The 5-Year Incidence and Risk Factors for Age-Related Maculopathy in a General Japanese Population: The Hisayama Study

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PURPOSE. To estimate the 5-year incidence and risk factors for age-related maculopathy (ARM) in a representative older Japanese population.

METHODS. A population-based cohort study was conducted in 1998 on 1,482 Hisayama residents aged 50 years or older, and 961 of these subjects attended the 5-year follow-up examinations in 2003. At both time points, the characteristics of ARM were determined by grading color fundus photographs according to the Wisconsin Age-Related Maculopathy Grading System. Using these cohort data, logistic regression analyses were performed to determine the risk factors for ARM. Nine possible risk factors were examined: age, sex, hypertension, diabetes, hyperlipidemia, smoking, alcohol intake, body mass index, and white blood cell count.

RESULTS. The 5-year incidence of early ARM was 8.5%, and that of late ARM was 0.8%. Men were found to have a significantly higher incidence of late ARM than did women. The incidence of both early and late ARM increased significantly with age. Multiple logistic regression analysis showed that age and smoking were significantly associated with early and late ARM.

CONCLUSIONS. The results suggest that the overall 5-year incidence of early ARM is 8.0% and that of late ARM is 0.8% in the general Japanese population and that higher age and smoking are relevant risk factors for early and late ARM in the Japanese. (Invest Ophthalmol Vis Sci. 2005;46:1907–1910) DOI:10.1167/iovs.04-0923

Age-related maculopathy (ARM) is a major cause of blindness and severe vision loss in older people in developed countries.¹–³ As the population ages in these countries, ARM will become an increasing public health problem. It is thus crucial that we identify the incidence and risk factors of the disease. Previous population-based studies have investigated several risk factors for ARM, including iris color,⁴ hypertension,⁵ atherosclerosis,⁶ a current smoking habit,⁷ and alcohol intake.⁸ In addition, we have reported the prevalence and risk factors for ARM in the representative Japanese community of Hisayama, by using cross-sectional data from the Hisayama study.⁹ However, although incidence data from the general population would be useful both for counseling patients and understanding the natural course of disease, there has been no population-based study estimating the incidence of ARM in Japan.

The purpose of this study was to describe the 5-year incidence of early and late ARM in a representative Japanese population-based cohort. A further goal was to investigate the major factors that contribute to early and late ARM, by using the cohort data obtained.

METHODS

Study Population

The Hisayama Study is an ongoing, prospective population survey that has been conducted in the town of Hisayama since 1961. Hisayama is a suburb of Fukuoka City, which is on the island of Kyushu in the southern part of Japan. The population of the town is approximately 17,500, a number that has remained stable for 40 years. According to the 1985 national census, the age distribution of the Hisayama population was almost identical with that of Japan as a whole.¹⁰ The occupations of the subjects were categorized into three types according to the Census for Labor and Products in Japan. Of the population aged 40 to 79 years in the town, 14.6% were engaged in a primary industry (agriculture, fishery, forestry), 29.8% in a secondary industry (mining, construction, manufacture), and 55.6% in a tertiary industry (commerce, restaurant, transport, communication, finance, insurance, supplier of electricity, gas or water, real estate business, service industry, and unclassified official business). The frequency distribution was very similar to that of all Japanese employees in the same age range: 14.5%, 35.4%, and 52.2%, respectively. As part of the follow-up survey, we performed a health examination, including an eye examination, of all Hisayama residents aged 50 years and older. The enrollment criteria, characteristics of the study population and overall design of this study have been described in detail in previous studies.⁹ The baseline eye examinations for the Hisayama Study were performed in 1998. Of the 3,054 residents in that age group, 1,844 (60.4%) consented to participate in the baseline eye examinations. Of these, 349 subjects underwent the health examination at home, whereas 13 subjects refused to participate in the ophthalmic examination. Ultimately, 1,482 (48.5%) individuals (596 men and 886 women, 44.3% of the male population and 51.9% of the female population in that age group) underwent baseline eye examinations. Five-year follow-up eye examinations for the Hisayama Study were conducted in 2003. Of the original cohort, 961 (31.4%) persons took part in the examinations, of whom 3 had to be excluded due to ungradable photographs of either eye.

Ophthalmic Examination and Definition of Age-Related Maculopathy

The methods used for the baseline eye examinations have been described in detail elsewhere.⁹ Briefly, each participant underwent ophthalmic examinations after pupil dilation with 1.0% tropicamide and 10% phenylephrine. Fundus photographs (45°) were taken (model TRC NW-5 fundus camera; Topcon Corp., Tokyo, Japan), and 35-mm color transparencies were made using slide film (Sensia II Fujichrome; Fujifilm, Tokyo, Japan). In the 5-year follow-up eye examinations, fundus photographs (45°) were taken using a digital fundus camera.
abnormalities (hyperpigmentation or hypopigmentation),\textsuperscript{13} within the soft distinct and soft indistinct or retinal pigment epithelial (RPE) magnification of the camera. This protocol divides ARM into early and late stages. Early-stage ARM was defined by the presence of drusen (soft distinct and soft indistinct) or retinal pigment epithelial (RPE) abnormalities (hyperpigmentation or hypopigmentation),\textsuperscript{13} within the grid in the absence of late ARM in either eye. Late-stage ARM was defined as the presence of neovascular age-related macular degeneration (AMD) or geographic atrophy (GA) involving the fovea. Neovascular AMD included serous or hemorrhagic detachment of the RPE or sensory retina, and the presence of subretinal or sub-RPE hemorrhages or subretinal fibrous scar tissue.\textsuperscript{13} GA was characterized by sharply edged, roughly round or oval areas of RPE hypopigmentation, with clearly visible choroidal vessels.\textsuperscript{13} The minimum area of GA was a circle 175 µm in diameter or larger. These definitions of early and late ARM were used in both the studies in Beaver Dam, Wisconsin, and Blue Mountains eye studies. In our study, two experienced graders (MM, TT), masked to the subject information, assessed the ARM. Inter- and intraobserver variability were analyzed by the κ statistic.\textsuperscript{14} The level of agreement between the graders was moderate (0.80–0.86) to substantial for most features.

Data Collection

Blood pressure was measured three times after the subject had rested 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 $\geq 140$ mm Hg, diastolic blood pressure $\geq 90$ mm Hg, or current use of antihypertensive medication. 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 $\geq 7.0$ mM, a 2-hour postload glucose level $\geq 11.1$ mM, or a medical history of diabetes. The total cholesterol and serum triglyceride levels were determined enzymatically with an autoanalyzer (TBA-808; Toshiba Inc., Tokyo, Japan), and hyperlipidemia was defined as a total cholesterol level $\geq 5.7$ mM, serum triglyceride level $\geq 1.7$ mM, or the current use of antihyperlipidemic medication. Information on alcohol consumption was obtained by interview, using a questionnaire that ascertained the usual weekly intake of alcoholic beverages over the previous several months. Subjects were classified as either light ($<34$ g/d of ethanol) or heavy ($\geq34$ g/d of ethanol) drinkers or as nondrinkers. Information on smoking habits was obtained with a standard questionnaire by trained interviewers at the initial examination, and the subjects were classified as either current or past habitual cigarette users or as nonusers. 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 meters squared. White blood cell counts (WBC) were determined with a counter (STKS; Beckman-Coulter Inc., Hialeah, FL).

Statistical Methods

The 5-year incidences were calculated. Incident early ARM was defined by the appearance at follow-up of either soft drusen or retinal pigmentary abnormalities in either eye of persons in whom no early or late ARM was present at baseline. Incident late ARM was defined by the development at follow-up of neovascular AMD or GA in either eye of persons in whom no early or late ARM was present at baseline. We examined the relationships between the risk factors at baseline and the incidence of early and late ARM. We considered the following nine possible risk factors for ARM: age, sex, hypertension, diabetes, hyperlipidemia, smoking habit, 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 either 1 or 0 depending on the presence or absence of the factor, respectively. Mean values were compared by the Student’s t test and frequencies by Pearson’s χ² test. We estimated the age-adjusted and multivariate odds ratios (ORs) of each potential risk factor by using a stepwise logistic regression analysis. Only variables with $P < 0.05$ were entered into or allowed to remain in the stepwise multivariate regression analysis. Statistical analyses were performed on computer (SAS software; SAS Institute, Cary, NC).\textsuperscript{14} A two-sided $P < 0.05$ was considered statistically significant.

Ethical Considerations

This study was approved by the Human Ethics Review Committee of Kyushu University Graduate School of Medical Sciences, and was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

RESULTS

Table 1 shows the comparison of baseline characteristics between the participants who were examined and those who were not examined at the 5-year follow-up. Those who did not participate at the 5-year follow-up examination were more likely at baseline to be older (68 years vs. 64 years), to have hypertension (56.4% vs. 46.7%), and to have diabetes (17.9% vs. 11.9%). There were no significant differences between the two groups with respect to the presence of ARM or lifestyle habits.

The 5-year incidences of early and late ARM lesions by sex are shown in Table 2. One hundred sixty-six participants with early or late ARM were excluded at the baseline eye examination; in 67 (8.5%) participants incident early ARM developed during the 5-year follow-up period. The incidence of early ARM was slightly but not significantly higher in men than in women. The incidence of retinal pigmentary abnormalities was significantly higher in men than in women. After 13 participants with late ARM were excluded at the baseline eye examination, development of incident late ARM was recorded in 8 (0.8%) participants during the 5-year follow-up period. All participants who had incident late ARM had early ARM at baseline. Five of the eight participants who had late ARM had soft drusen at baseline, and three of the eight had pigmentary abnormalities at baseline. The incidence of late ARM was significantly higher in men than in women. After adjustment for age, men were found to have a significantly higher incidence of late ARM than were women (OR, 2.62; 95% confidence interval [CI], 1.18–5.82). The incidences of GA and neovascular AMD were significantly higher in men than in women.

Age-specific 5-year incidences of early and late age-related maculopathy by sex are shown in Table 3. The incidence of

<table>
<thead>
<tr>
<th>Status at Baseline</th>
<th>Examined ($n = 961$)</th>
<th>Not Examined ($n = 521$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>64 ± 8</td>
<td>68 ± 10*ube</td>
</tr>
<tr>
<td>Sex (% men)</td>
<td>40.0</td>
<td>40.5</td>
</tr>
<tr>
<td>Early ARM (%)</td>
<td>17.3</td>
<td>15.6</td>
</tr>
<tr>
<td>Late ARM (%)</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>46.7</td>
<td>56.4*</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>11.9</td>
<td>17.9*</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>52.2</td>
<td>53.5</td>
</tr>
<tr>
<td>Smoking habit (%)</td>
<td>32.9</td>
<td>38.0</td>
</tr>
<tr>
<td>Alcohol intake (%)</td>
<td>39.3</td>
<td>38.6</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.2 ± 3.1</td>
<td>22.9 ± 3.4</td>
</tr>
<tr>
<td>White blood cells (×10³/mm³)</td>
<td>5.7 ± 1.5</td>
<td>5.9 ± 1.5</td>
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</table>

Data are expressed as the mean ± SD or percent. \* $P < 0.05$, \** $P < 0.01$, examined versus not examined.
early ARM significantly increased with advancing age in women. After adjustment for age, the incidence of early ARM was slightly but not significantly higher in men than in women (OR, 1.65; 95% CI, 0.98–2.49). The incidence of late ARM significantly increased with advancing age in men. After adjustment for age, men were found to have a significantly higher incidence of late ARM than were women (OR, 2.62; 95% CI, 1.18–5.82). The incidence of any ARM significantly increased with advancing age in all subjects.

The results of age and multivariate-adjusted logistic regression analyses of risk factors for the 5-year incidence of early and late ARM are shown in Table 4. After adjustment for age, habitual smoking was significantly associated with early and late ARM. The multivariate regression analysis showed that age and smoking were significantly associated with both early and late ARM.

**DISCUSSION**

To our knowledge, this is the first study to investigate the 5-year incidence and risk factors of ARM in Japan by using population-based cohort data. The results show that the overall 5-year incidence of early ARM was 8.5% and that of late ARM was 0.9%, and that both age and smoking were significantly associated with ARM.

Several prospective studies on the incidence of ARM have been conducted in various regions of the world.15–18 The results of the present study can be compared with those in the Beaver Dam Eye Study15 and the Blue Mountains Eye Study,16 since our methodology and grading system were almost identical with those used in these earlier works. Our early and late ARM incidences were similar to the reported incidences of early and late ARM in the Beaver Dam Eye Study15 (8.2% and 0.9% for early and late ARM, respectively) and the Blue Mountains Eye Study16 (8.7% and 1.1% for early and late ARM, respectively). A slightly lower incidence of early and late ARM was found in our study compared with the Blue Mountains Eye Study.16 This difference in ARM incidence among the three studies could be due to the differences in environmental exposure among the populations, to genetic factors, or perhaps to the differences in methodology among the three studies. In this study we used 45° fundus photographs to grade ARM. It is known that ARM, especially early ARM, is less likely to be detected by grading of fundus photographs than by grading of 30° fundus photographs. However, reliance on 45° fundus photographs theoretically could result in underestimation of the incidence of ARM by missing subtle early macular changes. This may be the reason for the lower incidence of early and late ARM observed in our study.

The present study, as well as the two previous studies15,16 found that the incidence of early ARM significantly increased with advancing age in women and that the incidence of late ARM significantly increased with advancing age in men. However, we found no such correlation between age and late ARM in women. This difference may have resulted from the relatively low incidence of late ARM among the women in our study.

We found a significantly higher incidence of late ARM among Japanese men than among Japanese women. We have already reported that early and late ARM are more prevalent among men than women in the representative Japanese community of Hisayama, using cross-sectional data from the Hisayama study.7 Yuzawa et al.19 have also reported that late ARM is more prevalent in men than in women in patients visiting ophthalmology departments in Japan. In contrast, ARM is more prevalent in women than in men in Western countries.20,21 In the Beaver Dam15 and Blue Mountains16 eye studies, the incidence was slightly higher in women than in men for both early and late ARM. For late ARM, the incidence in women was double that in men in the Blue Mountains Eye Study.16 The reason for this difference is not clear. However, smoking, which is known to be a major risk factor for ARM,22–25 is likely to have contributed to the observed difference in the incidence of ARM, because, in Japan, habitual smoking is significantly more prevalent in men than in women.

The results of this study provide prospective evidence that cigarette smoking increases the risk of development of ARM. Compared with those who never smoked, those who had smoked in the past or were currently smoking had 2.2 times the risk of ARM, after adjustment for other potential risk fac-

### Table 3. Age-Specific 5-Year Incidence of Early and Late ARM by Sex

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Men</th>
<th></th>
<th></th>
<th>Women</th>
<th></th>
<th></th>
<th>All Subjects</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Population at Risk</td>
<td>Incidence n (%)</td>
<td></td>
<td>Population at Risk</td>
<td>Incidence n (%)</td>
<td></td>
<td>Population at Risk</td>
<td>Incidence n (%)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Early ARM</td>
<td>Late ARM</td>
<td></td>
<td>Early ARM</td>
<td>Late ARM</td>
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<tr>
<td>50–59</td>
<td>102</td>
<td>9 (8.8)</td>
<td>119</td>
<td>0 (0.0)</td>
<td>162</td>
<td>6 (3.7)</td>
<td>186</td>
<td>0 (0.0)</td>
<td>264</td>
</tr>
<tr>
<td>60–69</td>
<td>130</td>
<td>13 (10.0)</td>
<td>160</td>
<td>4 (2.5)</td>
<td>217</td>
<td>14 (6.5)</td>
<td>251</td>
<td>0 (0.0)</td>
<td>347</td>
</tr>
<tr>
<td>70–79</td>
<td>69</td>
<td>9 (13.0)</td>
<td>90</td>
<td>2 (2.2)</td>
<td>102</td>
<td>11 (10.8)</td>
<td>125</td>
<td>1 (0.8)</td>
<td>171</td>
</tr>
<tr>
<td>80+</td>
<td>3</td>
<td>0 (0.0)</td>
<td>8</td>
<td>1 (12.5)</td>
<td>7</td>
<td>1 (14.3)</td>
<td>9</td>
<td>0 (0.0)</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>304</td>
<td>31 (10.2)</td>
<td>377</td>
<td>7 (1.9)</td>
<td>488</td>
<td>32 (6.6)</td>
<td>571</td>
<td>1 (0.2)</td>
<td>792</td>
</tr>
</tbody>
</table>

* *P < 0.01, men versus women.*
white blood cells, using the stepwise method. hyperlipidemia, smoking habit, alcohol intake, body mass index, and cohort data that showed that cigarette smoking is related to the development of ARM.7,22–27

This study had several limitations. First, our results could have been biased by the low response rate. Our data suggest that persons lost to follow-up were more likely at baseline to be slightly older, to have hypertension, and to have diabetes. As age is strongly associated with the prevalence of ARM, differential losses to follow-up due to differences in these characteristics could have resulted in an underestimation of the incidence of ARM in this population. However, there were no significant differences between the two groups in the presence of ARM or lifestyle habits. Although it is not possible to predict the magnitude of any such underestimation, we believe that it is not likely to be a major one. Second, drusen were defined as indistinct soft drusen in both the Beaver Dam15 and Blue Mountains16 eye studies. This distinction may be the reason for the differences in the incidence of early ARM among the three studies.

In conclusion, the results of this study suggest that the overall 5-year incidence of early ARM is 8.0% and that of late ARM is 0.8% in the general Japanese population and that higher age and smoking are relevant risk factors for early and late ARM in the Japanese.

References