

Risk Factors for Open-Angle Glaucoma in a Japanese Population

The Tajimi Study

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Purpose: To identify the risk factors associated with primary open-angle glaucoma (POAG) in the Tajimi Study.

Design: Population-based cross-sectional epidemiologic study.

Participants: One hundred nineteen POAG patients and 2755 controls.

Methods: Univariate and multivariate comparison of ocular factors and systemic factors between POAG patients and controls.

Main Outcome Measures: Difference in factors between POAG patients and controls, factors associated with POAG patients, and their odds ratio (OR).

Results: Intraocular pressure (IOP), age, myopia, and history of hypertension differed between POAG patients and controls in univariate analyses. Multivariate analysis with logistic regression with stepwise selection of variables demonstrated that higher IOP (OR, 1.12 [95% confidence interval (CI), 1.04–1.21]), myopia (ORs, 1.85 [95% CI, 1.03–3.31] for low myopia and 2.60 [95% CI, 1.56–4.35] for moderate to high myopia), and older age (OR, 1.06 [95% CI, 1.04–1.08]) were associated with an increased risk of having POAG.

Conclusions: Although the majority (92%) of POAG patients diagnosed in the Tajimi Study had IOP within the normal range, IOP was still identified as a significant risk factor for POAG. Together with IOP, myopia and age were significant risk factors for having POAG. *Ophthalmology* 2006;113:1613–1617 © 2006 by the American Academy of Ophthalmology.

Primary open-angle glaucoma (POAG) is the most prevalent form of glaucoma.^{1–10} Recently, various population studies of glaucoma have shown that high intraocular pressure (IOP), which has been considered a main cause or the most remarkable feature of POAG, is not always observed in POAG patients.^{1,3,5,6,8–10} Particularly, recently it has been realized that the prevalence of POAG patients in whom IOP is not elevated is very high in Japan.^{1,10} In a population study performed from September 2000 to October 2001 in Tajimi, Japan (Tajimi Study¹⁰), the prevalence of definitive POAG was as

high as 3.9% (95% confidence interval [CI], 3.2%–4.6%), and surprisingly, 92% of the POAG patients diagnosed had IOP lower than 22 mmHg at the screening. Mean (\pm standard deviation [SD]) IOPs of POAG patients were 15.4 ± 2.8 mmHg in the right eye and 15.2 ± 2.8 mmHg in the left eye, lower than in most previous reports,^{3,5,8,11–19} although higher than that of nonglaucoma subjects (14.5 ± 2.5 and 14.4 ± 2.6 mmHg in the right and left eyes, respectively).¹⁰

Thus, the population studied in Tajimi is unique in that the average IOP in POAG patients was 15.2–15.4 mmHg

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and 92% of the patients diagnosed had normal IOP.¹⁰ Therefore, this population affords a good opportunity to investigate the risk factors for glaucoma other than IOP. In the present study, we investigated the ocular and systemic parameters of POAG patients and nonglaucoma subjects to identify the risk factors associated with POAG in the Tajimi Study population.

Subjects and Methods

The detailed protocol of the Tajimi Study has been reported elsewhere.¹⁰ The Tajimi Study was conducted from September 2000 to October 2001 to investigate the prevalence of glaucoma in the city of Tajimi, located in central Japan. Four thousand subjects from the 54 165 residents 40 years or older living in Tajimi were selected randomly and examined ophthalmologically. All the selected subjects were encouraged to participate in the study by telephone and letter. When a subject could not participate in the study at the designated place, an ophthalmologist visited him or her at home for an interview and to conduct an ocular examination. Of the selected 4000 subjects, 48 died during the screening period, and 82 moved from Tajimi or could not be located in Tajimi. Of the eligible remaining 3870, 3021 (78.1%) participated in the examination. After informed written consent was obtained, participants underwent an interview including a questionnaire about having diabetes mellitus, hypertension, migraine, smoking, and a family history of glaucoma. Answers were recorded by participants under the guidance of questioners comprising doctors and paramedical staff. Then, weight, height, and systolic and diastolic blood pressure (BP) were measured. When the measured BP was abnormally high, the measurement was repeated after a 5-minute rest. When the second measurement still showed high BP, the procedure was repeated again and the measured value was recorded. After the interview and systemic examinations, ophthalmic screening examinations were conducted, including measurement of IOP by a Goldmann applanation tonometer, measurement of central corneal thickness, slit-lamp examination, fundus photography, and a screening visual field (VF) test using frequency doubling technology. When any ocular abnormalities were suspected, the subjects were referred for a definitive examination in which slit-lamp examination, IOP measurement by a Goldmann applanation tonometer, gonioscopy, a VF test using the Humphrey Field Analyzer 30-2 Swedish Interactive Thresholding Algorithm program (Carl Zeiss Meditec Inc., Dublin, CA), and optic disc and fundus examination were performed and stereoscopic disc photographs were taken. Optic disc and fundus examination was performed through dilated pupils, unless the angle of the eye was considered to be occludable. When the eye had a narrow angle, these examinations were performed through undilated pupils. A diagnosis of glaucoma was made based on optic disc appearance, perimetric results, and other ocular findings. In the Tajimi Study, 119 subjects were diagnosed with definitive POAG, and 63 subjects were diagnosed as POAG suspects.¹⁰

Ophthalmologic and systemic data of all the patients diagnosed with definitive POAG in the Tajimi Study were analyzed in the present study. As a control group, data of 2755 nonglaucoma subjects diagnosed in the Tajimi Study were used. Nonglaucoma subjects were those who did not have any type of glaucoma, were not glaucoma suspects, and did not have exfoliation in either eye. Subjects with uveitis or primary angle closure were also excluded, but subjects with ocular hypertension (defined as IOP > 21 mmHg) were included as nonglaucoma subjects. As for the data from ocular findings, data of the eye diagnosed with POAG were used in the POAG subjects, and those of the eyes that did not have

ocular disease affecting the ophthalmic parameters analyzed were used in control groups. When one of the eyes was aphakic or pseudophakic due to previous cataract surgery, the other eye was selected. When both eyes were eligible, one was selected randomly, and the data from the eye were used for the analyses.

The ocular parameters of IOP, myopia, corneal curvature radius, and central corneal thickness were selected for study. The IOP value analyzed was the one measured at the screening examination in which the IOP was measured 3 times by Goldmann applanation tonometry under topical anesthesia, and the median value was adopted. Refraction and corneal curvature radius were measured using an autokeratorefractometer (KP-8100PA, Topcon, Tokyo, Japan). Myopia was defined as myopic spherical equivalent (SE) of the eye > -1.0 diopter (D). Low myopia was defined as myopic SE of the eye > -1.0 D to < -3.0 D. Moderate to high myopia was defined in eyes with an SE of the eye of -3.0 D or greater. Eyes that had a history of cataract surgery were excluded from the analysis. Central corneal thickness was measured using a specular-type central corneal thickness measurement apparatus (SP-2000P, Topcon).

The systemic parameters of age, gender, body mass index, history of diabetes mellitus, migraine, smoking habit, family history of glaucoma, and history of hypertension were selected. Subjects' ages as of April 1, 2001 were used. Body mass index was calculated by dividing body weight (kilograms) by the square of height (meters), measured at the time of the screening examination. Histories of diabetes mellitus, migraine, and smoking and a family history of glaucoma were obtained from the questionnaire. As for history of hypertension, subjects who had a history of hypertension medication or had high systolic and/or diastolic BP were defined as having hypertension. Because subjects may have been anxious in the examination setting, we defined high BP rather strictly; when systolic BP was ≥ 160 mmHg or diastolic BP was ≥ 95 mmHg, the subject was said to have systemic hypertension.

For the statistical analyses, SAS software (version 8.02, SAS Institute Japan, Tokyo, Japan) was used. For univariate analysis, each parameter was compared between the POAG group and the control group. Student's *t* test, Wilcoxon rank sum test (for myopia), and the Fisher exact probability test were used for testing difference between groups. For multivariate analysis, logistic regression analysis was performed. Explanatory variables included IOP; myopia; corneal curvature radius; central corneal thickness; age; gender; body mass index; history of diabetes mellitus, migraine, and hypertension; smoking habit; and family history of glaucoma. Variables were stepwise selected according to the statistical significance affecting the discrimination between groups. Statistical significance was defined as a probability value of <5% for the comparison between groups and stepwise variable selection in logistic regression analysis.

Results

The results of the comparison of ocular and systemic parameters are summarized in Table 1. There was no statistical difference between POAG patients and controls in corneal curvature radius, central corneal thickness, gender, body mass index, history of diabetes mellitus and migraine, smoking habit, and family history of glaucoma.

The mean (\pm SD) IOP of POAG eyes was 15.2 ± 2.9 mmHg, which was higher than that of controls (14.4 ± 2.6 mmHg) ($P = 0.0015$). The mean age of POAG patients (63.8 ± 12.0 years) was higher than that of controls (57.8 ± 11.6) ($P < 0.0001$). The other parameter that differed between groups was a history or presence of hypertension ($P = 0.009$) and myopia ($P = 0.044$).

Multivariate logistic regression analysis with stepwise selection

Table 1. Difference of Parameters between POAG and Control

Parameter	POAG (n = 119)	Control (n = 2755)	P Value
Ocular			
Intraocular pressure (mmHg) (mean ± SD)	15.2±2.9	14.4±2.6	0.0015
Myopia			0.044
Low (−3 D < SE < −1 D)	17/107	372/2655	
Moderate to high (SE ≤ −3 D)	26/107	462/2655	
Corneal curvature radius (mm) (mean ± SD)	7.58±0.25	7.62±0.26	0.079
Central corneal thickness (mm) (mean ± SD)	0.52±0.03	0.52±0.03	0.38
Systemic			
Age (yrs) (mean ± SD)	63.8±12.0	57.8±11.6	<0.0001
Gender (male–female)	57–62	1220–1535	0.45
Body mass index (kg/m ²) (mean ± SD)	22.5±3.4	22.9±3.4	0.28
Diabetes mellitus	7/117	187/2731	0.85
Migraine	11/119	273/2740	>0.99
Smoking habit	51/119	1145/2737	0.85
Family history of glaucoma	5/119	152/2723	0.68
Hypertension	47/119	769/2733	0.0094

D = diopter; POAG = primary open-angle glaucoma; SD = standard deviation; SE = spherical equivalent of the eye.

of variables demonstrated that IOP, myopia, and age significantly affected the discrimination between POAG patients and controls (Table 2). Higher IOP (odds ratio [OR], 1.13 [95% confidence interval (CI), 1.05–1.21]), myopia (ORs, 1.85 [95% CI, 1.03–3.31] for low myopia and 2.60 [95% CI, 1.56–4.35] for moderate to high myopia), and older age (OR, 1.05 [95% CI, 1.04–1.07]) were associated with increased risk for having POAG.

Discussion

Because the majority (92%) of POAG patients diagnosed in the Tajimi Study had IOP within the normal range,¹⁰ this study population was thought to be suited for highlighting risk factors other than IOP. The IOP, however, was still identified as a significant risk factor for having POAG, together with age and myopia. It is well known that high IOP is a major risk factor not only for developing POAG but also for progression of POAG. Even in normal-tension glaucoma, the level of IOP was reported to be the most significant risk factor for VF defect progression.^{20,21} In the report of the POAG prevalence in the Tajimi Study and this article, the average IOP was higher in POAG patients than in nonglaucoma patients, though the difference was small (<1 mmHg). The OR for higher IOP obtained in the mul-

tivariate analysis was 1.13, which means that having an IOP 6 mmHg higher than average (20–21 mmHg) makes the risk for having POAG about twice.

Myopia was a significant risk factor for POAG. Odds ratios were 1.85 (95% CI, 1.03–3.31) for low myopia and 2.60 (95% CI, 1.56–4.35) for moderate to high myopia. There are 3 population-based studies suggesting association of myopia with the risk for POAG.^{22–24} In the Barbados Eye Study,²⁴ an association between myopia (≤−0.5 D) and glaucoma, including suspects, was found, with an OR of 1.5 (95% CI, 1.1–2.0). In the Blue Mountains Eye Study in Australia,²² low myopia (−1.0 to −3.0 D) had an OR of 2.3 (95% CI, 1.3–4.1), and moderate to high myopia (≤−3.0 D) had an OR of 3.3 (95% CI, 1.7–6.4). In the Beaver Dam Eye Study in the United States,²³ persons with myopia defined as an SE of ≤−1.0 D were 60% more likely to have glaucoma than emmetropia (OR, 1.6 [95% CI, 1.1–2.3]). There is also a report that the association of myopia and glaucoma was strong in glaucoma patients with low IOP, based on the data of the screening examination for the Early Manifest Glaucoma Trial.²⁵ Therefore, low average IOP of POAG patients may be one of the reasons that myopia was selected to be a significant risk factor for POAG in the present study.

Primary open-angle glaucoma is a disease that develops later in life; therefore, the result that age was a significant risk factor for having POAG is no surprise at all and is compatible with many previous results.* A history of hypertension differed significantly between POAG patients and controls in the univariate analysis but was not significant in the logistic regression analysis. The association between hypertension and POAG observed in the univariate analysis was mostly likely due to correlation of age and hypertension. The average age of subjects with hypertension was 63.0±11.1 years, which was significantly higher than that of subjects without hypertension (55.9±11.1) (*P*<0.0001, Stu-

Table 2. Multivariate Risk Factors for Having Primary Open-Angle Glaucoma

Parameter	Odds Ratio (95% Confidence Interval)	P Value
Intraocular pressure (mmHg)	1.12 (1.04–1.21)	0.0021
Myopia		0.0003
Low (−3 D < SE < −1 D)	1.85 (1.03–3.31)	
Moderate to high (SE ≤ −3 D)	2.60 (1.56–4.35)	
Age (yrs)	1.06 (1.04–1.08)	<0.0001

D = diopter; SE = spherical equivalent of the eye.

*See Refs. 1–3, 5–12, 14, 15, 17–19, 26–28.

dent's *t* test), and forced inclusion of hypertension in the logistic model made age an insignificant risk factor.

The other parameters investigated in this study (corneal curvature radius, central corneal thickness, gender, body mass index, history of diabetes mellitus, migraine, smoking, and family history of glaucoma) were not risk factors. A thick central cornea has been reported to be a factor associated with ocular hypertension²⁹ and a thin central cornea to be a factor associated with normal-tension glaucoma in some studies.^{30–32} In this study, 92% of POAG patients had normal IOP, but there was no significant difference in central corneal thickness between POAG patients and controls, agreeing with the previous reports.³³ A thin central cornea was reported to be a major risk factor for developing POAG in ocular hypertension patients (Ocular Hypertension Treatment Study³⁴). In the population of the present study, most of the POAG patients and control subjects had normal IOP, unlike those in the Ocular Hypertension Treatment Study. Therefore, the attribution of central corneal thickness to developing POAG may have differed from the conclusions of the Ocular Hypertension Treatment Study researchers.

Family history of glaucoma has been known to be associated with POAG.^{16,17,27,28,35–37} In the Tajimi Study, the information obtained in the interview with participants about the family history of glaucoma was very limited. Even of the POAG patients diagnosed in the Tajimi Study, only 6.7% knew they had glaucoma. Therefore, we cannot draw any conclusions from the present study concerning the association of family history with POAG.

There are several limitations in the present analyses. First, there were several factors not included in the present analysis but reported to be associated with the development of POAG, such as systemic medications,¹⁶ other ocular diseases,¹⁶ and computer use.³⁸ Second, the information about some of the factors investigated was not defined thoroughly. Diagnosis of diabetes mellitus, smoking, and migraine depended entirely on participants' own reports, and detailed information such as severity and duration was not obtained. We did not obtain detailed information about smoking (i.e., whether the subjects were current or former smokers). It is desirable that a future population-based study in which systemic and ophthalmologic parameters are more deliberately selected and estimated be performed.

In summary, the present study showed that IOP was still a significant risk factor despite the rather low average IOP (~15 mmHg in the POAG population), and myopia was also a significant risk factor. Considering that there are a large number of myopic subjects in Japan³⁸ and that the life expectancy of Japanese is the longest in the world, these findings have significant clinical implications.

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