Prevalence and Risk Factors for Myopic Retinopathy in a Japanese Population The Hisayama Study

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Prevalence and risk factors for myopic retinopathy in a Japanese population: the Hisayama Study

Running title: Prevalence of myopic retinopathy

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Abstract

Purpose: To examine the prevalence of myopic retinopathy and its risk factors in a general Japanese population.

Design: Population-based, cross-sectional study.

Participants: In 2005, a total of 1,969 Hisayama residents aged 40 years or older consented to participate in this study. Of these, 1,892 subjects with adequate data were enrolled.

Methods: Each participant underwent comprehensive physical and eye examinations that included measurements of refractive error, axial lengths, and color fundus photography. Myopic retinopathy was defined as the presence of diffuse chorioretinal atrophy, patchy chorioretinal atrophy, lacquer cracks, or macular atrophy.

Main Outcome Measures: Prevalence of myopic retinopathy.

Results: Thirty-three participants had myopic retinopathy and the prevalence was 1.7% (2.2% in women and 1.2% in men). The prevalence of myopic retinopathy increased significantly with advancing age. Diffuse chorioretinal atrophy, patchy chorioretinal atrophy, lacquer cracks and macular atrophy were present in 1.7%, 0.4%, 0.2%, and 0.4% of subjects, respectively. In multivariate analysis, myopic retinopathy was significantly associated with older age (per 1 year: odds ratio [OR], 1.12; 95% confidence interval [CI], 1.07 to 1.18), female gender (OR, 3.29; 95% CI, 1.09 to 9.92), and longer axial length (per 1 mm: OR, 4.20; 95% CI, 3.03 to 5.83).

Conclusions: The prevalence of myopic retinopathy was 1.7% in a general Japanese

population. Older age, female sex, and longer axial length were significant risk factors for myopic retinopathy.

Pathologic myopia is one of the major causes of visual impairment and blindness worldwide, especially in East Asia. According to the Tajimi Study, myopic macular degeneration is the third leading cause of low vision, and the leading cause of blindness in Japan.[1] In the Shihpai Eye Study, it was the second most frequent cause of visual impairment and blindness in Taiwan.[2] In the Beijing Eye Study, myopic macular degeneration was the second most common cause of low vision/blindness in China.[3] Although myopia was found to be less prevalent in Western countries, myopic macular degeneration has also been reported to be the second to fourth most frequent cause of blindness in Caucasians.[4-8] Myopic retinopathy often has bilateral impacts, and patients are frequently middle aged and working people.[9,10] Thus, it is very important to identify the prevalence of the disease and its risk factors. However, only two population-based studies from Australia and China have provided valuable information on the prevalence and risk factors for myopic retinopathy to date.[10,11]

It is well known that prevalence of high myopia is higher in Asian populations than other racial populations[12], so the prevalence of myopic retinopathy may be higher in Asian countries than in western countries. It would be of value to compare the prevalence of myopic retinopathy between Asians and whites.

The purpose of this study was to examine the prevalence of myopic retinopathy and its risk factors in a cross-sectional analysis of a general Japanese population.

Materials and Methods

Study population

The Hisayama Study is an ongoing long-term cohort study on cardiovascular disease and its risk factors in Hisayama, a town adjoining Fukuoka City, a metropolitan area in southern Japan.[13,14] As a part of the study, we performed a cross-sectional eye examination among Hisayama residents aged 40 years or older in 2005. Among the total of 4,439 residents in this age group, 1,969 individuals consented to participate in the study. Of these, 1,895 (96.2%) underwent the ophthalmic examination. After excluding three subjects who had ungradable photographs of either eye, 1,892 were enrolled in the present study.

Ophthalmic examination and definition of myopic retinopathy

Each participant underwent a comprehensive ophthalmic examination, including measurements of objective refraction, axial length, non-contact tonometry, and color fundus photography of both eyes. Objective refraction was measured by automatic refractometry (Auto Refractometer AR-660; Nidek, Co., Ltd., Aichi, Japan) without cycloplegia. A spherical equivalent was used for the calculations of refractive error. The spherical equivalent (SE) was defined as a sphere plus half of the cylindrical refraction. None of the participants had undergone refractive surgery. Axial length measurements were performed with noncontact partial coherence laser interferometry (IOL Master; Carl Zeiss, Hennigsdorf, Germany). Nonstereoscopic fundus photographs (45-degrees) were taken using a nonmydriatic digital fundus camera (TRC NW-200; Topcon

Corporation, Tokyo, Japan). We photographed one field, centered at a point midway between the temporal edge of the optic disc and the fovea in both eyes.

The presence of myopic retinopathy was determined based on the grading of the color fundus photographs. All photographs were evaluated independently by two experienced ophthalmologists (T.A. and M.Y.) to whom the participants' data were masked. In cases of a disagreement, the photographs were reexamined by three retinal specialists (T.A., M.Y., T.I.) and the final judgment was determined after discussion.

We defined myopic retinopathy as the presence of at least one of the following lesions according to the classification by Hayashi et al.[9]: diffuse chorioretinal atrophy at the posterior pole, patchy chorioretinal atrophy, lacquer cracks, or macular atrophy. This classification was based on the long-term longitudinal observations of a large number of patients with pathologic myopia.

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 ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or current use of antihypertensive medication. Plasma glucose levels were determined by the glucose-oxidase method, and diabetes was diagnosed on the basis of fasting plasma glucose of ≥7.0 mmol/L or postprandial plasma glucose of ≥11.1 mmol/L, or current treatment with insulin or oral medication. White blood cell counts were determined using a Coulter counter (STKS; Coulter Inc., Hialeah,

FL). Information on smoking habits and alcohol intake was obtained by trained interviewers using a standard questionnaire. Smoking habits and alcohol intake were classified as either current habitual use or not. Body height and weight were measured in light clothing without shoes, and the body mass index was calculated as the weight in kilograms divided by the height in meters squared.

Statistical methods

We considered the following 12 possible risk factors for myopic retinopathy: age, sex, axial length, spherical equivalent refraction, height, body mass index, diabetes, hypertension, total cholesterol, white blood cell count, smoking habits, and alcohol intake. In the analysis using a spherical equivalent refraction, eyes with a history of cataract surgery were excluded. Age, height, axial length, spherical equivalent refraction, body mass index, total cholesterol, and white blood cell count 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. Mean values were compared by the Student's *t*-test, and frequencies by chi-square test. Mantel-Haenszel chi-square test statistics were used to assess trends. Age-specific prevalence of myopic retinopathy was calculated per person, while the prevalence of myopic retinopathy according to axial length levels or spherical equivalent refraction levels was computed per eye. The associations between risk factors and the prevalence of myopic retinopathy were studied by logistic regression analysis. Odds ratios (OR) and their 95% confidence intervals (CI) were estimated using

a generalized estimating equations (GEE) model to take into account the correlations between the two eyes in a single person.[15,16] The SAS software package (version 9.2; SAS Institute, Cary, NC, USA) was used to perform all statistical analyses. A two-sided p-value of less than 0.05 was considered statistically significant.

Ethical considerations

This study was approved by the Kyushu University Institutional Review Board for Clinical Research, and was carried out in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

Results

Table 1 shows the comparison of characteristics of the study population by sex. Men were older, taller, and had longer axial length than women. The frequencies of diabetes, hypertension, smoking habits, and alcohol intake, and mean white blood cell count were higher for men than for women, whereas mean total cholesterol was higher for women. There was no difference in mean body mass index, mean spherical equivalent refraction, or frequencies of history of cataract surgery between the genders.

The prevalence of myopic retinopathy by the four lesions is shown in Table 2. Myopic retinopathy was present in 47 eyes of 33 participants (1.7% of the population). Of the four lesions associated with myopic retinopathy (diffuse chorioretinal atrophy, patchy chorioretinal atrophy, lacquer cracks, and myopic atrophy), diffuse chorioretinal atrophy was the most commonly observed (present in 44 eyes of 32 participants, 1.7%

of the entire population), followed by patchy chorioretinal atrophy (10 eyes of 8 participants, 0.4%) and myopic atrophy (9 eyes of 7 participants, 0.4%), whereas lacquer cracks were found in the lowest percentage (4 eyes of 3 participants, 0.2%). The frequency was higher in women than in men for each of the four lesions of myopic retinopathy. Bilateral involvement was present in 42% of the subjects with myopic retinopathy.

The subjects with myopic retinopathy (mean age: 70.0 years) were significantly older ($P<0.001$) than those without myopic retinopathy (mean age: 63.3 years). Table 3 shows the age-specific prevalence of myopic retinopathy by sex. A statistically significant age-related trend was present ($P=0.001$). Women were found to have a higher prevalence of myopic retinopathy (2.2%) than men (1.2%), but the difference was not significant ($P=0.11$). Table 4 presents the prevalence of myopic retinopathy according to axial length levels. The prevalence of myopic retinopathy significantly increased with longer axial length ($P<0.001$), from 0.1% in eyes with an axial length < 26 mm to 53.7% in eyes with an axial length of at least 28 mm. Likewise, the prevalence of myopic retinopathy significantly increased with higher myopic refraction ($P<0.001$), from 0.3% in eyes with a myopic refractive error of < -6.0 diopters (D) to 36.8% in eyes with a myopic refractive error of at least -10.0 D (Table 5).

The results of age- and sex-adjusted and multivariate-adjusted logistic regression analyses of relevant risk factors for myopic retinopathy are shown in Table 6. After adjusting for age and sex, we found that older age (per 1 year: OR, 1.07; 95% CI, 1.03

to 1.11; P<0.001), longer axial length (per 1 mm: OR, 4.2; 95% CI, 3.03 to 5.83; P<0.001), and myopic refractive error (per -1 diopter: OR, 1.76; 95% CI, 1.52 to 2.03; P<0.001) were significantly associated with myopic retinopathy. The multivariate analysis with age, sex, and axial length showed that older age (per 1 year: OR, 1.12; 95% CI, 1.07 to 1.18; P<0.001), female gender (OR, 3.29; 95% CI, 1.09 to 9.92; P=0.03), and longer axial length (per 1 mm: OR, 4.2; 95% CI, 3.03 to 5.83; P<0.001) were significantly associated with myopic retinopathy.

Discussion

To our knowledge, this is the first population-based study which investigated the prevalence of and risk factors for myopic retinopathy in Japan. The findings showed that the overall prevalence of myopic retinopathy was 1.7%, and that older age, female gender, and longer axial length were independently associated with myopic retinopathy.

In a Japanese hospital-based study, Tokoro[17] reported a prevalence of myopic retinopathy of 2.2% and estimated the general population prevalence to be approximately 1.0%. The prevalence of myopic retinopathy found in our population-based study is comparable to the prevalence rate reported by Tokoro. Previously, two population-based studies estimated the prevalence of myopic retinopathy. In the Blue Mountains Eye Study in Australia, which focused on a white population, the prevalence of myopic retinopathy was 1.2%.[10] In contrast, The Beijing Eye Study performed in a Chinese population reported the prevalence was 3.1%.[11] It has

been reported that high myopia is more common among Asian populations, especially in East Asian countries, than among whites, black, or Hispanic people.[12] Thus, the prevalence of myopic retinopathy may be higher in East Asian populations than in white populations. The prevalence of myopia (SE<0.5D) in the current study was 37.7%, which is higher than that in the Beijing Eye Study (21.8%) and that in the Blue Mountains Eye Study (14.4%). In the current study, the prevalence of high myopia (SE<-5.0D) was 5.7%, which is still higher than that in the Beijing Eye Study (3.3%) and much higher than that in the Blue Mountains Eye Study (2.2%).[10,18,19] Although the prevalence of myopic retinopathy in the current study (1.7%) was higher than that reported in the Blue Mountains Eye Study (1.2%), it was lower than that found in the Beijing Eye Study (3.1%). The precise reason for racial differences in the prevalence of myopic retinopathy is unknown, but it could be related to differences in the characteristics of study participants (for example, the age and proportion of either sex), differences in the methodology or study design (for example, the definition of myopic retinopathy), or perhaps to genetic factors (Table 7). Further investigations of other populations worldwide are expected.

The current study found that the prevalence of myopic retinopathy significantly increased with advancing age. The association with increasing age found in this study agrees with other epidemiological studies.[10,11,20] Histological studies have shown a decreased density of photo receptors, ganglion cells, retinal pigment epithelium and optic nerve fibers with age.[21,22] In addition, several studies using OCT have shown a

negative relationship between retinal thickness and age.[23,24] Therefore, along with the axial elongation of the eyeball in highly myopic eyes, increasing age may contribute to the pathogenesis of myopic retinopathy by causing retinal thinning.

Although men had longer axial length than did women (P<0.001 for both eyes), we found a higher prevalence of myopic retinopathy in women (2.2%) than in men (1.2%). After adjustment for age, sex, and axial length, we found a 3-fold increased risk of myopic retinopathy in women. Similar findings were observed in a number of hospital-based studies.[25-27] For example, Hayashi *et al.* showed that of 429 consecutive patients with pathologic myopia, 147 were men and 282 were women, making the incidence in women approximately double that in men.[9] Comparable findings were also observed in the Blue Mountains Eye Study and in the Beijing Eye Study. This suggests that not only greater axial length but also other risk factors, such as genetic factors and lifestyle risk factors, may contribute to the pathogenesis of myopic retinopathy.

The strengths of our study include the high reproducibility of the biometric measurements using the IOL Master, and the standardized assessments of anthropometric measures and blood pressure. Several limitations of our study should also be mentioned. First, the low response rate could have introduced selection bias, resulting in either an underestimation or overestimation of the prevalence of myopic retinopathy. Second, we used non-stereoscopic 45° fundus photographs to grade myopic retinopathy, whereas other studies used 30° stereoscopic fundus photographs. Non-stereoscopic photographs might have resulted in an under-estimation of the

prevalence of myopic retinopathy by missing backward bowing of the fundus in the region of the staphyloma. Posterior staphyloma is one of the causes of the development of myopic retinopathy and not the reverse.[9] Third, we could not evaluate the visual significance of those with or without myopic retinopathy, because we did not measure visual acuity in this study.

In conclusion, the prevalence of myopic retinopathy in a Japanese population was 1.7%. Myopic retinopathy was independently associated with higher age, female sex, and longer axial length.

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Table 1. Characteristics of the study population by sex

Variables	Men (n=776)		Women (n=1,116)	
Age (year)	64±11		63±11	
Height (cm)	163.7±6.6		151.3±6.3	
Body mass index (kg/m^2)	23.2±3.0		22.9±3.5	
Diabetes (%)	15.7		9.1	
Hypertension (%)	51.7		42.2	
Total cholesterol (mmol/L)	5.1±0.8		5.5±0.8	
White blood cells (×10^3/mm^3)	6.3±1.6		5.5±1.4	
Smoking habits (%)	32.4		4.9	
Alcohol intake (%)	72.6		30.9	
	(Right eye)	(Left eye)	(Right eye)	(Left eye)
Axial length (mm)	23.8±1.3	23.8±1.3	23.4±1.4	23.4±1.4
Median (Range)	23.6 (21.1 to 33.6)	23.6 (20.2 to 33.0)	23.1 (20.3 to 33.2)	23.1 (20.3 to 31.7)
Spherical equivalent refraction (diopter)	-0.63±2.4	-0.45±2.5	-0.50±2.4	-0.45±2.5
Median (Range)	-0.25 (-16.9 to +6.0)	0.0 (–17.3 to +10.1)	-0.13 (–12.8 to+9.6)	-0.13 (–20.5 to +8.1)
Cataract surgery (%)	11.2	10.2	10.2	10.2

Values are expressed as the means ± standard deviation or percentages.

Table 2. Prevalence of myopic retinopathy by four lesions

	Diffuse chorioretinal atrophy	Patchy chorioretinal atrophy	Lacquer cracks	Macular atrophy	Myopic retinopathy
No. of subjects (% of the entire study population)	32 (1.7%)	8 (0.4%)	3 (0.2%)	7 (0.4%)	33 (1.7%)
Age (year)	70±10	76±5	79±4	76±7	70±10
Women: n (% of subjects with this sign)	23 (72%)	7 (88%)	3 (100%)	7 (100%)	24 (73%)
Bilateral involvement: n (% of subjects with this sign)	12 (38%)	2 (25%)	1 (33%)	2 (29%)	14 (42%)
No. of eyes	44	10	4	9	47
Mean axial length (mm) ± SD	28.3±2.1	29.7±3.0	28.5±0.8	28.7±2.0	28.2±2.2
Mean spherical equivalent refraction[#] (diopter) ± SD	-8.3±5.2	-3.5±3.6	-9.9±5.6	-4.4±4.9	-8.3±5.2
Cataract surgery: n (% of eyes with this sign)	18 (41%)	7 (70%)	2 (50%)	6 (67%)	21(45%)

SD = standard deviation

Excludes eyes with history of cataract surgery.

Table 3. Age-specific prevalence of myopic retinopathy by sex

Age (Years)	Men N (%)	Women N (%)	Total N (%)
40-49	1/84 (1.2%)	1/146 (0.7%)	2/230 (0.9%)
50-59	1/163 (0.6%)	2/292 (0.7%)	3/455 (0.7%)
60-69	2/271 (0.7%)	6/346 (1.7%)	8/617 (1.3%)
70+	5/258 (1.9%)	15/332 (4.5%)	20/590 (3.4%)
All ages	9/776 (1.2%)	24/1116 (2.2%)	33/1892 (1.7%)
P for trend	0.33	0.001	0.001

N = number of subjects.

Table 4. Prevalence of myopic retinopathy according to axial length levels

Axial length (mm)	No. of Eyes* (%)	Myopic Retionopathy
<23	1374 (36.6%)	0 (0.0%)
23 - 23.99	1296 (34.5%)	2 (0.2%)
24 - 24.99	635 (16.9%)	1 (0.2%)
25 - 25.99	246 (6.6%)	2 (0.8%)
26 - 26.99	118 (3.1%)	8 (6.8%)
27 - 27.99	47 (1.3%)	11 (23.4%)
28≤	41 (1.1%)	22 (53.7%)
All axial length	3757 (100%)	46 (1.2%)

*Excludes 27 eyes with unavailable axial length data.

Table 5. Prevalence of myopic retinopathy according to spherical equivalent refraction levels of myopia

Spherical equivalent refraction (diopters)	No. of eyes* (%)	Myopic retinopathy
>0.00	1685 (51.0%)	1 (0.1%)
0.00 to -1.99	1033 (31.3%)	1 (0.1%)
-2.00 to -3.99	301 (9.1%)	4 (1.3%)
-4.00 to -5.99	165 (5.0%)	3 (1.8%)
-6.00 to -7.99	75 (2.3%)	4 (5.3%)
-8.00 to -9.99	26 (0.8%)	5 (19.2%)
≤-10.00	19 (0.6%)	7 (36.8%)
All Spherical equivalent refraction	3304 (100%)	25 (0.8%)

*Excludes 480 eyes with history of cataract surgery or unavailable spherical equivalent refraction data.

Table 6. Age- and sex-adjusted and multivariate-adjusted odds ratios of risk factors for myopic retinopathy

Risk factor	Myopic retinopathy					
	Age- and sex-adjusted[#]			Multivariate adjusted		
	OR	(95%CI)	P value	OR	(95%CI)	P value
Age (per 1 year)	1.07**	1.03-1.11	<0.001	1.12**	1.07-1.18	<0.001
Sex (women)	2.28	0.99-5.27	0.05	3.29*	1.09-9.92	0.03
Axial length (per 1 mm)	4.20**	3.03-5.83	<0.001	4.20**	3.03-5.83	<0.001
Spherical equivalent refraction[†] (per -1diopter)	1.76**	1.52-2.03	<0.001			
Height (cm)	0.99	0.93-1.05	0.77			
Body mass index (per 1 kg/m^2)	1.07	0.96-1.20	0.21			
Diabetes (%)	1.62	0.62-4.24	0.32			
Hypertension (%)	1.26	0.56-2.87	0.57			
Total cholesterol (per 1 mmol/L)	1.27	0.72-2.22	0.41			
White blood cells ($\times 10^3/mm^3$)	0.92	0.70-1.22	0.58			
Smoking habits (%)	0.42	0.10-1.84	0.25			
Alcohol intake (%)	0.89	0.41-1.91	0.76			

OR = odds ratio, CI = confidence interval, *p<0.05, **p<0.001

[#]Age is sex-adjusted and sex is age-adjusted.

[†]Eyes with history of cataract surgery were excluded.

Multivariate adjustment was made for age, sex, and axial length in a generalized estimating equations (GEE) models.

Table 7. Comparison of prevalence of myopia, high myopia, and myopic retinopathy in previous population-based studies

Study	Participants	Definition of myopic retinopathy	Prevalence of myopic retinopathy	Prevalence of myopia (<-0.5D)	Prevalence of high myopia (<-5.0D)
Blue Mountains Eye Study[10,19] (Australia)	n=3,653 age ≥49 years	staphyloma chorioretinal atrophy Fuchs's spot lacquer cracks	1.2%	14.4%	2.2%
Beijing Eye Study[11,18] (China)	n=4,319 age ≥40 years	staphyloma chorioretinal atrophy Fuchs's spot lacquer cracks	3.1%	21.8%	3.3%
Hisayama Study (Japan)	n=1,892 age ≥40 years	diffuse chorioretinal atrophy patchy chorioretinal atrophy lacquer cracks macular atrophy	1.7%	37.7%	5.7%

D=diopters