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ORIGINAL RESEARCH

# Risk factors for primary open-angle glaucoma in Japanese subjects attending community health screenings

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**Background/aims:** To describe risk factors associated with primary open-angle glaucoma (POAG) in Japanese subjects who participated in community health screenings.

**Methods:** Residents of Akita, Japan, participating in a community health checkup were selected to undergo a comprehensive ophthalmic examination. Glaucoma was diagnosed based on optic disk appearance, perimetric results, and other ocular findings. Systemic blood pressure and intraocular pressure were measured and ocular perfusion pressure was calculated. Logistic regression analysis was performed to determine risk factors for POAG patients.

**Results and conclusion:** Of the 710 subjects examined, 26 had POAG. The estimated prevalence of POAG was 3.7%. After adjusting for age, the prevalence of POAG was similar to that found in the Tajimi Study of Japanese subjects. Multivariate logistic regression analysis demonstrated that older age (≥60 years, odds ratio [OR]: 3.49), lower diastolic blood pressure (≤58 mmHg, OR: 2.11), higher intraocular pressure (≥19 mmHg, OR: 4.12), and lower ocular perfusion pressure (≤34 mmHg, OR: 5.78) were associated with increased risk of having POAG. These findings may be relevant for identifying high risk groups.

**Keywords:** glaucoma, community health screening, risk factors

## Introduction

Glaucoma is the leading cause of blindness, and 22.5 million people worldwide are estimated to suffer from it. The Tajimi screening study estimated that the prevalence of primary open-angle glaucoma (POAG) in Japanese subjects older than 40 years was 3.9%, of which 93.3% were previously undiagnosed.[1] There is good evidence that age, family history, intraocular pressure (IOP), and African ancestry are risk factors for POAG.[2–4] To better identify persons at risk for developing glaucoma, it is very important to determine what other risk factors for POAG also exist.

According to the vascular hypothesis of POAG pathogenesis,[5] low blood pressure (BP) relative to IOP could lead to low ocular perfusion pressure (OPP), thus impairing perfusion of the optic nerve and causing glaucomatous loss of the visual field. In this context, vascular factors have been investigated with attention to BP and OPP.[6–10] Recently, the population-based cohort study[11,12] revealed that low systolic BP and low OPP were risk factors for POAG. However, there are only a few studies that have reported associations between POAG and BP-related factors in Japanese[13] and other Asians.[14,15]

Recently, we conducted a community health checkup project in the city of Akita, located in northeastern Japan. The project involved glaucoma screening as well as general physical examinations. The purpose of this study was to identify the systemic and ocular risk factors associated with POAG in this population.

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## Subjects and methods

This was a cross-sectional study in an institutional setting. Subjects older than 30 years were recruited at an annual community health checkup project held in the city of Akita (population 325,537), the capital of Akita Prefecture, Japan. A total of 1173 subjects participated in the comprehensive examinations from September 10, 2007 to October 26, 2007. Of these, 710 individuals underwent glaucoma screening. All of the participants were ethnically Japanese.

This study was performed after approval by the Ethics Committee of Akita Prefecture Health Care Foundation. All study procedures adhered to the principles outlined in the Declaration of Helsinki for research involving human subjects, and all participants gave written informed consent for this research prior to their participation.

## Screening examination

The screening examination included the recording of systemic and ocular disorder history, height, weight, blood hemoglobin A1c ($HbA_{1c}$) status, alanine aminotransferase (ALT), serum cholesterol, and BPs. The initial noncontact ocular examination was conducted by trained non-ophthalmologists and included measurement of refraction and keratometry (KR-8100PA; Topcon, Tokyo, Japan), IOP by noncontact pneumotonometry (Topcon CT-90A), angle width (Scanning Peripheral Anterior Chamber Analyzer; Takagi Seiko, Nagano, Japan), non-mydriatic optic disk photography by stereoscopic fundus camera (30° angle, 3-DX/NM; Nidek, Gamagori, Japan), and confocal laser scanning tomography (Retina Tomograph II, software v 3.0; Heidelberg Instruments, Heidelberg, Germany). IOP was measured three times, and the mean value was used.

## Definitive examination

A definitive examination was performed when a subject was suspected to have glaucoma based upon the findings of the initial noncontact ocular examination. The definitive examination consisted of the following procedures: slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, and optic nerve head evaluation using a Goldmann three-mirror lens (Haag-Streit International, Koeniz, Switzerland) and a visual field test with the Humphrey Field Analyzer II 24-2 SITA Standard Program (Carl Zeiss Meditec Inc, Dublin, CA). Diagnosis of glaucoma was made based on optic disk appearance, including cup-to-disk ratio, rim width, nerve fiber layer defect, the visual field test, and the clinical records that were obtained through screening and definitive examinations. When present or suspected, glaucoma was categorized based upon the criteria of previous population studies (Table 1).[1,16] In the definitive diagnosis, anomalous disks, including tilted disks, were carefully excluded.

## Assessment of risk factors

The systemic variables of age, gender, body mass index (BMI), systolic (SBP) and diastolic blood pressure (DBP), diagnosis of hypertension, blood pressure-lowering treatment, diabetic status (glycated hemoglobin, $HbA_{1c} \geq 5.8\%$ and/or previous diagnosis as diabetes mellitus),[17] liver dysfunction (ALT $\geq$ 40 IU and/or previous diagnosis as liver dysfunction), and hypercholesterolemia were selected as possible risk factors. BMI was calculated as weight (kilograms) divided by the height (meters) squared. Blood pressure was measured after participants had been seated comfortably for at least 5 minutes. A single measure of SBP and DBP was used. Hypertension was defined using the 2003 World Health Organization guideline[18] with SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg. Subjects who had a history of hypertension medication were also defined as having hypertension. Hypercholesterolemia was defined when cholesterol levels were greater than the upper limit of the normal range (220 mg/dL).[19]

**Table 1** The criteria for primary open-angle glaucoma diagnosis

**Category 1**
The vertical cup-to-disk ratio of the optic nerve head is 0.7 or more, or the rim width at the superior portion (11–1 o'clock) or the inferior portion (5–7 o'clock) is 0.1 or less of the disk diameter, or the difference of the vertical cup-to-disk ratio is 0.2 or more between both eyes, or a nerve fiber layer defect is found, and the hemifield-based visual field abnormality is compatible with optic disk appearance or nerve fiber layer defect.

**Category 2**
When the visual field test is not reliable or available, the cup-to-disk ratio of the optic nerve head is 0.9 or more, or the rim width at the superior portion (11–1 o'clock) or the inferior portion (5–7 o'clock) is 0.05 or less of the disk diameter, or the difference of the vertical cup-to-disk ratio is 0.3 or more between both eyes.

**Glaucoma suspect**
When the cup-to-disk ratio of the optic nerve head is 0.7 or more but less than 0.9, or the rim width at the superior portion (11–1 o'clock) or the inferior portion (5–7 o'clock) is 0.1 or less but more than 0.05 of the disk diameter, or the difference of the vertical cup-to-disk ratio is 0.2 or more but less than 0.3 between both eyes, or the nerve fiber defect is found, and the visual field test is not reliable or available or does not show hemifield-based compatible defect, the eye is diagnosed with suspected glaucoma.

In addition, the ocular variables of IOP, OPP, and myopia were selected for study. Myopia was defined as myopic spherical equivalent (SE) $<-1.0$ diopter. If only one eye of the POAG patient was affected, the IOP, OPP, or SE was defined as the value of the glaucomatous eye. For control subjects and for bilateral POAG patients, the IOP was defined as the highest mean value in either eye. By contrast, OPP and SE were defined as the lowest value in either eye. The OPP was calculated as 2/3(mean arterial pressure) – IOP, where the mean arterial pressure = DBP + 1/3(SBP − DBP).

## Data analysis

All of the participants' private information was kept in the protection of the Department of Ophthalmology, Akita Graduate University Faculty of Medicine. The data were double-checked and analyzed using the Statistical Package for the Biosciences (v 9.53; SPBS, Nankodo Publisher, Tokyo, Japan) on a personal computer. Systemic and ophthalmologic data of all participants diagnosed with definitive POAG were analyzed in the present study.

The prevalence of glaucoma and 95% confidence interval (95% CI) were calculated for each age group. To compare prevalence of POAG in our population with that in the Tajimi Study population,[1] we determined the age-specific risk of POAG using a standardized mortality ratio (SMR). The SMR for POAG was the age-specific ratio between the observed number of POAG subjects in the study population and the expected number of POAG subjects calculated from the Tajimi study population. The age group of 30–39 years, including 42 normal persons and one POAG patient, was excluded from our analysis because the Tajimi Study did not include comparable data.

Continuous variables were recorded as means ± standard deviations. For the assessment of risk factors, mean values were compared by Student's $t$-test and frequencies by the chi-square test. A control group was selected in this study population, and consisted of 634 participants who did not have glaucoma or suspected glaucoma, and who had no other

ocular diseases including congenital disk anomalies that could affect the disk shape.[3] We estimated the multivariate-adjusted odds ratios (OR) and the 95% CI for each potential risk factor by using logistic regression analysis. Explanatory variables included in the analyses were age, gender, BMI, SBP, DBP, hypertension, blood pressure-lowering treatment, diabetic status, liver dysfunction, hypercholesterolemia, IOP, OPP, and myopia. Continuous data such as age, DBP, IOP, and OPP were analyzed as categorical variables using quartile values based on the study population. These risk factors were adjusted for age, gender, blood pressure-lowering treatment, IOP, and OPP. For all analyses, $P$-values were two-sided and were considered statistically significant when the values were less than 0.05.

## Results

The average age of all 710 participants (384 male, 326 female) was $54.7 \pm 9.8$ years. Of the 710 participants examined in the initial screening, 163 (23.0%) were referred for definitive examination, but 29 declined or were unable to participate. After definitive examination, 29 of the 134 participants were diagnosed with glaucoma, and 29 participants with suspected glaucoma. Previously undiagnosed glaucoma was present in 26 of the 29 subjects with glaucoma (89.6%). Of the 29 patients with glaucoma, 26 had POAG. The other three had primary angle-closure glaucoma and were not included in this study. The prevalence of all glaucoma in each age group was shown in Table 2. The prevalence of POAG was 3.7% (95% CI: 2.8%–5.5%), and 24 were diagnosed with Category 1 disease and two with Category 2 disease. In 96.2% of glaucoma patients, the IOP was 21 mmHg or less. There was no significant difference in the prevalence of POAG between the present study and the Tajimi Study based upon the SMR, 1.28 ($P > 0.05$; Table 3).

There were no statistical differences between non-POAG subjects and POAG patients in gender, BMI, SBP, history or presence of hypertension, blood pressure-lowering treatment, diabetic status, liver dysfunction, serum cholesterol,

**Table 2** Age-specific prevalence of all glaucoma

| Age groups (years) | Primary open-angle glaucoma patients/age population (%, 95% confidence interval) | | |
| --- | --- | --- | --- |
| | **Male** | **Female** | **All** |
| 30–39 | 1/22 (4.5%, 0.1–22.5) | 0/21 (0.0%, −) | 1/43 (2.3%, 0.1–12.3) |
| 40–49 | 0/112 (0.0%, −) | 3/104 (2.9%, 0.6–8.2) | 3/216 (1.4%, 0.3–4.0) |
| 50–59 | 5/140 (3.6%, 1.2–8.1) | 5/123 (4.1%, 1.3–9.2) | 10/263 (3.8%, 1.8–6.8) |
| 60–69 | 8/75 (10.7%, 4.7–19.9) | 3/58 (5.2%, 1.1–14.4) | 11/133 (8.3%, 4.2–14.3) |
| 70 and older | 2/35 (5.7%, 5.7–19.2) | 2/20 (10.0%, 1.2–31.7) | 4/55 (7.3%, 2.0–17.6) |
| All subjects | 16/384 (4.2%, 2.4–6.7) | 13/326 (4.0%, 2.1–6.7) | 29/710 (4.1%, 2.8–5.8) |

**Table 3** Expected and observed number of POAG and standardized mortality ratio (SMR) in relation to age

| Age (years) | Examined number | Prevalence of POAG in Tajimi | Expected number | Observed number | SMR | Statistical significance |
|---|---|---|---|---|---|---|
| 40–49 | 199 | 2.0% | 3.98 | 3 | 0.75 | NS |
| 50–59 | 242 | 2.7% | 6.53 | 8 | 1.23 | NS |
| 60–69 | 126 | 4.7% | 5.92 | 11 | 1.86 | NS |
| 70– | 54 | 7.6% | 4.10 | 4 | 0.98 | NS |
| All | 621 | 3.9% | 20.53 | 26 | 1.28 | NS |

**Note:** NS means there is no statistically significant difference in the prevalence of POAG between the present study and the Tajimi study.

and myopia (Table 4). The mean age of POAG patients, $58.8 \pm 10.6$ years, was higher than that of non-POAG subjects ($P = 0.008$). The IOP of POAG patients, $17.2 \pm 3.3$ mmHg, was higher than that of non-POAG subjects, ($P < 0.001$; Table 4), while the DBP and OPP, $61.9 \pm 9.5$ mmHg and $41.1 \pm 3.0$ mmHg respectively, were lower than in non-POAG subjects ($P = 0.025$ and 0.035, respectively).

Multivariate logistic regression analysis of possible confounders for POAG demonstrated that gender, BMI, hypertension, blood pressure-lowering treatment, diabetic status, liver dysfunction, hypercholesterolemia, and myopia were unrelated to risk (Table 5). By contrast, older age ($\geq$75th percentile, 60 years old), lower DBP ($\leq$25th percentile, 58 mmHg), higher IOP ($\geq$75th percentile, 19 mmHg), and lower OPP ($\leq$25th percentile, 34 mmHg) significantly improved the discrimination between POAG patients and controls (Table 6).

## Discussion

In our cross-sectional examination of Japanese subjects who participated in the community health screening, the prevalence of POAG was 3.7%. Among those with POAG, the rate of previously undiagnosed glaucoma was 89.6%. After adjusting for age, the prevalence of POAG was similar to the results of the Tajimi Study of Japanese subjects. In the assessment of risk factors between non-glaucoma participants and POAG patients, we showed that lower DBP and lower OPP were significant in addition to the established risk factors of age and IOP. These findings indicate a multifactorial etiology of POAG.

The finding that low DBP is a risk factor for POAG is in agreement with a recent review, which concluded that hypotension is a stronger POAG risk factor than hypertension.[20] Lower BP is associated with increased optic disk cupping and a thinner neuroretinal rim in persons without glaucoma,[21] thereby strengthening the possibility of a vascular link to glaucoma.[22] Lower ocular perfusion pressure in our study was also significantly related to POAG risk. Similar results were found in various other epidemiologic studies in which low perfusion pressures are a consistent finding.[6–12] As summarized in various reviews,[10,23,24] lower perfusion pressures at the optic disk would compromise

**Table 4** Differences in main characteristics between control and POAG

| | Control | POAG | *P* value |
|---|---|---|---|
| Systemic | | | |
| Age (years), mean $\pm$ SD | $53.4 \pm 9.9$ | $58.8 \pm 10.6$ | 0.008 |
| Gender (male) | 348 | 15 | 0.84 |
| Body mass index (kg/m$^2$) | $2.35 \pm 3.3$ | $23.6 \pm 3.2$ | 0.58 |
| Systolic blood pressure (mmHg) | $112.6 \pm 19.0$ | $115.0 \pm 17.9$ | 0.51 |
| Diastolic blood pressure (mmHg) | $68.2 \pm 12.9$ | $61.9 \pm 9.5$ | 0.025 |
| Hypertension | 125 | 5 | 0.98 |
| Blood pressure-lowering treatment | 120 | 5 | 0.99 |
| Diabetic status | 54 | 2 | 0.97 |
| Liver dysfunction | 94 | 4 | 0.99 |
| Cholesterol (mg/dL) | $211.1 \pm 33.2$ | $211.0 \pm 31.2$ | 0.90 |
| Ocular | | | |
| Intraocular pressure (mmHg) | $15.0 \pm 2.9$ | $17.2 \pm 3.3$ | $P < 0.001$ |
| Ocular perfusion pressure (mmHg) | $43.2 \pm 5.0$ | $41.1 \pm 3.0$ | 0.035 |
| Myopia | 326 | 11 | 0.96 |

**Abbreviations:** POAG, primary open-angle glaucoma; SD, standard deviation.

**Table 5** Adjusted odds ratios of possible confounders for POAG

| | Adjusted odds ratio* | 95% confidence interval |
|---|---|---|
| Gender | | |
| Male | 1.00 | Reference |
| Female | 1.69 | 0.76–3.75 |
| Body mass index | | |
| <25 | 1.00 | Reference |
| ≥25 | 1.73 | 0.76–3.99 |
| Hypertension | | |
| No | 1.00 | Reference |
| Yes | 1.07 | 0.41–2.78 |
| Blood pressure-lowering treatment | | |
| No | 1.00 | Reference |
| Yes | 9.06 | 0.10–14.8 |
| Diabetic status | | |
| No | 1.00 | Reference |
| Yes | 1.58 | 0.35–7.14 |
| Liver dysfunction | | |
| No | 1.00 | Reference |
| Yes | 1.01 | 0.30–3.82 |
| Hypercholesterolemia | | |
| Chr < 220 mg/dL | 1.00 | Reference |
| Chr ≥ 220 mg/dL | 1.13 | 0.51–2.55 |
| Myopia | | |
| No | 1.00 | Reference |
| Yes | 1.23 | 0.89–1.45 |

**Note:** *Based on multivariate logistic regression analysis adjusted for age, gender, diastolic blood pressure. intraocular pressure, and ocular perfusion pressure.

ocular blood flow and thus lead to glaucomatous damage. In this context, we also examined the effects of blood pressure-lowering treatment, but found no associations with POAG, supporting the conclusion that lower perfusion pressures are the important risk factor. The other demographic factors investigated in this study, gender, BMI, SBP, a history or presence of hypertension, diabetic status, liver dysfunction, serum cholesterol, and myopia, were not associated with POAG in our analyses. Our result concerning myopia is inconsistent with a previous report in Japanese.[25]

There are several limitations in the present analyses. First is the small sample size, which resulted in estimates of association with relatively broad confidence intervals. Second, this study was not a population-based survey because the subjects who participated may have been highly interested in glaucoma. Thus to a degree, they were self-selected to participate in the screening, and may not have been representative of the general population. This could have introduced a selection bias resulting in an overestimation of the prevalence of POAG. Third, we did not perform definitive examinations of participants whose eyes appeared normal in the initial screening examination. Therefore, some subjects with glaucoma may have been overlooked, resulting in an underestimation of the prevalence of POAG. In the present study, we excluded tilted disks from analysis to have precise diagnosis. However, there is a potential problem in excluding such eyes, as myopia is thought to be a risk factor for glaucoma: we could be underestimating the prevalence of glaucoma.[26] Finally, there were several factors not included in the present analysis but reported to be associated with the development of POAG, such as systemic medications,[9,27] other ocular diseases,[9] and computer use.[28] Family history of glaucoma is associated with the development of the condition;[29–32] however, we obtained only limited information regarding family histories of glaucoma.

Because of the irreversible nature of glaucoma, early disease detection through screening will likely provide a substantial benefit by reducing blindness. However, the value of glaucoma screening has been a topic of debate for many years. Prior evaluations of screening effectiveness have concluded that there is insufficient economic evidence to recommend screening for POAG.[33] Since screening is sensitive to the prevalence of glaucoma in the study population,[34] identifying and targeting high-risk patients should improve the program's cost-effectiveness. The present study has proposed potential risk factors for POAG. These include

**Table 6** Odds ratios of risk factors for POAG

| | Odds ratio[1] (95% confidence limit) | Adjusted odds ratio[2] (95% confidence limit) | Adjusted odds ratio[3] (95% confidence limit) |
|---|---|---|---|
| Age ≥ 60 years | 2.56 (1.22–5.41) | 3.49 (1.41–8.62) | 3.54 (1.42–8.81) |
| DBP ≤ 58 mmHg | 2.08 (1.21–5.45) | 2.11 (1.69–6.67) | 2.50 (1.11–10.05) |
| IOP ≥ 19 mmHg | 4.19 (1.91–9.16) | 4.12 (1.35–12.56) | 3.38 (1.02–11.18) |
| OPP ≤ 34 mmHg | 5.44 (1.11–8.26) | 5.78 (1.21–7.92) | 5.54 (1.12–6.18) |

**Notes:** [1]Based on Yates chi-square test; [2]based on multivariate logistic regression analysis adjusted for age, gender, diastolic blood pressure, intraocular pressure, and ocular perfusion pressure; [3]based on multivariate logistic regression analysis adjusted for age, gender, BMI, diastolic blood pressure, hypertension, hypercholesterolemia, intraocular pressure, and ocular perfusion pressure.
**Abbreviations:** DBP, diastolic blood pressure; IOP, intraocular pressure; OPP, ocular perfusion pressure.

older age, higher IOP, lower diastolic pressure, and lower ocular perfusion pressure. These risk factors may provide effective guidelines for targeting community glaucoma screening to the highest risk populations.

## Acknowledgment

## Disclosure

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