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Glaucoma

Prevalence of Glaucoma and Its Systemic Risk Factors in a General Japanese Population: The Hisayama Study

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Purpose: To estimate the prevalence of glaucoma and its risk factors in a Japanese community.

Methods: This study included 3405 Japanese community dwellers who were ≥40 years of age and enrolled in the Hisayama Study. This population-based, cross-sectional study was conducted from 2017 to 2018. A glaucoma screening test was performed using stereo fundus images and swept-source optical coherence tomography. Glaucoma was defined based on the International Society of Geographical and Epidemiological Ophthalmology criteria.

Results: The prevalence of glaucoma was 7.6% (95% confidence interval [CI], 6.7–8.6) overall. The prevalence of primary open-angle glaucoma (POAG) was 5.8% (95% CI, 5.0–6.6); that of primary angle-closure glaucoma (PACG) was 0.7% (95% CI, 0.5–1.1); and that of exfoliation glaucoma was 1.1% (95% CI, 0.7–1.4). In addition to aging, lower estimated glomerular filtration rate (eGFR) (odds ratio [OR] = 1.15; 95% CI, 1.02–1.33), higher intraocular pressure (OR = 1.06; 95% CI, 1.01–1.12), longer axial length (OR = 1.44; 95% CI, 1.31–1.59), and thinner central corneal thickness (CCT) (OR = 1.09; 95% CI, 1.04–1.15) were significant risk factors for POAG. Diabetes (OR = 2.81; 95% CI, 1.19–6.62) was a significant risk factor for PACG, and diabetes (OR = 2.15; 95% CI, 1.03–4.47) and thinner CCT (OR = 1.14; 95% CI, 1.02–1.28) were significant risk factors for exfoliation glaucoma.

Conclusions: The prevalence of glaucoma was approximately 8%, probably due to the increase in the Japanese aging population. Not only ocular factors but also lower eGFR for POAG and diabetes for PACG and exfoliation glaucoma were risk factors in a general Japanese population.

Translational Relevance: Systemic factors such as eGFR and diabetes must also be considered when implementing preventive measures against glaucoma.

Introduction

Glaucoma is the leading cause of blindness and vision loss worldwide and thus has a significant impact on quality of life.[1] Because the prevalence of glaucoma increases with age, there is a concern that the number of patients with glaucoma and/or its related risk factors will further increase as Japan becomes a super-aged society.[2]

In previous epidemiological studies, glaucoma has been diagnosed by the evaluation of characteristic structural and functional abnormalities of the optic nerve, based on the International Society of Geographical and Epidemiological Ophthalmology (ISGEO) criteria.[3] Glaucoma is known to be influenced not only by ocular factors but also by systemic factors, such as renal function[4] and diabetes mellitus.[5] Because glaucoma is a multifactorial disease, more comprehensive analysis is needed to prevent an increase in glaucoma incidence. Therefore, it is worthwhile to clarify the association between glaucoma subtypes and their possible risk factors, including ocular factors (i.e., intraocular pressure, axial length, and central corneal thickness) or comprehensive systemic factors, such as renal function and diabetes defined using a glucose tolerance test. Herein, we conducted a cross-sectional study to identify the risk factors for and prevalence of glaucoma subtypes in a cohort from southwest Japan that has previously been used for the comprehensive study of numerous systemic diseases.[6,7]

Methods

Study Population

The Hisayama Study is an ongoing, long-term cohort study on cardiovascular disease and its risk factors in Hisayama,[6,7] a town adjacent to the metropolitan area of the city of Fukuoka in southwest Japan. As a part of the overall study, a population-based epidemiologic ophthalmic survey among residents of the town has been underway since 1998.[8] From 2017 to 2018, a total of 3405 of the 4997 residents (68.1%) who were ≥40 years of age consented to participate and underwent an ophthalmic examination for the present study.

Measurement of Ophthalmic Indices

All of the ophthalmic examinations were undertaken by ophthalmologists trained in glaucoma diagnosis. The intraocular pressure (IOP) was measured three consecutive times with an ocular response analyzer (Reichert Corporation, Carrollton, TX)[9] or a Non-Contact Tonopachy NT-530P (Nidek Co., Ltd., Aichi, Japan). Both instruments were calibrated using a Goldmann applanation tonometer. Axial length measurements were performed with non-contact partial coherence laser interferometry (OA-2000 Optical Biometer; Tomey Corporation, Aichi, Japan). The central corneal thickness (CCT) was measured using an anterior-segment CCT measurement apparatus (CASIA2; Tomey). Angle width was evaluated according to the van Herick method.[10] When angle width was greater than van Herick grade 3, the pupil was dilated with 0.5% tropicamide and 0.5% phenylephrine hydrochloride, stereoscopic disc photographs (nonmyd WX; Kowa Company, Tokyo, Japan)[11] were obtained, and detailed slit-lamp biomicroscopic examinations and indirect ophthalmoscopy were carried out. A visual acuity test was performed using a chart of Landolt rings with refractive correction at a distance of 5 m. Digital color photographs of the fundus and optical coherence tomography (OCT) scans were obtained of the dilated pupils using Triton (Topcon) swept-source OCT.[12,13] When the participants were unable to come to the facilities, ophthalmologists visited them in their homes and performed the examinations using a hand-held slit lamp, an indirect ophthalmoscope, and a portable digital fundus camera system (VersaCam; Nidek).

Diagnostic Procedure for Glaucoma

Figure 1 shows the flow of participants through the study and the diagnostic process. Two examiners (KF and SN) independently evaluated the stereo fundus photographs, and two examiners (SH and EU) independently evaluated OCT to screen for nerve fiber layer defects.[14] The rim border was determined based on shadows, gradations of color, texture, and the curvature of the blood vessels,[15] and the vertical cup-to-disc ratio and rim width were evaluated using a Kowa nonmyd WX stereoscopic optic disc measurement system.[11] When at least one examiner noted any findings suggesting glaucomatous changes, the individuals were recruited for definitive examination.

Diagnostic Definitions for Glaucoma

Individuals with glaucoma were assigned to one of three categories according to the ISGEO criteria, which are shown in Supplementary Table S1.[3] A glaucomatous visual field defect was determined based on the criteria proposed by Anderson and Patella.[16] The hemifield was judged to be abnormal

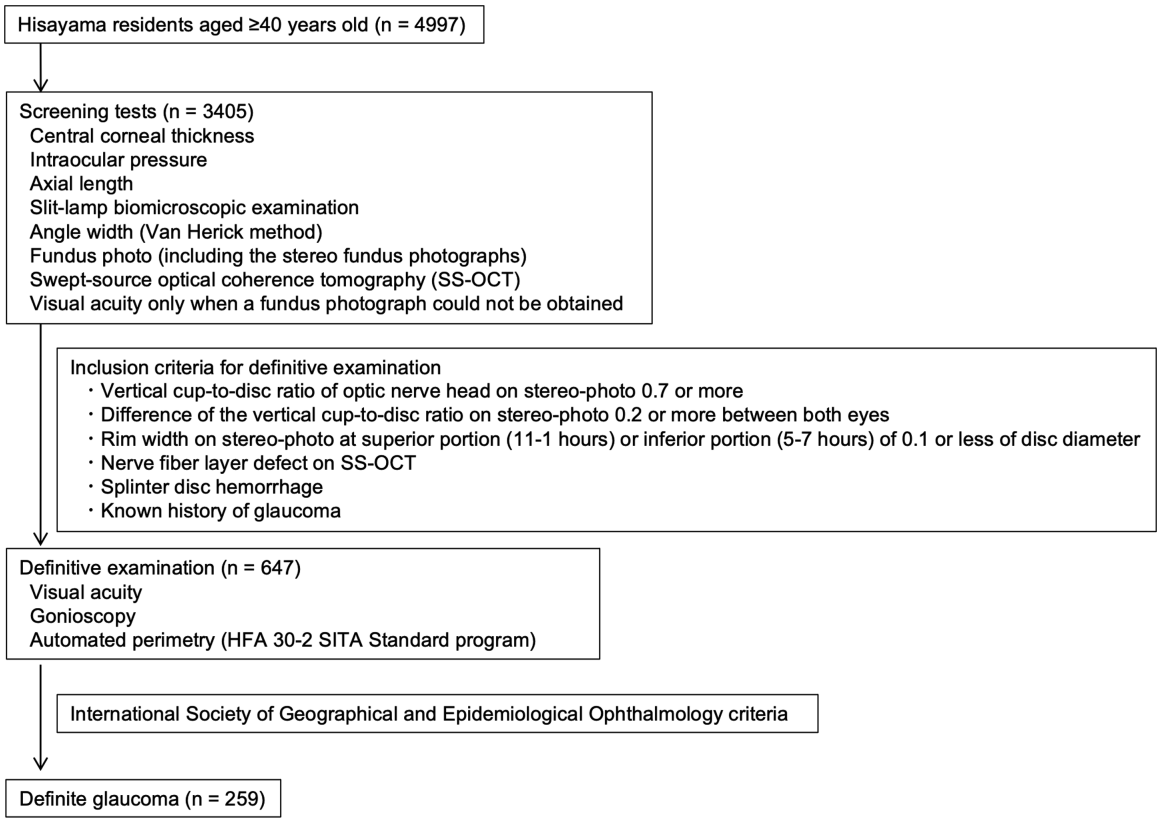

Figure 1. Flow of participants through the Hisayama Study.

when the pattern deviation probability plot showed a cluster of three or more non-edged contiguous points having sensitivity with a probability of less than 5% in the upper or lower hemifield and in one of these with a probability of less than 1%. The visual field test was repeated if the test reliability was not satisfactory (fixation loss, <33%; false-positive and false-negative results, <20%). Participants with definitive examinations were further examined by gonioscopy. The same glaucoma fellowship–trained ophthalmologist (KF) performed all gonioscopy using a Goldmann two-mirror lens under standard dark illumination. A narrow, vertical, 1-mm beam was offset vertically for superior and inferior quadrants and horizontally for nasal and temporal quadrants. Subtypes of glaucoma were defined according to the ISGEO criteria,[3] as shown in Supplemental Table S2. Exfoliation glaucoma (EXG) included participants with glaucoma and pseudoexfoliation. Pseudoexfoliation was diagnosed on slit-lamp biomicroscopy if whitish pseudoexfoliation material was present along the pupillary margin and/or the anterior lens capsule. Participants were classified as having pseudoexfoliation if any exfoliation material was present in either eye.

An occludable angle was defined as one in which the posterior trabecular meshwork was not visible during static gonioscopy in at least three quarters of the angle circumference in the primary position without manipulation or indentation.[3,17] In individuals after cataract surgery, both the findings of the operated eye (laser iridotomy, pseudoexfoliation, history of glaucoma surgery) and the findings of the fellow eye were considered as much as possible to rule out other subtypes of glaucoma.[18] Final identification, adjudication, and classification of glaucoma individuals were reviewed by one of the authors (TY) and two glaucoma fellowship–trained ophthalmologists (TK and TN).

Clinical Evaluation and Laboratory Measurements

Clinical evaluation and laboratory measurements were performed in the screening examination. Each individual's blood pressure was measured by automated sphygmomanometer three times after the individual had rested for ≥5 minutes in a 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 the current use of antihypertensive medication. Blood samples were collected from an antecubital vein after an overnight fast of ≥12 hours. Among 3084 participants for whom ophthalmic examinations and blood sample data were available, 2579 participants (83.6%) had a 75-g oral glucose tolerance test (OGTT) after fasting for at least 12 hours, and the remaining 505 participants underwent a single measurement of fasting or postprandial plasma glucose concentrations. Plasma glucose levels were measured by the hexokinase method. Diabetes was defined as a fasting plasma glucose level ≥ 7.0 mmol/L, a 2-hour 75-g oral glucose postload or casual glucose level ≥ 11.1 mmol/L, or current use of any anti-diabetes medication (oral hypoglycemic agents, injectable glucagon-like peptide analogs, or insulin). Serum total cholesterol levels were determined enzymatically. Each individual's body height and weight were measured in light clothing without shoes, and the body mass index (BMI; kg/m^2) was calculated. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease–Epidemiology Collaboration equation with a Japanese coefficient[19] of 0.813. Information on exercise during leisure time, smoking habits, and alcohol intake was obtained through the use of a standard questionnaire. The questionnaire was administered to each individual prior to initiation of this study and was checked by trained interviewers at the screening. Smoking habits and alcohol intake were classified as current habitual use or no current habitual use. Patients engaging in sports at least three times a week during their leisure time were defined as the regular exercise group.

Statistical Analysis

SAS 9.4 (SAS Institute, Cary, NC) was used to perform all statistical analyses. The age-standardized prevalence was adjusted for age by the direct method using the World Health Organization standard population in 1998 as a standard population. Differences in the mean values and frequencies were compared by *t*-test and the χ^2 test, respectively. The associations of risk factors with the presence of glaucoma were estimated by a logistic regression analysis. Note that, in this analysis, the ophthalmic data from the right eye were used for individuals in whom either the right eye or both eyes had glaucoma; if only the left eye had glaucoma, the ophthalmic data from the left eye were used. The risk factors for glaucoma were selected from the known and plausible risk factors for glaucoma (age, sex, hypertension, diabetes, serum total cholesterol, BMI, eGFR, smoking habits, alcohol intake, regular exercise, IOP, axial length, and CCT) by a logistic regression analysis with a forward selection, in which the variables for which $P < 0.05$ were allowed to remain in the relevant model. A two-tailed value of $P < 0.05$ was considered statistically significant in all analyses.

Ethical Considerations

This study was conducted with the approval of the Kyushu University Institutional Review Board for Clinical Research, and it was carried out in accordance with the tenets of the Declaration of Helsinki. Written informed consent to participate was obtained from all individuals.

Results

The mean values and frequencies of related factors categorized by the sex of the participants are summarized in Table 1. The mean ± SD age was 64.6 ± 13.9 years, and the proportion of men was 43.7% (1489 participants). The values for BMI, axial length, and CCT and the frequencies of hypertension, diabetes, current smoking, current drinking, and regular exercise were significantly higher for the men compared to the women. The mean values of age, serum total cholesterol, and eGFR were higher for the women compared to the men.

The number of individuals with glaucoma was 259. Of these, 134 had glaucoma in both eyes, 51 in only the right eye, and 74 in only the left eye. The ophthalmic data from the right eye were used for individuals with glaucoma in both eyes. Of these, 234 individuals were diagnosed with category 1 glaucoma and 25 with category 2 glaucoma. No participants had category 3 glaucoma. The crude prevalences of glaucoma were 7.6% (95% confidence interval [CI], 6.7%–8.6%) for all individuals, 8.0% (95% CI, 6.7%–9.5%) for men, and 7.3% (95% CI, 6.1%–8.5%) for women. The difference in prevalence between men and women was not significant. Glaucoma medications had been prescribed to 69 individuals (26.6%). The crude and age-standardized prevalence rates of glaucoma and glaucoma subtypes are shown in Supplemental Table S3. The crude prevalence of primary open-angle glaucoma (POAG) was 5.8% (95% CI, 5.0%–6.6%); that of primary angle-closure glaucoma (PACG) was 0.7% (95% CI, 0.5%–1.1%); that of EXG was 1.1% (95% CI, 0.7%–1.4%); and that of secondary glaucoma excluding EXG was 0.1% (95% CI, 0.01%–0.2%). The prevalence of POAG, PACG, and EXG increased significantly with age

Table 1. Characteristics of the Study Population

Variable	All ($N = 3405$)	Men ($n = 1489$)	Women ($n = 1916$)	P[a]
Age (y), mean ± SD	64.6 ± 13.9	63.9 ± 13.5	65.1 ± 14.2	0.01
Hypertension (%)	49.5	54.0	46.0	<0.001
Diabetes (%)	18.5	25.1	13.4	<0.001
Serum total cholesterol (mmol/L), mean ± SD	5.34 ± 0.96	5.11 ± 0.93	5.53 ± 0.95	<0.001
BMI (kg/m^2), mean ± SD	23.1 ± 3.7	23.6 ± 3.4	22.6 ± 3.8	<0.001
eGFR (mL/min/1.73 m^2), mean ± SD	70.1 ± 14.7	69.2 ± 14.9	70.9 ± 14.4	0.001
Current smoking (%)	15.3	25.9	7.2	<0.001
Current drinking (%)	50.2	70.1	34.7	<0.001
Regular exercise (%)	15.0	18.3	12.4	<0.001
IOP (mmHg),[b] mean ± SD	13.2 ± 3.2	13.1 ± 3.3	13.3 ± 3.1	0.06
Axial length (mm),[b] mean ± SD	23.9 ± 1.4	24.1 ± 1.4	23.6 ± 1.4	<0.001
CCT (μm),[b] mean ± SD	531.6 ± 33.8	534.7 ± 33.3	529.1 ± 34.1	<0.001

[a]Men versus women.

[b]Ophthalmic data gathered from the right eye were used for individuals in whom either the right eye or both eyes had glaucoma; if only the left eye had glaucoma, ophthalmic data from the left eye were used.

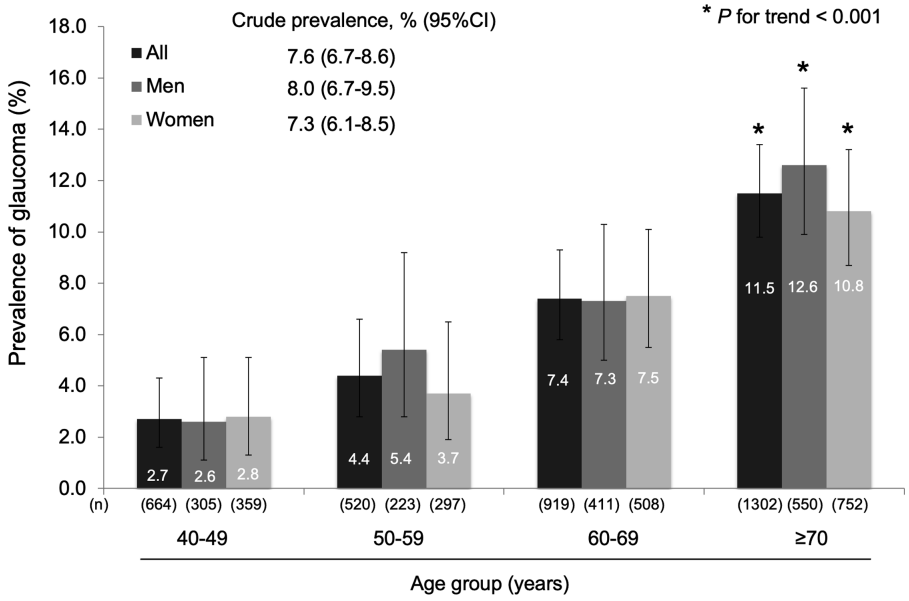

Figure 2. Age-specific prevalence of glaucoma. The crude prevalence of glaucoma increased significantly with age ($P < 0.001$ for trend).

($P < 0.001$, $P = 0.001$, and $P < 0.001$ for trend, respectively) (Supplemental Table S3). Developmental glaucoma was not found in the present study.

Figure 2 shows the crude prevalence of glaucoma in all individuals stratified by age. The crude prevalence of glaucoma increased significantly with age ($P < 0.001$ for trend). Figure 3 shows age-specific frequencies of glaucoma subtypes. The most common subtype of glaucoma in individuals overall was POAG. Supplemental Figure S1 shows the distributions of IOP, axial length, and CCT in right eyes. The mean IOP among the participants without glaucoma therapy in the study population was 13.2 mmHg; among those with glaucoma, it was 13.1 mmHg ($P = 0.65$). The mean axial length among the participants without glaucoma was 23.8 mm; among those with glaucoma, it was 24.3 mm ($P = 0.001$). The mean CCT was 532 mm in the participants without glaucoma and 524 mm in those with glaucoma ($P = 0.002$).

The results of age- and sex-adjusted and multivariable-adjusted logistic regression analyses of risk factors for POAG, PACG, and EXG are shown in Table 2 and Supplementary Table S4. Individuals with missing covariate data (321 individuals out

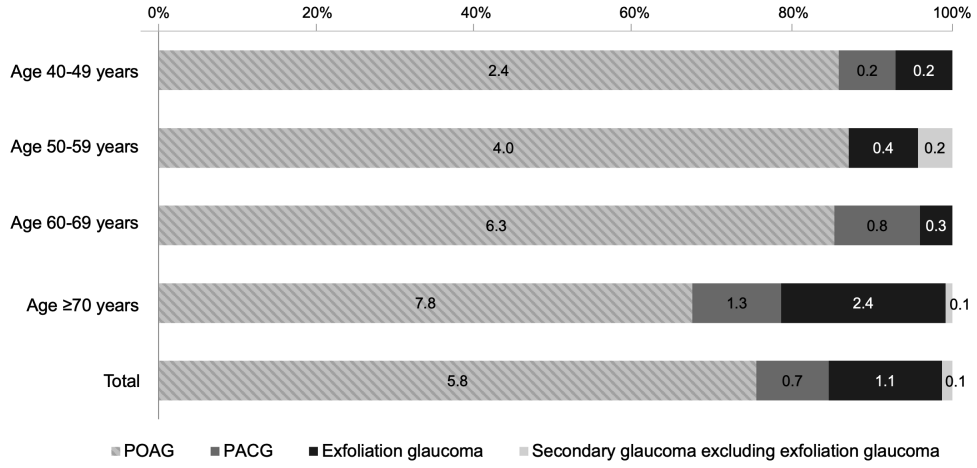

Figure 3. Age-specific frequencies of glaucoma subtypes. The most common subtype of glaucoma in individuals overall was POAG followed by EXG.

Table 2. Multivariable-Adjusted Odds Ratios of Risk Factors for Subtypes of Glaucoma

	POAG			PACG			Exfoliation Glaucoma		
Variable	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Age per 10-y increase	1.48	1.25–1.74	<0.001	1.71	1.16–2.54	0.01	2.99	2.04–4.37	<0.001
Women vs. men	—	—	—	3.08	0.98–9.73	0.05	—	—	—
Diabetes (yes vs. no)	—	—	—	2.74	1.16–6.47	0.02	2.15	1.03–4.47	0.04
eGFR per 10-mL/min/1.73 m^2 decrease	1.15	1.02–1.33	0.04	—	—	—	—	—	—
Current drinking (yes vs. no)	—	—	—	0.36	0.11–1.14	0.08	—	—	—
IOP per 1-mmHg increase	1.06	1.01–1.12	0.02	—	—	—	—	—	—
Axial length per 1-mm increase	1.44	1.31–1.59	<0.001	—	—	—	—	—	—
CCT per 10-µm decrease	1.09	1.04–1.15	0.001	—	—	—	1.14	1.02–1.28	0.03

Multivariate regression analysis was performed with a forward selection procedure.

of 3405) were excluded from the analysis. Among the individuals with missing covariate data, 10 were diagnosed as having glaucoma (four individuals with POAG, two with PACG, and four with EXG). The significant risk factors for POAG were age (per 10-year increase: odds ratio [OR] = 1.48; 95% CI, 1.25–1.74; $P < 0.001$), eGFR (per 10-mL/min/1.73 m^2 decrease: OR = 1.15; 95% CI, 1.02–1.33; $P = 0.04$), IOP (per 1-mmHg increase: OR = 1.06; 95% CI, 1.01–1.12; $P = 0.02$), axial length (per 1-mm increase: OR = 1.44; 95% CI, 1.31–1.59; $P < 0.001$), and CCT (per 10-µm decrease: OR = 1.09; 95% CI, 1.04–1.15; $P = 0.001$). Significant risk factors for PACG were age (per 10-year increase: OR = 1.71; 95% CI, 1.16–2.54; $P = 0.01$), female sex (OR = 3.08; 95% CI, 0.98–9.73; $P = 0.05$), and diabetes (OR = 2.74; 95% CI, 1.16–6.47; $P = 0.02$). Significant risk factors for EXG were age (per 10-year increase: OR = 2.99; 95% CI, 2.04–4.37; $P < 0.001$), diabetes (OR = 2.15; 95% CI, 1.03–4.47; $P = 0.04$), and CCT (per 10-µm decrease: OR = 1.14; 95% CI, 1.02–1.28; $P = 0.03$).

Discussion

We found that the overall prevalence of glaucoma in a general Japanese population 40 years of age or older was 7.6%; for the glaucoma subtypes, the overall prevalences were 5.8% for POAG, 0.7% for PACG, 1.1% for EXG, and 0.1% for secondary glaucoma. The prevalence of glaucoma increased significantly with advancing age. Additionally, we observed that the factors independently associated with risk for POAG were older age, longer axial length, thinner CCT, and lower eGFR; those for PACG were older age and diabetes; and those for EXG were older age,

diabetes, and thinner CCT. In addition to describing the recent prevalence of glaucoma and its subtypes, this study demonstrates the precise relationship between glaucoma and various systemic factors adjusted for the effect of other factors in a general Japanese population.

The prevalence of glaucoma has been estimated in other population-based studies.[2,20,21] The Tajimi Study, which was conducted from 2000 to 2001, reported that the prevalence of glaucoma was 5.0% in an inland city in central Japan,[2,20] which was lower than the prevalence in the present study. However, the difference in the prevalence of glaucoma between these two studies from Japan may be mainly attributable to a difference in the proportion of older individuals, because the mean age of the participants in the present study (64.6 years) was higher than that in the Tajimi Study (58.4 years). Aging is the one of the most common risk factors for glaucoma, and the association with increasing age found in the present study is similar to that found in other studies.[2,21,22] In fact, the age-specific prevalence of glaucoma was similar for the present study and the Tajimi Study, resulting in a similar age- and sex-adjusted prevalence for these two studies conducted in Japan of approximately 5.0% (6.0% in the Tajimi Study and 7.0% in the present study using the Japanese population in 2015).[23] Twenty-two subjects in whom we could not detect glaucomatous changes by stereo fundus photographs were newly diagnosed with glaucoma by OCT. This result suggested that using OCT examination may lead to an increase in the prevalence of glaucoma. On the other hand, a meta-analysis reported that the prevalence of glaucoma was 2.8% in individuals of European ancestry, 6.1% in those of African ancestry, and 2.8% in Asians mainly from China and India.[21] These findings suggest that the prevalence of glaucoma in Japan may be higher than that in Europe and other Asian countries, and the number of individuals with glaucoma will further increase in conjunction with the continued growth of the aging population in Japan.

Previous population-based studies have revealed that longer axial length, thinner CCT, and lower eGFR are risk factors for POAG,[4,22,24] in agreement with our present findings. With regard to the association between CCT and POAG, it has been well documented that CCT can affect the IOP value of tonometric readings.[25] However, in this multivariable analysis including IOP, thinner CCT was independently associated with POAG. CCT may be correlated with other ocular biomechanical and structural characteristics that can affect the integrity of the lamina cribrosa and contribute to disk damage independently of IOP. In addition, the significant association between eGFR and POAG may be specific to East Asians, considering the similarities in genetic profiles among these three ethnic groups (Chinese, Koreans, and Japanese).[26] A common pathogenic mechanism (i.e., renin–angiotensin system dysfunction) is considered to underlie both lower eGFR and POAG.[27,28] However, this hypothesis will require confirmation in future studies evaluating the risk of POAG.

In regard to the prevalence of PACG, the Tajimi Study[2] and the Kumejima Study[22] (a study conducted in southwest Japan from 2005 to 2006) reported PACG prevalences of 0.6% and 2.2%, respectively. The value in the present study was almost the same as that in the Tajimi Study but lower than that in the Kumejima Study, further suggesting the existence of regional differences in PACG prevalence in Japan. There have been no population-based studies demonstrating an association between diabetes diagnosed by OGTT and subtypes of glaucoma, as was found in the present study. Previous studies reported that individuals with diabetes have shallower anterior chambers and thicker lenses than those without diabetes.[29,30] Our results, together with previous reports, suggest that diabetes could be a risk factor for angle-closure glaucoma.

In a previous study, the prevalence of EXG ranged between 0% and 2.1%.[31] The age-standardized prevalence of EXG in our analysis was 0.5%, which was almost the same as the values in the Tajimi Study (0.1%) and the Kumejima Study (0.2%). It has also been reported that aging is a risk factor for EXG,[31] which would result in higher frequencies of EXG among older individuals. Because the risk of EXG increases with age and EXG is more progressive than POAG,[32] it is necessary to take EXG into account when assessing an older population. Notably, the present study reported a significant association between diabetes and EXG. The precise mechanisms underlying the association between diabetes defined using the OGTT and EXG are unknown. Pseudoexfoliation was reported to be associated with IOP fluctuation,[33] and the latter condition results in gliosis, neuroinflammation, and neurodegeneration.[34] Taken together, these results suggest that the additive IOP fluctuations induced by pseudoexfoliation and diabetes may be more likely to lead to EXG.

The strengths of the present study are its population-based design and its more detailed analysis of the relationship between systemic factors (i.e., renal function and diabetes defined using a glucose tolerance test) and glaucoma compared to other studies. Nevertheless, there is a potential limitation that should be noted. Because this is a cross-sectional study, the interpretation of the causal relationship between possible risk factors and glaucoma is limited. However, we believe that our finding of systemic factors that appear

to be associated with POAG, PACG, or EXG has clinical relevance, because glaucoma itself is unlikely to modify such systemic factors. Second, not all of the participants could be evaluated with stereo fundus photography and OCT; therefore, it is possible that we somewhat underestimated the prevalence of glaucoma. Taking this limitation into account, the association between risk factors and glaucoma might have been even stronger than suggested. Finally, in the multivariable analysis, we used a forward selection for covariate selection, because the number of glaucoma subtypes was limited; therefore, it is possible that undetected systemic factors associated with glaucoma exist. Further large-scale studies will be needed to elucidate this issue.

In conclusion, our findings indicate that the prevalence of glaucoma in Japan is higher than reported in other Japanese populations 16 to 20 years ago. Our results strengthen the existing evidence that glaucoma prevalence increases with age and that ocular factors and decreased kidney function are independent risk factors for POAG, whereas diabetes is an independent risk factor for PACG and EXG. At the same time, they suggest that systemic factors such as diabetes and renal function must also be considered when implementing preventive measures against glaucoma.

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