an ophthalmic examination. The presence of ARM was determined by grading from fundus examination by indirect ophthalmoscopy, slit lamp examination, and colour fundus photographs. Using these cross sectional data, logistic regression analyses were performed to determine the risk factors for ARM. The following 10 possible risk factors were used: age, cataract, hypertension (history), hypertension (history or examination), diabetes, hyperlipidaemia, current smoker, alcohol intake, BMI, and WBC.

Results: ARM was detected in 19.5% of men and 14.9% of women. Men were found to have a significantly higher prevalence of ARM than women. Multiple logistic regression analysis showed that age and hypertension (history or examination) were significantly associated with ARM in men, whereas only age was a significant risk factor for ARM in women.

Conclusions: This study suggests that higher age and male sex are relevant risk factors for ARM in Japan. In addition, hypertension is a relevant risk factor in men.

Age related maculopathy (ARM) is a major cause of blindness and severe vision loss in older people in developed countries.[1] With the ageing population, ARM will become an increasing public health problem in the future. Therefore, it is crucial to identify risk factors for ARM to enhance understanding of the disease. Several risk factors for ARM have been investigated in population based[2–8] and case-control studies.[9–11] The risk factors examined include refractive error,[9] iris colour,[2] cataract,[3 4] hypertension,[5] atherosclerosis,[6] current smoker,[7] alcohol intake,[8] white blood cell count,[10] and sunlight.[11] To the best of our knowledge, however, no population based studies have assessed risk factors for ARM in Japan.

We have already reported the prevalence of early and late stage ARM in a representative Japanese community, Hisayama (the Hisayama study).[12] In this study, we investigate the important factors that contribute to ARM, using cross sectional data.

PATIENTS AND METHODS

Study population

A prospective population based follow up study of cardiovascular diseases has been carried out since 1961 in Hisayama.[13 14] The population of the town is approximately 7500, and it has been shown to be demographically representative of Japan based on the national census.[15] As part of the follow up survey, we performed a health examination, including an eye examination, of Hisayama residents aged 50 years or older in 1998. Of the 3054 residents in that age group, 1844 (60.4%) consented to participate in the study. Of these, 349 subjects underwent the health examination at home, while 13 subjects refused to participate in the ophthalmic examination. Ultimately, 1482 individuals (596 men and 886 women, 44.3% of the male population and 51.9% of the female population in that age group) underwent the ophthalmic examination.

Ophthalmic examination and definition of age related maculopathy

The methods of the ophthalmic examination and the definition of ARM were described in detail previously.[12] Briefly, each participant underwent a comprehensive ophthalmic examination, including lens grading using a slit lamp, stereoscopic fundus examination using indirect ophthalmoscopy, and examination with a slit lamp biomicroscope with a "Superfield lens" (Volk, Mentor, OH, USA) after pupil dilatation with 1.0% tropicamide and 10% phenylephrine. Forty five degree fundus photographs were taken using a Topcon "non-mydriatic" TRC NW-5 fundus camera (Topcon, Tokyo) and Fujichrome slide film (Sensia II Fujifilm Co, Tokyo). The photographs were taken using a previously described method with a minor modification.[16] Briefly, photographs were taken of a field centred horizontally and vertically on a point midway between the temporal edge of the optic disc and the fovea. The photographic image included the area above and below the temporal arcades and the areas just nasal to the disc and temporal to the macula. The 35 mm slide transparencies were mounted in clear plastic sheets and graded at Kyushu University by two experienced graders (Y Oshima and T Ishibashi).

The presence of ARM was based on the grading of fundus examinations by indirect ophthalmoscopy, slit lamp, and colour fundus photographs. Two experienced ophthalmologists, without knowledge of clinical information, examined all the participants following the International ARM Epidemiological Study Group grading protocol and the grids of the Wisconsin Age Related Maculopathy Grading system.[17 18] ARM was classified as either early or late stage. Early stage ARM was defined by the presence of drusen (soft distinct and soft intermediate) or retinal pigment epithelium (RPE) pigmentary abnormalities within the grid in the absence of late stage ARM in either eye. Late stage ARM was further divided into neovascular age related macular degeneration (AMD), also termed "wet AMD," and geographic atrophy of the retinal pigment epithelium (RPE) in the absence of neovascular AMD,

Table 1 Age specific prevalence of early and late age related maculopathy by sex, the Hisayama Study, 1998

	Men			Women		
		No (%)			No (%)	
Age	Population at risk	Early ARM	Late ARM	Population at risk	Early ARM	Late ARM
50–59	154	19 (12.3)	1 (0.7)	284	34 (12.0)	0 (0.0)
60–69	231	43 (18.6)	2 (0.9)	335	41 (12.2)	0 (0.0)
70–79	178	36 (20.2)	2 (1.1)	212	40 (18.9)	1 (0.5)
80+	33	12 (36.4)	1 (3.0)	55	16 (29.1)	0 (0.0)
Total	596	110 (18.5)	6 (1.0)	886	131 (14.8)	1 (0.1)

Table 2 Mean values or frequencies of risk factors for age related maculopathy by sex, the Hisayama Study, 1998

	Men		Women	
Risk factor	Non-ARM (n=480)	ARM (n=116)	Non-ARM (n=754)	ARM (n=132)
Age (year) (SD)	65 (9)	68 (9)**	64 (9)	68 (10)**
Cataract (%)	61.3	68.1	65.5	75.0*
Hypertension (history) (%)	30.4	42.2*	32.0	31.1
Hypertension (history or examination) (%)	51.3	63.8*	47.0	51.5
Diabetes (%)	19.6	16.4	10.1	13.6
Hyperlipidaemia (%)	44.2	40.5	59.7	58.3
Current smoker (%)	34.8	33.6	4.5	4.6
Alcohol intake (%)	65.8	61.2	13.4	9.9
Body mass index (kg/m^2) (SD)	23.1 (3.0)	23.2 (2.9)	23.1 (3.3)	23.0 (3.6)
White blood cells (×10^6/l) (SD)	6.3 (1.7)	6.0 (1.4)	5.5 (1.3)	5.3 (1.4)

**p<0.01, ARM *v* non-ARM. *p<0.05, ARM *v* non-ARM.

also termed "dry AMD." Neovascular AMD included serous or haemorrhagic detachment of the RPE or sensory retina, and the presence of subretinal or sub-RPE haemorrhages or subretinal fibrous scar tissue. Dry AMD was characterised by sharply edged, roughly round or oval areas of RPE hypopigmentation, with clearly visible choroidal vessels. The minimum area of geographic atrophy was a circle 175 μm in diameter or larger.

The methods used to assess ARM were described in detail previously.[12] Briefly, two experienced graders, masked to subject information, assessed the ARM. The analysis included people with gradable photographs of either eye providing the clearest macular characteristics detected by stereoscopic eye examination. Interobserver and intraobserver variability were analysed using kappa statistics. The level of agreement was moderate to substantial for most features.

Data collection

We defined the presence of cataract by whether the subject had nuclear or cortical senile lens changes or a history of cataract surgery in either eye. We adopted the definition of cataract used in the Health and Nutrition Examination Survey (HANES).[19] Briefly, the lens was evaluated by slit lamp and then by the direct ophthalmoscopy with a +20 dioptre lens. Opacities observed with both instruments and decreased lucency of the nucleus observed with a slit lamp was noted by two experienced graders. For the purposes of this study, cataract cases included people with a past history of cataract surgery.

Blood pressure was measured three times after resting for at least 5 minutes in the sitting position. The average of the three measurements was used for the analysis. Hypertension was defined as systolic blood pressure = 140 mm Hg, diastolic blood pressure = 90 mm Hg, or current use of antihypertensive medication. A history of hypertension was obtained using a standard questionnaire. Blood samples were collected from the antecubital vein after an overnight fast. After taking the fasting blood specimen, a 75 g oral glucose tolerance test was performed with a 75 g glucose equivalent carbohydrate load (Trelan G; Shimizu Pharmaceutical Inc, Shimizu, Japan). Diabetes was defined as a fasting plasma glucose level = 7.0 mmol/l or a 2 hour postloading glucose level = 11.1 mmol/l, in addition to a medical history of diabetes. The total cholesterol and serum triglyceride levels were determined enzymatically using an autoanalyser (TBA-80S; Toshiba Inc, Tokyo, Japan), and hyperlipidaemia was defined as a total cholesterol level = 5.7 mmol/l, serum triglyceride level = 1.7 mmol/l, or the current use of antihyperlipidaemic medication. Information on smoking habits, and alcohol intake was obtained using a standard questionnaire, and these factors were classified into either current habitual use or non-use. Body height and weight were measured in light clothing without shoes, and the body mass index (BMI) was calculated as the weight in kilograms divided by the height in metres squared. White blood cell counts (WBC) were determined using a Coulter counter (STKS; Coulter Inc, USA).

Statistical methods

We defined a subject as having ARM if the subject had early or late stage ARM in at least one eye. We considered the following 10 possible risk factors for ARM: age, cataract, hypertension (history), hypertension (history or examination), diabetes, hyperlipidaemia, current smoker, alcohol intake, BMI, and WBC. Age, BMI, and WBC were treated as continuous variables and the others as categorical variables. Each categorical variable was coded as either 1 or 0 depending on the presence or absence of the factor, respectively. The association of the variables with ARM was assessed using Student's *t* test for the continuous variables and the Pearson χ^2 test for the categorical variables. Logistic regression analysis was performed to determine risk factors for ARM using odds ratio

Table 3 Crude and age adjusted odds ratios of risk factors for ARM by sex, the Hisayama Study, 1998

	Men				Women			
	Crude		Age adjusted		Crude		Age adjusted	
Risk factor	OR†	95%CI‡	OR†	95%CI‡	OR†	95%CI‡	OR†	95%CI‡
Age	1.04**	1.01 to 1.06			1.04**	1.02 to 1.06		
Cataract	1.35	0.88 to 2.08	1.05	0.66 to 1.70	1.58*	1.04 to 2.41	1.17	0.74 to 1.86
Hypertension (history)	1.67*	1.10 to 2.54	1.55*	1.02 to 2.37	0.97	0.65 to 1.44	0.83	0.55 to 1.25
Hypertension (history or examination)	1.68*	1.10 to 2.55	1.58*	1.04 to 2.42	1.20	0.83 to 1.74	0.96	0.65 to 1.42
Diabetes	0.80	0.47 to 1.38	0.80	0.46 to 1.37	1.41	0.81 to 2.44	1.30	0.75 to 2.27
Hyperlipidaemia	0.86	0.57 to 1.30	0.95	0.62 to 1.44	0.95	0.65 to 1.38	0.94	0.64 to 1.37
Current smoker	0.95	0.62 to 1.46	1.01	0.65 to 1.55	1.01	0.42 to 2.45	1.13	0.46 to 2.77
Alcohol intake	0.82	0.54 to 1.24	0.91	0.59 to 1.39	0.52	0.28 to 1.05	0.58	0.32 to 1.07
Body mass index	1.01	0.94 to 1.08	1.04	0.96 to 1.11	0.99	0.93 to 1.04	1.00	0.94 to 1.06
White blood cells	0.86	0.76 to 1.09	0.89	0.77 to 1.01	0.88	0.76 to 1.02	0.87	0.75 to 1.01

† OR; odds ratio ‡ CI; confidence interval. **p<0.01, *p<0.05.

Table 4 Stepwise multivariate logistic analysis of risk factors for ARM by sex, the Hisayama Study, 1998

	Men			Women		
Risk factor	Estimated coefficient	OR†	95%CI‡	Estimated coefficient	OR†	95%CI‡
Age	0.029	1.03**	1.01 to 1.06	0.040	1.04**	1.02 to 1.06
Hypertansion (history or examination)	0.456	1.58*	1.03 to 2.41			

†OR; odds ratio ‡CI; confidence interval. **p<0.01, *p<0.05.

estimates with 95% confidence intervals. Furthermore, a stepwise multivariate regression analysis was performed, with p value less than 0.05 being required for entering the model and remaining there. The SAS software package (SAS Institute, Cary, NC, USA) was used to perform the statistical analyses.[20] A two sided p value less than 0.05 was considered statistically significant.

RESULTS

Of the 1482 subjects examined, 248 had ARM. Of the subjects with ARM, most (97.2%) had early stage ARM. Table 1 shows the age specific prevalence of early and late stage ARM by sex. Early stage ARM significantly increased with advancing age in both sexes. In both sexes, about one third of the subjects aged 80 years or older had ARM. In each age group, the prevalence of ARM was consistently higher in men than in women, and after adjusting for age, men were found to have a significantly higher prevalence of ARM than women (odds ratio (OR), 1.32; 95% confidence interval (CI), 1.01 to 1.72).

We compared the distribution of possible risk factors in subjects with and without ARM by sex (Table 2). The subjects with ARM were older than those without ARM, in both sexes ($p<0.01$). Cataracts were more frequent in those with ARM, in women ($p<0.05$). Of the 320 men with hypertension, 154 (48.1%) had used of antihypertensive medications, while 221 of 422 (52.4%) women with hypertension had used antihypertensive medications. In men, the subjects with ARM were diagnosed with hypertension from history or examination more frequently ($p<0.05$).

The results of the crude and age adjusted logistic regression analyses of risk factors for ARM are shown in Table 3. In the crude analysis, age and hypertension either diagnosed from history or diagnosed from examination were significantly associated with ARM in men, while age and cataract were significantly associated with ARM in women. After adjusting for age, hypertension either diagnosed from history or from examination remained a significant risk factor in men, while no factor was significant in women.

The stepwise multivariate regression analysis showed that age and hypertension diagnosed from examination were significantly associated with ARM in men, whereas only age was a significant risk factor for ARM in women (Table 4).

DISCUSSION

To our knowledge, this is the first study to investigate the prevalence and risk factors of ARM in Japan, using a population based sample. The results show that age is significantly associated with ARM in both sexes, and hypertension is an additional risk factor in men.

There have been inconsistent results on the association between hypertension and ARM in previous studies.[5 19 21 22] Some studies found a positive association with increased blood pressure,[19 21] while others did not.[22] In the Framingham Eye Study, the prevalence of ARM progressively increased with the duration of systemic hypertension.[5] We found that hypertension diagnosed from either history or examination remained a significant risk factor in men, and that hypertension increased the risk of ARM by 59% in the multivariate regression analysis. The exact aetiology of ARM is unclear, but patients with ARM are reported to have prolonged filling of the choroidal capillaries, probably due to thickening of Bruch's membranes and decreased perfusion of the choroidal capillaries.[6 23 24] These findings suggest that long standing hypertension promotes atherosclerotic changes in the choroidal vessels, which might consequently decrease choroidal blood flow, thus resulting in an increased risk of ARM.

In our Japanese subjects, ARM was more prevalent among men than women. Yuzawa *et al* have also reported that exudative AMD was more prevalent in men than in women in patients visiting ophthalmology departments in Japan.[25] By contrast, ARM is more prevalent in women than in men in Western countries.[26 27] The reason for this difference is not clear. Some studies have reported racial differences in the prevalence of ARM,[27 28] which might explain the discrepancy between studies conducted in Japan and Western countries, and genetic or environmental factors might be the cause. However, we should mention the possibility of ascertainment bias since less than half of the available population consented to be studied (1482/3054 = 48.5%). The higher prevalence of

ARM in men might be the result of an ascertainment bias, because working men were less likely than women to enrol in the study unless they had visual symptoms.

The Beaver Dam Eye Study[3] reported that nuclear sclerotic cataracts were associated with early stage ARM in a cross sectional population based study. However, cataracts were not associated with the incidence and progression of ARM in a 5 year follow up study.[29] Sperduto *et al* found that the incidence of ARM increased with the presence of cortical lens changes and decreased with nuclear sclerosis.[4] Our data showed that the prevalence of both ARM and cataracts increased with age. Statistical analysis demonstrated that cataracts were significantly associated with ARM in both sexes, but the association was not significant after adjusting for age. Therefore, in our study, cataract is not considered an independent risk factor for ARM. Further investigation based on anatomical classification of cataract, which was not available in our study, would help clarify the relation between cataracts and ARM in more detail.

Although smoking is considered a risk factor for AMD in some studies,[7 30 31] we failed to find a significant association between smoking and ARM. In the Beaver Dam Eye Study, there was no association between smoking and early stage ARM, but there was a significant association between smoking and exudative AMD.[7] Smoking might promote the development and progression of subretinal neovascularisation, and different stages of ARM might have different aetiologies.[7] In our study, smoking was not associated with ARM, possibly because there were too few subjects with late stage ARM.

Several factors limit the interpretation of the results of this study. Firstly, many previous studies have examined risk factors for AMD (late stage ARM). However, we could not examine the risk factors for early and late stage ARM separately, because of the small number of subjects with late stage ARM. Secondly, the rate of participation in the examination was low. As a result of the participation rate, the study is probably subject to selection bias, which could have influenced the results. Hypertension and late stage ARM resulting in impaired vision would have been major motivations for men to participate. Consequently, the study might have examined a higher proportion of hypertensive and visually impaired men than it would have done from a representative sample.

In conclusion, our population based study in a sample Japanese population suggests that the prevalence of ARM is significantly higher in men than in women, that age is significantly associated with ARM in both sexes, and that hypertension is an additional risk factor in men. Additional prospective studies will help clarify the causal relations between hypertension and ARM.

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