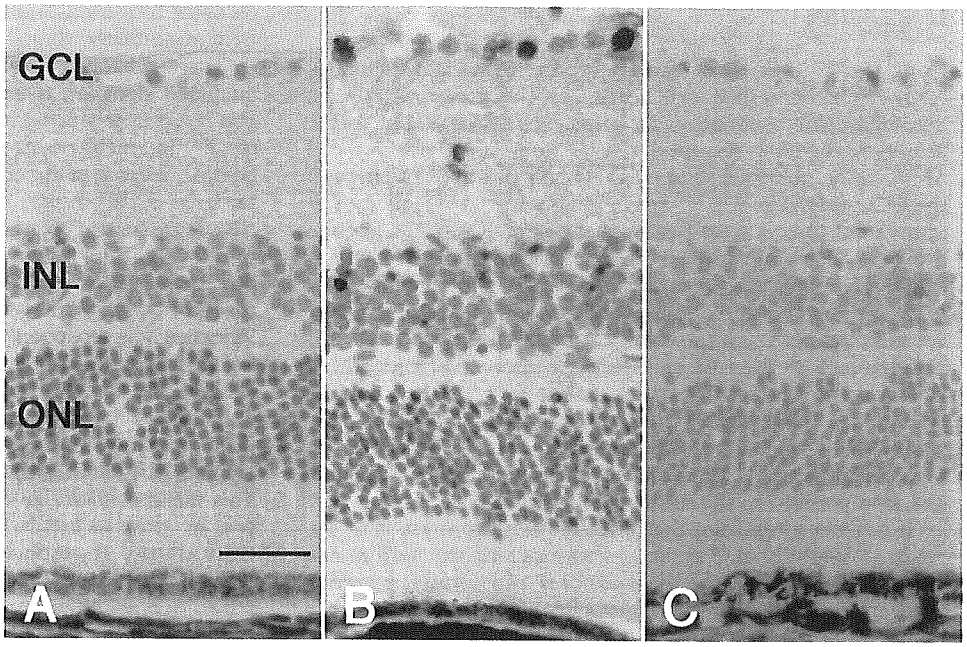

FIGURE 1. TUNEL staining of retinas at 12 hours after intravitreal administration of NMDA (30 nanomoles) or vehicle. (**A**) Vehicle in wild-type; (**B**) NMDA in wild-type; and (**C**) NMDA in tPA-deficient mice. TUNEL-positive cells appeared in the GCL and INL. Scale bar, 25 μm.

ded in paraffin. Sections 3 μm thick were cut along the vertical meridian through the optic nerve. To detect the retinal cells undergoing DNA fragmentation in the course of apoptosis, TUNEL staining was performed according to a method previously described.[12] The number of labeled cells in the ganglion cell layer (GCL), inner nuclear layer (INL), and outer nuclear layer (ONL) was counted in two central areas of the retina, approximately 250 μm long each, chosen from both sides of the optic nerve head.[13] Data were analyzed independently by two coauthors (MK, MN) in a blinded fashion. The number of TUNEL-positive cells per 250-μm length of the area in each retinal layer were averaged and plotted as the number of TUNEL-positive cells. The experimental results are expressed as the mean ± SD. Statistical analyses were performed by analysis of variance (ANOVA) with the Fisher protected least significant difference (Fisher's PLSD) test.

RESULTS

On the basis of preliminary experiments, we injected 30 nanomoles of NMDA intravitreally and dissected the eyes 12 hours later. To determine the association of apoptosis and the fibrinolytic system in retinal cell damage, we first compared NMDA-induced retinal damage in $tPA^{-/-}$ and wild-type mice. TUNEL-positive cells in both the GCL and INL in $tPA^{-/-}$ mice after intravitreal injection of NMDA were significantly fewer than in wild-type mice (Figs. 1, 2A). This result strongly indicates that endogenous tPA acts as a facilitator in NMDA-induced retinal cell damage.

To confirm the specificity of tPA, next we examined the contribution of another type of endogenous plasminogen activator, uPA. No significant difference in TUNEL-positive cells was observed between $uPA^{-/-}$ and wild-type mice in the GCL and INL after intravitreal injection of NMDA (Fig. 2B).

Endogenous tPA and uPA activity is negatively regulated by the endogenous inhibitory factor PAI-1. NMDA was injected intravitreally in $PAI\text{-}1^{-/-}$ mice to determine the role of endogenous PAI-1 in retinal damage. The number of TUNEL-positive cells in the GCL and INL after intravitreal injection of NMDA was significantly greater in $PAI^{-/-}$ mice than in wild-type mice (Fig. 2C).

tPA and uPA are serine proteases that convert plasminogen into plasmin, and α2 AP is an inhibitor of plasmin. To clarify whether plasmin is the key factor in the facilitative effect of tPA against the retinal cell damage induced by intravitreal injection of NMDA, we determined the contribution of endogenous α2 AP. After administration of NMDA, no significant difference was observed between $\alpha 2\ AP^{-/-}$ and wild-type mice (Fig. 2D).

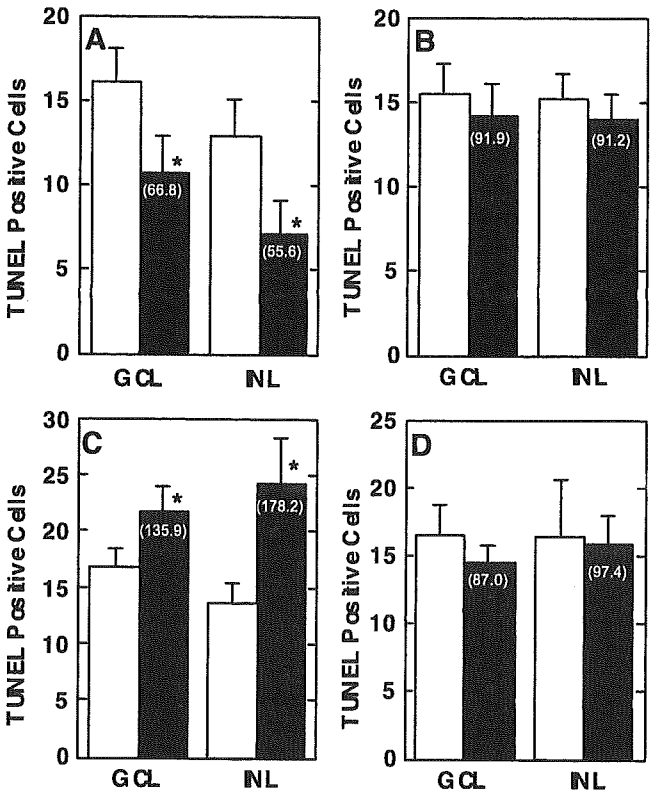

FIGURE 2. TUNEL-positive cells counted in the GCL and INL 12 hours after intravitreal injection of NMDA (30 nanomoles) in wild-type (□) and in (■) $tPA^{-/-}$ (**A**), $uPA^{-/-}$ (**B**), $PAI\text{-}1^{-/-}$ (**C**) or $\alpha 2\ AP^{-/-}$ (**D**) mice. Results are expressed as the mean ± SD (n = 12–18 eyes; six to nine mice). *Significant difference from the wild-type group at $P < 0.05$. Numbers in parenthesis indicate the percentage of TUNEL-positive cells versus each strain of wild-type mice.

Discussion

Using $tPA^{-/-}$ mice we recently reported that tPA facilitates NMDA-induced retinal cell death.[9] In the present study, to investigate the association of retinal cell damage and the fibrinolytic system, we used $tPA^{-/-}$, $uPA^{-/-}$, $PAI\text{-}1^{-/-}$, $\alpha 2AP^{-/-}$ mice, and their wild types. TUNEL-positive cells in both the GCL and INL in $tPA^{-/-}$ mice, but not in $uPA^{-/-}$ mice, after intravitreal injection of NMDA were significantly fewer than those in the wild type. Because endogenous tPA activity is negatively regulated by the endogenous inhibitory factor PAI-1, to determine the role of endogenous PAI-1 in retinal damage, we injected NMDA intravitreally into $PAI\text{-}1^{-/-}$ mice. TUNEL-positive cells in the GCL and INL after intravitreal injection of NMDA were significantly greater in $PAI^{-/-}$ mice than in wild-type mice. These results strongly suggest that tPA acts as a facilitator in NMDA-induced retinal cell damage, and that its mechanism may not be associated with cleavage of plasminogen into plasmin in the fibrinolytic cascade.

It has been reported that tPA and uPA are present in the retina. Tripathi et al.[14] examined various structures of human and monkey eyes for the presence of tPA by using the peroxidase-antiperoxidase immunohistochemical technique with a monoclonal antibody specific for human tPA. As a result, the anterior layers of the retina were weakly stained. In many of the tissues examined, uPA appeared to coexist with tPA. Tripathi et al.[15] investigated the presence of uPA in various structures of the human eye by using an immunohistochemical technique. A moderately intense to intermediate reaction product was seen in the anterior layers of the retina, a weak reaction product appeared in the posterior layers of the retina, and the retinal pigment epithelium contained both tPA and uPA. Therefore, the defect of PAI-1 would enhance endogenous tPA activity in the inner retina and lead to retinal cell death.

tPA is synthesized in basal conditions and is stored in vesicles.[16-19] However, in hippocampal CA1 neurons, tPA is undetectable in basal conditions, but is transiently induced after excitotoxic injury,[20] suggesting that induced tPA facilitates NMDA-induced CA1 damage. Although the precise role of constitutive or induced tPA in excitotoxic injury has not yet been determined, our results in tPA-deficient mice support the hypothesis that endogenous tPA is an essential factor in NMDA-mediated neuronal degeneration.

Our preliminary results showed that intravitreal injection of NMDA induces a dose-dependent loss of inner retinal elements, and there was a time-related appearance of TUNEL-positive nuclei in the inner retina. Lam et al.[21] showed intense labeling of nuclei between 12 and 24 hours after injection of NMDA. In the inner retina, retinal ganglion cells are particularly affected by extracellular glutamate, but a small percentage of cells in the INL are also stimulated. Although several different cell types in the INL express NMDA receptor subunits, only amacrine cells appear to express the same subunits as those detected in retinal ganglion cells. Amacrine cells may be adversely affected by NMDA.[22,23] The neuronal damage by NMDA is caused by calcium entry through the NMDA receptor, and elevation of intracellular calcium concentrations activate calcium-dependent protease, leading to neuronal death.[24,25]

tPA promotes NMDA-induced neuronal degeneration in brain hippocampal CA1 neurons.[26] Together with our present results, we can say that endogenous tPA is a common and important factor in NMDA-mediated neuronal degeneration. However, although it has been reported that tPA promotes not only NMDA-, but also transient ischemia-induced neuronal degeneration in the brain,[3] $tPA^{-/-}$ mice showed resistance to NMDA- but not transient ischemia-induced neuronal damage in the retina.[9] We therefore speculate that in addition to NMDA receptor activation, another mechanism is involved in transient ischemia-induced retinal damage.

The mechanism by which tPA modulates NMDA-receptor-mediated signaling is unknown, but Nicole et al.[27] reported that tPA potentiates signaling mediated by glutamatergic receptors by interacting with and cleaving the NR1 subunit of the NMDA receptor in the cerebral cortical neuron cultures. At the same time, they report that this interaction between tPA and NR1 is prevented by pretreatment with recombinant PAI-1, a protein that blocks the tPA catalytic site.[28] It has been suggested that tPA interacts with the NR1 subunit of the NMDA receptor through its catalytic site.[27] However, Matys and Strickland[29] questioned the data of Nicole et al.,[27] by suggesting that the anti-NR1 antibody used in their experiments was not specific for NR1 and may cross-react with plasminogen. They additionally indicated that Nicole et al.[27] used cultures maintained in serum-supplemented medium to coimmunoprecipitate and identify the NR1 subunit as a substrate for tPA. This method could have led to misidentification of plasminogen or plasmin bands as the NR1 subunit in its native or cleaved form. In response, Nicole et al. stated that the excitotoxic injury and cleavage experiments were all conducted in serum-free solutions. A casein gel zymography assay did not detect the presence of active plasmin, thereby excluding a possible contamination of their samples. Our results show that tPA increased NMDA-induced retinal cell damage, not associated with another function of tPA, cleavage of plasminogen into plasmin. Our data are consistent with the results of Nicole et al., but whether this effect is due to cleavage of the NR1 subunit by tPA is a subject of future studies.

In summary, tPA increased NMDA-induced retinal cell damage, and its mechanism is probably not associated with cleavage of plasminogen into plasmin in the fibrinolytic cascade. Retinal ganglion cell death is a common feature of many ophthalmic disorders, such as glaucoma and central artery or vein occlusion. Although the mechanism underlying retinal cell death in these diseases is not well understood, glaucoma in humans and monkeys is associated with a significant elevation in vitreal glutamate concentration.[7] Therefore, it is reasonable to hypothesize that retinal damage in ophthalmic diseases involves ischemia-reperfusion injury and the action of glutamate as an excitotoxin. Our study has provided key information on the mechanisms underlying retinal cell death and provides a basis for further investigation to identify fully all the mechanisms involved and novel therapeutic avenues for the treatment of various ophthalmic disorders.

Acknowledgments

The authors thank Kyoko Takahashi for her technical assistance.

References

1. Sappino AP, Madani R, Huarte J, et al. Extracellular proteolysis in the adult murine brain. *J Clin Invest.* 1993;92:679-685.
2. Tsirka SE, Gualandris A, Amaral DG, et al. Excitotoxin-induced neuronal degeneration and seizure are mediated by tissue plasminogen activator. *Nature.* 1995;377:340-344.
3. Wang YF, Tsirka SE, Strickland S, et al. Tissue plasminogen activator (tPA) increases neuronal damage after focal cerebral ischemia in wild-type and tPA-deficient mice. *Nat Med.* 1998;4:228-231.
4. Choi DW. Glutamate neurotoxicity and diseases of the nervous system. *Neuron.* 1988;1:623-634.
5. Meldrum B, Garthwaite J. Excitatory amino acid neurotoxicity and neurodegenerative disease. *Trends Pharmacol Sci.* 1990;11:379-387.
6. Tsirka SE, Rogove AD, Strickland S. Neuronal cell death and tPA. *Nature.* 1996;384:123-124.

7. Dreyer EB, Zurakowski D, Schumer RA, et al. Elevated glutamate in the vitreous body of humans and monkeys with glaucoma. *Arch Ophthalmol.* 1996;114:299-305.
8. Louzada-Junior P, Dias JJ, Santos WF, et al. Glutamate release in experimental ischaemia of the retina: an approach using microdialysis. *J Neurochem.* 1992;59:358-363.
9. Kumada M, Niwa M, Wang X, et al. Endogenous tissue type plasminogen activator facilitates NMDA-induced retinal damage. *Toxicol Appl Pharmacol.* 2004;200:48-53.
10. Collen D, Lijnen HR. Basic and clinical aspects of fibrinolysis and thrombolysis. *Blood.* 1991;78:3114-3124.
11. Carmeliet P, Schoonjans L, Kieckens L, et al. Physiological consequences of loss of plasminogen activator gene function in mice. *Nature.* 1994;368:419-424.
12. Hara A, Niwa M, Iwai T, et al. Neuronal apoptosis studied by a sequential TUNEL technique: a method for tract-tracing. *Brain Res Brain Res Protoc.* 1999;4:140-146.
13. Daugeliene L, Niwa M, Hara A, et al. Transient ischemic injury in the rat retina caused by thrombotic occlusion-thrombolytic reperfusion. *Invest Ophthalmol Vis Sci.* 2000;41:2743-2747.
14. Tripathi BJ, Geanon JD, Tripathi RC. Distribution of tissue plasminogen activator in human and monkey eyes: an immunohistochemical study. *Ophthalmology.* 1987;94:1434-1438.
15. Tripathi RC, Tripathi BJ, Park JK. Localization of urokinase-type plasminogen activator in human eyes: an immunocytochemical study. *Exp Eye Res.* 1990;51:545-552.
16. Baranes D, López-García JC, et al. Reconstitution of the hippocampal mossy fiber and associational-commissural pathways in a novel dissociated cell culture system. *Proc Natl Acad Sci USA.* 1996;93:4706-4711.
17. Gualandris A, Jones TE, Strickland S, et al. Membrane depolarization induces calcium-dependent secretion of tissue plasminogen activator. *J Neurosci.* 1996;16:2220-2225.
18. Parmer RJ, Mahata M, Mahata S, et al. Tissue plasminogen activator (t-PA) is targeted to the regulated secretory pathway: catecholamine storage vesicles as a reservoir for the rapid release of t-PA. *J Biol Chem.* 1997;272:1976-1982.
19. Lochner JE, Kingma M, Kuhn S, et al. Real-time imaging of the axonal transport of granules containing a tissue plasminogen activator/green fluorescent protein hybrid. *Mol Biol Cell.* 1998;9:2463-2476.
20. Salles FJ, Strickland S. Localization and regulation of the tissue plasminogen activator-plasmin system in the hippocampus. *J Neurosci.* 2002;22:2125-2234.
21. Lam TT, Abler AS, Kwong JM, Tso MO. *N*-methy-D-aspartate (NMDA)-induced apoptosis in rat retina. *Invest Ophthalmol Vis Sci.* 1999;40:2391-2397.
22. Li Y, Schlamp CL, Nickells RW. Experimental induction of retinal ganglion cell death in adult mice. *Invest Ophthalmol Vis Sci.* 1999;40:1004-1008.
23. Siliprandi R, Canella R, Carmignoto G, et al. N-methyl-D-aspartate induced neurotoxicity in the adult rat retina. *Vis Neurosci.* 1992;8:567-573.
24. Hahn JS, Aizenman E, Lipton SA. Central mammalian neurons normally resistant to glutamate toxicity are made sensitive by elevated extracellular Ca2+: toxicity is blocked by the N-methyl-D-aspartate antagonist MK-801. *Proc Natl Acad Sci USA.* 1988;85:6556-6560.
25. Ferreira IL, Duarte CB, Carvalho AP. Ca2+ influx through glutamate receptor-associated channels in retina Ca2+ cells correlates with neuronal cell death. *Eur J Pharmacol.* 1996;302:153-162.
26. Tsirka SE, Rogove AD, Strickland S. Neuronal cell death and tPA. *Nature.* 1996;384:123-124.
27. Nicole O, Docagne F, Ali C, et al. The proteolytic activity of tissue-plasminogen activator enhances NMDA receptor-mediated signaling. *Nat Med.* 2001;7:59-64.
28. Gilis A, Declerck JP. Proteinase specificity and functional diversity in point mutants of plasminogen activator inhibitor 1. *J Biol Chem.* 1997;272:12662-12666.
29. Matys T, Strickland S. Tissue plasminogen activator and NMDA receptor cleavage. *Nat Med.* 2003;9:371-373.

The Tajimi Study Report 2

Prevalence of Primary Angle Closure and Secondary Glaucoma in a Japanese Population

Tetsuya Yamamoto, MD, PhD,[1] Aiko Iwase, MD, PhD,[2] Makoto Araie, MD, PhD,[3] Yasuyuki Suzuki, MD, PhD,[4] Haruki Abe, MD, PhD,[5] Shiroaki Shirato, MD, PhD,[6] Yasuaki Kuwayama, MD, PhD,[7] Hiromu K. Mishima, MD, PhD,[8] Hiroyuki Shimizu, MD, PhD,[9] Goji Tomita, MD, PhD,[3] Yoichi Inoue, MD, PhD,[10] Yoshiaki Kitazawa, MD, PhD,[11] Tajimi Study Group, Japan Glaucoma Society

Purpose: To determine the prevalence of primary angle-closure glaucoma (PACG), secondary glaucoma (SG), and all glaucoma in a Japanese population as a part of the Tajimi Study.

Design: Population-based epidemiological survey.

Participants: A random sample of residents 40 years or older from Tajimi, Japan.

Intervention: Each subject underwent a screening program comprising an interview and an ophthalmic examination, including Goldmann applanation tonometry, slit-lamp examination, a van Herick test, fundus photography, and a screening visual field (VF) test using frequency-doubling technology. If glaucoma was suspected, the subject was referred for a definitive examination that included slit-lamp examination, gonioscopy, intraocular pressure measurement, a VF test, and optic disc and fundus examination. A diagnosis of PACG or SG was made based on slit-lamp examination, gonioscopy, optic disc appearance, and perimetric results.

Main Outcome Measures: Prevalences of PACG, SG, and all cases of glaucoma.

Results: Of 3870 eligible people, 3021 (78.1%) participated in the study. Estimated prevalences of PACG and SG in those over 40 years were 0.6% (95% confidence interval [CI], 0.4%–0.9%) and 0.5% (95% CI, 0.2%–0.7%), respectively. Prevalences of all glaucoma and glaucoma/suspected glaucoma were estimated to be 5.0% (95% CI, 4.2%–5.8%) and 7.5% (95% CI, 6.5%–8.4%), respectively.

Conclusions: Prevalences were 0.6%, 0.5%, and 5.0%, respectively, for PACG, SG, and all glaucoma in subjects over 40 years from Tajimi, Japan. *Ophthalmology 2005;112:1661–1669 © 2005 by the American Academy of Ophthalmology.*

Glaucoma is one of the most common causes of visual loss, and 22.5 million are estimated to suffer from glaucoma worldwide.[1,2] Primary angle-closure glaucoma (PACG) and primary angle closure (PAC) are more common in East Asian countries than in Western countries, and the former often results in bilateral blindness. Foster and Johnson[3] estimated that in China PACG accounted for 1.6 million cases of blindness, whereas primary open-angle glaucoma (POAG) accounted for 0.16 million cases. The prevalence of glaucoma depends on many factors, including ethnicity,

Originally received: October 13, 2004.
Accepted: May 18, 2005. Manuscript no. 2004-183.

[1] Department of Ophthalmology, Gifu University Graduate School of Medicine, Gifu, Japan.

[2] Department of Ophthalmology, Tajimi Municipal Hospital, Tajimi, Japan.

[3] Department of Ophthalmology, University of Tokyo Graduate School of Medicine, Tokyo, Japan.

[4] Department of Ophthalmology, Ichihara Hospital, Teikyo University School of Medicine, Ichihara, Japan.

[5] Department of Ophthalmology, Niigata University Graduate School of Medicine, Niigata, Japan.

[6] Department of Ophthalmology, Hachioji Medical Center, Tokyo Medical University, Hachioji, Japan.

[7] Department of Ophthalmology, Osaka Kosei-Nenkin Hospital, Osaka, Japan.

[8] Department of Ophthalmology, Hiroshima University Graduate School of Biomedical Sciences, Hiroshima, Japan.

[9] Department of Epidemiology and Preventive Medicine, Gifu University Graduate School of Medicine, Gifu, Japan.

[10] Olympia Eye Hospital, Tokyo, Japan.

[11] Akasaka Kitazawa Eye Clinic, Tokyo, Japan.

Presented in part as a poster at: American Academy of Ophthalmology annual meeting, November, 2003; Anaheim, California.

Financial support: Japan National Society for the Prevention of Blindness, Tokyo, Japan, and Japan Ophthalmologists Association, Tokyo, Japan.

No author has any proprietary interest in any products described in the article.

Correspondence to Tetsuya Yamamoto, MD, PhD, Department of Ophthalmology, Gifu University Graduate School of Medicine, 1-1 Yanagido, Gifu-shi, 501-1194, Japan. E-mail: mmc-gif@umin.ac.jp.

Reprint requests to The Tajimi Study Group, Japan Glaucoma Society, #501 Asai Building, 7-2-4, Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan.

ISSN 0161-6420/05/$–see front matter
doi:10.1016/j.ophtha.2005.05.012

age, gender, and geographic region. Further, differences in diagnostic instruments and methodologies for detecting the disease can markedly influence epidemiological findings. The prevalence of PACG was reported to be 1.4% in Mongolia,[4] 1.0% in Singapore,[5] and 0.5% to 1.08% in India,[6,7] whereas in Caucasians it ranged from 0.1% to 0.97%.[8–10] Primary angle-closure glaucoma develops in an age-dependent manner[11–15] and is more prevalent in women.[14–20] With the dark irides commonly seen in Asians, so-called creeping angle closure is thought to be the most common type of angle closure.[21–23] The majority of PAC is chronic and asymptomatic. For this reason, it is important to detect the disease early in its course.

Secondary glaucoma (SG) results from numerous ocular or systemic disorders or conditions, which may include uveitis, diabetic retinopathy, central retinal vein occlusion, and others. Clinically, SG often shows a poor response to ocular hypotensive agents or filtering surgery, especially in its late stages. Thus, like PACG, early detection is important in many types of SG to maximize the chance of a therapeutic response.

We recently reported that the prevalence of POAG, including normal-tension glaucoma, in the city of Tajimi, Japan was 3.9%,[24] which was about 50% higher than that previously estimated.[25] In this second report of the Tajimi Study, we focus on the age- and gender-specific prevalence of glaucomas other than POAG in the same population. In addition, we report the prevalence of all glaucoma.

Subjects and Methods

The subjects of the present study were identical to those in the first report of the Tajimi Study, which dealt with the prevalence of POAG in this population.[24] Thus, the fundamental methodology is identical to that reported previously, and is briefly summarized below.

Population Sampling

We screened the entire ≥40-year-old population of Tajimi City in central Japan. This epidemiological study was designed as a part of the Eye Health Care Project in Tajimi, and was conducted between September 2000 and October 2001. The investigation followed the tenets of the World Medical Association's Declaration of Helsinki and the municipal law of Tajimi City for protecting private information, and the study protocol was approved by the ethics committee of Tajimi City. Informed consent was obtained in written form from all the participants.

Of the 54 165 inhabitants 40 years or older in Tajimi City as of August 1, 2000, 4000 were selected randomly without stratification and were encouraged to participate in the epidemiological study. Although not stratified, the selected individuals were distributed evenly among all age groups.

Screening Examination

The screening examinations included not only ophthalmic examinations but also measurement of height, weight, and blood pressure. All examinations were performed by ophthalmologists trained in the diagnosis of glaucoma. Refractive status was measured using an autorefractometer (KP-8100PA, Topcon, Tokyo, Japan), and visual acuity (VA) was measured using a chart of Landolt rings at a distance of 5 m with refractive correction using the data obtained with an autorefractometer to start with. Central corneal thickness was measured using a specular-type pachymeter (SP-2000P, Topcon). Angle width was evaluated according to the van Herick method. Intraocular pressure (IOP) was measured 3 times by Goldmann applanation tonometry under topical anesthesia, and the median value was adopted. Digital color photographs of the fundus were taken with the pupil undilated using the IMAGEnet digital fundus camera system (NW6S, Topcon) with angles of 30° and 45°. The visual field (VF) was evaluated using a frequency-doubling technology (FDT) screener (Humphrey Instruments, San Leandro, CA) with the C-20-1 screening test. When participants were unable to come to the facilities, the doctors visited them at their homes and performed the examinations using a handheld slit lamp, direct and indirect ophthalmoscopes, and a Perkins applanation tonometer in the majority of the cases or a Tonopen XL (Bio-Rad Laboratories, Inc., Hercules, CA) in the remaining cases where Perkins tonometry could not be performed, and gonioscopy when necessary. As for the fundus examination, 3 examiners (the Photograph Screening Committee) independently evaluated the color fundus photographs for any abnormal findings including a glaucomatous optic disc appearance and nerve fiber layer defects. The rim border was determined based on shadows, gradations of color, texture, and the course of the blood vessels, and the vertical cup-to-disc (C/D) ratio and rim width were evaluated by units of 0.05 using a ruler. When at least 1 examiner noted any findings suggesting the presence of abnormality including glaucomatous changes, the subjects were recruited for the definitive examination.

Definitive Examination

Subjects were referred for definitive examination as having suspected glaucoma or other ocular diseases when their screening findings met one or more of the following criteria: corrected VA <

Table 1. Age-Specific Prevalence of Primary Angle-

Age Groups (yrs)	PACG (Percentage, 95% CI)		
	Male	*Female*	*All*
40–49	0/338 (0.0, 0.0–0.0)	0/445 (0.0, 0.0–0.0)	0/783 (0.0, 0.0–0.0)
50–59	0/427 (0.0, 0.0–0.0)	2/532 (0.4, 0.0–0.90)	2/959 (0.2, 0.0–0.50)
60–69	1/324 (0.3, 0.0–0.92)	5/360 (1.4, 0.18–2.60)	6/684 (0.9, 0.18–1.58)
70–79	3/190 (1.6, 0.0–3.35)	3/238 (1.3, 0.0–2.68)	6/428 (1.4, 0.29–2.51)
≥80	1/55 (1.8, 0.0–5.35)	4/112 (3.6, 0.13–7.01)	5/167 (3.0, 0.41–5.57)
All subjects	5/1334 (0.3, 0.01–0.67)	14/1687 (0.9, 0.45–1.31)	19/3021 (0.6, 0.35–0.91)

CI = confidence interval.

20/30; IOP > 19 mmHg (to refer all subjects whose IOP was statistically outside the normal limits); vertical C/D ratio of optic nerve head ≥ 0.6; difference of the vertical C/D ratio ≥ 0.2 between both eyes; rim width at superior portion (from the 11-o'clock position to the 1-o'clock position) or inferior portion (from the 5-o'clock position to the 7-o'clock position) ≤ 0.2 of the disc diameter; nerve fiber layer defect or splinter disc hemorrhage; any abnormal findings in the slit-lamp examination or fundus photographs, including low-quality fundus photographs; angle width ≤ grade 2 (van Herick method[26]); or at least one abnormal test point in the FDT VF test.

The definitive examination included slit-lamp examination, applanation tonometry, gonioscopy, and optic nerve head evaluation in a dark room with a Goldmann 2-mirror lens (Haag-Streit, Koeniz, Switzerland) and VF testing with the Humphrey Field Analyzer Central 30-2 Swedish Interactive Thresholding Algorithm Standard program (Humphrey Instruments). When the bottom of the angle was invisible, the part was observed with indentation to the opposite part of the angle using the 2-mirror lens. Unless the gonioscopy revealed a narrow angle of grade 2 or less by Shaffer's classification, the pupil was dilated to enable the taking of stereoscopic disc photographs (3-DX NM, Nidek, Gamagori, Japan) and the observation of the ocular fundus in detail. When the subject eye had a narrow angle, these examinations were carried out with the pupils undilated. Slit lamp examination, applanation tonometry, gonioscopy, and optic nerve head evaluation were carried out by glaucoma specialists who were voluntary council members of the Japan Glaucoma Society.

Evaluation of the Optic Disc, Nerve Fiber Layer Defect, and Visual Field

The details of the methods used here are described elsewhere[24] and are briefly summarized below.

Four glaucoma specialists (Photograph Reading Committee), to whom other information on the eyes was not revealed, evaluated the fundus photographs, including the stereoscopic photographs, of all the participants in a definitive examination. The vertical C/D ratio and rim width were again measured on the disc photographs by a glaucoma specialist (AI) with reference to the stereoscopic photographs. Each photograph was evaluated independently by 3 other examiners to confirm the measurements and to detect any nerve fiber layer defect, which was considered to be suggestive of glaucoma when its width at the disc edge was larger than a major retinal vessel, diverging in an arcuate or wedge shape. When the assessments by the examiners were not consistent, consensus was obtained by discussion while referring to the fundus color photographs and stereophotographs.

The results of the Humphrey Field Analyzer 30-2 Swedish Interactive Thresholding Algorithm Standard program were examined by 2 glaucoma specialists (the Visual Field Reading Committee), to whom other information on the eye in question was not revealed. Of all the VF data collected in the definitive examination (1799 eyes of 967 subjects), we excluded from evaluation only those apparently unreliable (fixation loss > 50%, false positive and false negative > 50%). Abnormal VF data were defined as the presence of at least one abnormal hemifield, which was determined based on the criteria proposed by Anderson and Patella.[27] The hemifield was judged to be abnormal when the pattern deviation probability plot showed a cluster of ≥3 non-edge contiguous points having sensitivity with a probability of <5% in the upper or lower hemifield and in one of these with a probability of <1%.

Diagnosis of Glaucomas

The final identification of glaucomas was based on clinical records obtained through all the examinations, by a panel of 6 glaucoma specialists. The presence of glaucoma was diagnosed only according to the results of evaluation of the optic disc and nerve fiber layer, and the VF as described elsewhere.[24] The diagnosis is briefly summarized below.

The criteria for glaucoma diagnosis were based upon the criteria of previous population studies.[28–31] First, the eye was diagnosed as having glaucoma (category 1) when the vertical C/D ratio of the optic nerve head was ≥0.7, the rim width at the superior portion (from the 11-o'clock position to the 1-o'clock position) or inferior portion (from the 5-o'clock position to the 7-o'clock position) was ≤0.1 of the disc diameter, the difference of the vertical C/D ratio was ≥0.2 between both eyes, or a nerve fiber layer defect was found, and the hemifield-based VF abnormality was compatible with the optic disc appearance or nerve fiber layer defect. Next, when the VF test result was not reliable or available, the diagnosis was obtained when the vertical C/D ratio was ≥0.9, the rim width at the superior portion (from the 11-o'clock position to the 1-o'clock position) or inferior portion (from the 5-o'clock position to the 7-o'clock position) was ≤0.05, or the difference of the vertical C/D ratio was ≥0.3 between both eyes (category 2). When a participant could not complete the VF testing and his or her optic disc was not visible, the diagnosis was made if the VA was ≤20/400 and the IOP percentile value for Japanese was 99.5—that is, ≥23 mmHg, or if the participant had a history of glaucoma surgery (category 3). The eye was diagnosed as having suspected glaucoma (glaucoma suspect) when the C/D ratios were ≥0.7 and <0.9, the rim width at the superior portion (from the 11-o'clock position to the 1-o'clock position) or inferior portion (from the 5-o'clock position to the 7-o'clock position) was ≤0.1 but >0.05 of the disc diameter, the difference of the vertical C/D ratio was ≥0.2 but <0.3 between both eyes, or a nerve fiber layer defect was found, and the VF test was not reliable or available or did not show a compatible hemifield-based defect. In a definitive

Closure Glaucoma (PACG) and Suspected PACG

Suspected PACG (Percentage, 95% CI)		
Male	*Female*	*All*
0/338 (0.0, 0.0–0.0)	0/445 (0.0, 0.0–0.0)	0/783 (0.0, 0.0–0.0)
1/427 (0.2, 0.0–0.68)	0/532 (0.0, 0.0–0.00)	1/959 (0.1, 0.0–0.30)
0/324 (0.0, 0.0–0.0)	1/360 (0.3, 0.0–0.83)	1/684 (0.2, 0.0–0.44)
1/190 (0.5, 0.0–1.56)	2/238 (0.8, 0.0–2.00)	3/428 (0.7, 0.0–1.49)
0/55 (0.0, 0.0–0.0)	1/112 (0.9, 0.0–2.63)	1/167 (0.6, 0.0–1.77)
2/1334 (0.1, 0.0–0.35)	4/1687 (0.3, 0.07–0.53)	6/3021 (0.2, 0.06–0.38)

Table 2. Age-Specific Prevalence of Primary Angle Closure (PAC) Excluding Primary Angle-Closure Glaucoma (PACG) and Suspected PACG

Age Groups (yrs)	PAC (Percentage, 95% CI)		
	Male	*Female*	*All*
40–49	0/338 (0.0, 0.0–0.0)	1/445 (0.2, 0.0–0.66)	1/783 (0.1, 0.0–0.38)
50–59	0/427 (0.0, 0.0–0.0)	2/532 (0.4, 0.0–0.90)	2/959 (0.2, 0.0–0.50)
60–69	1/324 (0.3, 0.0–0.92)	2/360 (0.6, 0.0–1.33)	3/684 (0.4, 0.0–0.94)
70–79	0/190 (0.0, 0.0–0.0)	6/238 (2.5, 0.53–4.51)	6/428 (1.4, 0.29–2.51)
≥80	0/55 (0.0, 0.0–0.0)	2/112 (1.8, 0.0–4.25)	2/167 (1.2, 0.0–2.85)
All subjects	1/1334 (0.1, 0.0–0.22)	13/1687 (0.9, 0.52–1.35)	14/3021 (0.5, 0.26–0.74)

CI = confidence interval.

diagnosis, anomalous discs, including tilted discs, were carefully excluded.

An occludable angle was defined as pigmented trabecular meshwork not visible in at least three quarters of the angle circumference. A diagnosis of PAC was made when the following criteria were met: at least one eye having a narrow angle of grade 2 or less by Shaffer's classification without other ocular findings that could have caused narrowing of the angle, and the existence of one or more of the following 4 conditions: IOP > 21 mmHg; a peripheral anterior synechia reaching the scleral spur or beyond; <90° of visibility of the pigmented trabecular meshwork in the primary position; and evidence of a history of an acute IOP rise, including the presence of iris atrophy, glaukomflecken, dilated nonreactive pupil, or a certified medical record of the subject having PAC. Primary angle-closure glaucoma or suspected PACG was diagnosed as PAC and glaucoma (category 1, 2, or 3) or suspected glaucoma as determined from the optic disc and VF findings as above.

Secondary glaucoma and suspected SG were diagnosed when the following criteria were met: positive history and/or ocular findings of intraocular inflammation, the presence of iris or angle neovascularization, presence of exfoliation materials on the iris margin or the lens surface, or other abnormal ocular findings that could cause prior or current IOP elevation and glaucoma (category 1, 2, or 3) or suspected glaucoma as determined above.

Early-onset developmental glaucoma and suspected cases were diagnosed when the following criteria were met: a developmental anomaly of the chamber angle that may cause IOP elevation; characteristic corneal changes such as diameter enlargement or Haab's striae; and/or related ocular anomalies such as seen in Axenfeld–Rieger syndrome, aniridia, and glaucoma (category 1, 2, or 3) or suspected glaucoma as determined above.

Primary angle closure, PACG and suspected PACG, SG and suspected SG, and early-onset developmental glaucoma and suspected cases were diagnosed on an individual basis. For example, if a patient had PACG in one eye and PAC in the other eye, the case was classified as PACG.

Data Analysis

All information was kept under the protection of participants' privacy at the Data Analysis Center of Tajimi Municipal Hospital. The data were double checked and validated through inspection and were analyzed using SAS version 6.12 (SAS Institute Japan, Tokyo, Japan) on a personal computer. Differences among the groups were evaluated using Student's *t* test. The Dunnett correction for multiple comparison was used when necessary. The prevalence of glaucoma and its confidence interval (CI) were calculated for each age group assuming that prevalences in participants and nonparticipants were equal. The prevalence rates were calculated by direct age-standardization from the population of Tajimi City. Association of age and gender with prevalence was evaluated using linear regression analysis and the chi-square test, respectively.

Results

Among the selected sample of 4000 subjects, 48 died and 82 were not actual residents or had moved from Tajimi City during the screening period. Of the 3870 remaining eligible persons, 3021 participated in the screening examinations, which resulted in a response rate of 78.1%. Response rates were similar in all age groups. There were 1065 subjects referred for a definitive examination after the initial screening examination. Of these 1065, 1051 received a definitive examination, whereas the remaining 14 declined or were unable to participate. For the 14 subjects who could not take the definitive examination, diagnosis was made based on the findings obtained in the screening examination, but none of them met the criteria of category 2 or glaucoma suspect. Of the 1065, 135 (4.5% of all subjects) showed grade 2 or less by the van

Table 3. Age-Specific Prevalence of Secondary Glaucoma (SG)

Age Groups (yrs)	SG (Percentage, 95% CI)		
	Male	*Female*	*All*
40–49	0/338 (0.0, 0.0–0.0)	1/445 (0.2, 0.0–0.66)	1/783 (0.1, 0.0–0.38)
50–59	0/427 (0.0, 0.0–0.0)	0/532 (0.0, 0.0–0.0)	0/959 (0.0, 0.0–0.0)
60–69	1/324 (0.3, 0.0–0.92)	1/360 (0.3, 0.0–0.83)	2/684 (0.3, 0.0–0.69)
70–79	2/190 (1.1, 0.0–2.50)	2/238 (0.8, 0.0–2.00)	4/428 (0.9, 0.02–1.84)
≥80	1/55 (1.8, 0.0–5.35)	1/112 (0.9, 0.0–2.63)	2/167 (1.2, 0.0–2.85)
All subjects	4/1334 (0.3, 0.0–0.57)	5/1687 (0.4, 0.09–0.61)	9/3021 (0.3, 0.13–0.51)

CI = confidence interval.

Herick method in at least one eye, of whom 19 (0.6%) showed grade 1 by the van Herick method. For females, numbers of subjects and age-specific prevalences of grade 2 or less by the van Herick method were 8 (1.8%), 27 (5.1%), 32 (8.9%), 28 (11.8%), 15 (13.4%), and 110 (6.5%) for those in their 40s, 50s, 60s, 70s, and 80s and above and for all cases, respectively; for males, these were 1 (0.3%), 8 (1.9%), 11 (3.4%), 4 (2.1%), 1 (1.8%), and 25 (1.9%), respectively. All cases with a van Herick grade of 1 had a gonioscopically narrow angle graded ≤2 by Shaffer's classification, and 81 cases (69.8%) with a van Herick grade of 2 also showed a narrow angle.

Tables 1 and 2 show age-specific prevalences of PACG and PAC. Overall prevalences of PACG and suspected PACG were 0.6% (95% CI, 0.4%–0.9%) and 0.2% (95% CI, 0.1%–0.4%), respectively. The prevalence significantly increased with age ($P<0.0001$ for PACG and $P<0.0001$ for PACG and suspected PACG, linear regression analysis) but did not significantly differ between women and men ($P = 0.1162$ for PACG and $P = 0.1023$ for PACG and suspected PACG, chi-square test). The prevalence of PAC including PACG and suspected PACG was 1.3% (95% CI, 0.9%–1.7%), and that of PAC excluding PACG and suspected PACG was 0.5% (95% CI, 0.3%–0.7%). The prevalence of PAC including PACG and suspected PACG significantly increased with age ($P<0.0001$, linear regression analysis). Furthermore, a significant difference was observed in the prevalence of PAC including PACG and suspected PACG between women and men ($P = 0.0028$, chi-square test). There were 19 cases of PACG, with 11 being diagnosed with category 1 criteria, 2 with category 2 criteria, and the remaining 6 with category 3 criteria. No cases showed gonioscopic findings suggestive of plateau iris syndrome. Central corneal thicknesses of both PACG and suspected PACG averaged 526±40 μm in the right eye and 530±39 μm in the left eye.

The prevalence of SG excluding exfoliation glaucoma was 0.3% (95% CI, 0.1%–0.5%; Table 3). The prevalence of suspected SG was 0.1% (95% CI, 0.0%–0.2%; Table 3). The prevalence significantly increased with age ($P = 0.0034$ for SG and $P = 0.0014$ for SG and suspected SG, linear regression analysis) but did not significantly differ between women and men ($P = 1.0$ for SG and $P = 0.8618$ for SG and suspected SG, chi-square test). Numbers of SG and suspected SG cases were 9 and 3, respectively. Of the 12 patients with SG or suspected SG, 8 had uveitis, 2 had ocular trauma, and 2 had iris and angle neovascularization. Of the 9 SG cases, 4 were diagnosed with category 1 criteria, 2 with category 2 criteria, and the remaining 3 with category 3 criteria. In addition to SG and suspected SG, 3 cases demonstrated secondary IOP elevation or a history of secondary IOP elevation with no sign of glaucoma.

Table 4 shows the prevalence of confirmed and suspected exfoliation glaucoma, defined as the presence of exfoliation materials on the iris margin or the lens surface and IOP elevation, and glaucoma (category 1, 2, or 3) or suspected glaucoma. Prevalences of exfoliation glaucoma and suspected cases were 0.2% (95% CI, 0.0%–0.3%) and 0.1% (95% CI, 0.0%–0.2%), respectively. The prevalence significantly increased with age ($P = 0.0183$ for exfoliation glaucoma and $P = 0.0073$ for exfoliation glaucoma and suspected cases, linear regression analysis) but did not significantly differ between women and men ($P = 0.2442$ for exfoliation glaucoma and $P = 0.4904$ for exfoliation glaucoma and suspected cases, chi-square test). The numbers of exfoliation glaucoma cases and suspected cases were 5 and 3, respectively. Of the 5 exfoliation glaucoma cases, 3 were diagnosed with category 1 criteria and 2 with category 2 criteria; none were diagnosed with category 3 criteria. No subjects showed secondary IOP elevation without a sign of glaucoma due to exfoliation syndrome. Table 5 demonstrates the prevalence of exfoliation syndrome excluding confirmed and suspected exfoliation glaucoma. The prevalence was 0.8% (95% CI, 0.5%–1.1%). The prevalence of exfoliation syndrome including confirmed and suspected exfoliation glaucoma significantly increased with age ($P<0.0001$, linear regression analysis) but did not differ between genders ($P = 0.7809$, chi-square test).

No patient was found to have confirmed or suspected early-onset developmental glaucoma.

As for the impact of glaucoma on the quality of vision, one PACG patient had VA in one eye of <20/400 (i.e., the World Health Organization's criterion for blindness), and there was one case each of uveitic, traumatic, and neovascular glaucoma with VA of <20/400 in one eye.

Based on the present and previous data,[24] the prevalence of all glaucoma (categories 1, 2, and 3) in Tajimi was calculated to be 5.0% (95% CI, 4.2%–5.8%), and that including suspected cases was 7.5% (95% CI, 6.5%–8.4%). Table 6 shows the standardized prevalence of glaucoma and suspected cases.

Discussion

Epidemiological studies should be performed based on clear definitions of the targeted diseases. Until recently, the nomenclature for PACG and related conditions such as PAC was not well established. In actuality, there was little information about glaucomatous optic nerve damage in many of the classic articles dealing with PACG. For that reason, care must be taken in the interpretation and comparison of the previous literature on PACG. Recently, a new epidemiologic definition clarifying angle closure has been proposed,[31,32] in which the term *glaucoma* is applied only to cases of glaucomatous optic neuropathy and its corresponding VF loss. These efforts toward a standardized definition of PAC will facilitate both the diagnosis and com-

and Suspected SG, Excluding Exfoliation Glaucoma

Suspected SG (Percentage, 95% CI)		
Male	*Female*	*All*
0/338 (0.0, 0.0–0.0)	0/445 (0.0, 0.0–0.0)	0/783 (0.0, 0.0–0.0)
0/427 (0.0, 0.0–0.0)	0/532 (0.0, 0.0–0.0)	0/959 (0.0, 0.0–0.0)
1/324 (0.3, 0.0–0.92)	1/360 (0.3, 0.0–0.83)	2/684 (0.3, 0.0–0.69)
0/190 (0.0, 0.0–0.0)	1/238 (0.4, 0.0–1.24)	1/428 (0.2, 0.0–0.68)
0/55 (0.0, 0.0–0.0)	0/112 (0.0, 0.0–0.0)	0/167 (0.0, 0.0–0.0)
1/1334 (0.1, 0.0–0.22)	2/1687 (0.1, 0.0–0.31)	3/3021 (0.1, 0.0–0.21)

Table 4. Age-Specific Prevalence of Exfoliation

Age Groups (yrs)	Exfoliation Glaucoma (Percentage, 95% CI)		
	Male	*Female*	*All*
40–49	0/338 (0.0, 0.0–0.0)	0/445 (0.0, 0.0–0.0)	0/783 (0.0, 0.0–0.0)
50–59	0/427 (0.0, 0.0–0.0)	0/532 (0.0, 0.0–0.0)	0/959 (0.0, 0.0–0.0)
60–69	2/324 (0.6, 0.0–1.47)	1/360 (0.3, 0.0–0.83)	3/684 (0.4, 0.0–0.94)
70–79	0/190 (0.0, 0.0–0.0)	0/238 (0.0, 0.0–0.0)	0/428 (0.0, 0.0–0.0)
≥80	2/55 (3.6, 0.0–8.59)	0/112 (0.0, 0.0–0.0)	2/167 (1.2, 0.0–2.85)
All subjects	4/1334 (0.3, 0.0–0.58)	1/1687 (0.1, 0.0–0.17)	5/3021 (0.2, 0.02–0.30)

CI = confidence interval.

parison among diverse epidemiological studies. Such nomenclature would also be applicable to SG, which is more complicated due to the variety of ocular hypertensive mechanisms involved.

In the present study, all subjects were screened for narrow angles using the van Herick method, which was reported to be highly specific in detecting narrow angles of Shaffer grade 2 or less, though some controversy existed.[33] Okabe et al reported 77% sensitivity and 94% specificity for the van Herick method in detecting eyes with Shaffer grade 2 narrow angles in Japanese.[34] Thus, some cases of Shaffer grade 2 narrow angle in the present study might not have been detected because gonioscopy was not performed in the screening examination. However, because the sensitivity and specificity of detecting Shaffer grade 1 narrow angles in Japanese were reported to be 93% and 98%, respectively,[34] such an extremely narrow angle must have been detected appropriately. Besides, the diagnosis of glaucoma was established based mainly on optic disc change and the VF. In all cases referred for the definitive examination, the ocular fundus was observed via a 2-mirror goniolens with the pupil dilated, except in narrow-angled eyes. All cases with poor-quality fundus IMAGEnet photographs were also referred for the definitive examination. Additionally, we applied an FDT screener to all participants for the screening VF test. The FDT screener has been reported to detect glaucomatous VF defects with high sensitivity and even earlier than conventional perimetries.[35–37] We did not employ red-free photography because the nerve fiber layer is observed quite easily even without it in a melanin-rich fundus such as seen in Japanese. Thus, the diagnosis of confirmed and suspected PACG was thought to be made with reasonable accuracy in the present study.

Racial or geographic differences in the prevalence of PAC or PACG are well known. Among Caucasians and African Americans, the prevalence of PACG has been reported to be relatively low. The Baltimore Eye Survey found a potentially occludable angle in 0.8% of Caucasians and 0.6% of African Americans, where an occludable angle was defined as at least 9 clock hours of the angle having a slit or closed appearance on gonioscopy, evidence of previous episodes of angle closure such as peripheral synechiae, or both.[38] The Melbourne Visual Impairment Project in Australia reported only a 0.1% prevalence of PACG diagnosed at the discretion of the ophthalmologists.[8] The Egna–Neumarkt Study conducted in northern Italy found a 0.6% prevalence of PACG in a population 40 years or older in which PACG was defined as glaucomatous optic neuropathy and chamber angle partly or totally closed or goniosynechiae extending to at least one third of the circumference, or with a very narrow angle clearly prone to occlusion.[10] In a Hispanic population 40 years or older, there was a 0.10% prevalence of PACG, which was defined as bilateral appositional angle closure combined with optic nerve damage.[28] In an African tribe, a 0.1% prevalence was found with PACG defined as glaucomatous optic neuropathy and an occludable drainage angle, meaning that the pigmented trabecular meshwork was visible for <90° in the primary position,[29] whereas, in a Tanzanian population, a 0.59% prevalence was reported with PACG defined as an occludable angle and one of the following in addition to Shaffer grade 2 or less in at least 8 clock hours in the fellow eye: IOP > 24 mmHg, structural optic disc abnormality, definite reliable VF damage, or a history compatible with an episode of acute angle closure.[39] By contrast, an Inuit population showed a surprisingly high prevalence of PACG/PAC, and 17% of those 50 years or older showed an occludable angle, defined as a trabecular meshwork not visible in 3 quarters of the angle and the ciliary body not visible in 2 quarters.[40]

In Asian countries, the prevalence of PACG has been recognized to be intermediate. In southern India, 2 studies have been reported recently.[6,7] The Andhra Pradesh Eye Disease Study demonstrated, in participants 40 years or older, that prevalences of occludable angles without ACG and manifest PACG, defined as IOP of ≥22 mmHg or glaucomatous optic disc damage in the presence of an occludable angle, were 2.21% and 1.08%, respectively.[6] Whereas, according to a recent article from the Aravind Comprehensive Eye Survey, the prevalence of manifest PACG—defined as glaucomatous optic disc damage or glaucomatous VF defects with the anterior chamber angle partly or totally closed, appositional angle closure or synechiae in the angle, and absence of signs of secondary angle closure—was 0.5%.[7] The prevalence of PACG in Chinese residents in urban Singapore was reported to be 1.0%,[5] in a study where glaucoma was defined as glaucomatous optic neuropathy and an occludable drainage angle, and in which the pigmented/posterior trabecular meshwork could be seen for <90° of the angle circumference. In Mongolia,[4] the prevalence of occludable angles, defined as a pigmented trabecular meshwork that was not visible throughout ≥3

Glaucoma and Suspected Cases

Suspected Exfoliation Glaucoma (Percentage, 95% CI)		
Male	*Female*	*All*
0/338 (0.0, 0.0–0.0)	1/445 (0.2, 0.0–0.66)	1/783 (0.1, 0.0–0.38)
0/427 (0.0, 0.0–0.0)	0/532 (0.0, 0.0–0.0)	0/959 (0.0, 0.0–0.0)
0/324 (0.0, 0.0–0.0)	0/360 (0.0, 0.0–0.0)	0/684 (0.0, 0.0–0.0)
1/190 (0.5, 0.0–1.56)	0/238 (0.0, 0.0–0.0)	1/428 (0.2, 0.0–0.68)
0/55 (0.0, 0.0–0.0)	1/112 (0.9, 0.0–2.63)	1/167 (0.6, 0.0–1.77)
1/1334 (0.1, 0.0–0.21)	2/1687 (0.3, 0.07–0.53)	3/3021 (0.1, 0.0–0.22)

quarters of the angle circumference in the primary position, or PACG, defined as an occludable angle and a raised IOP and/or glaucomatous optic neuropathy, was reported to be 6.4% or 1.4%, respectively, which is higher than that in other Asian countries. In the present study, prevalences of PAC including PACG and suspected PACG, and PACG alone, were 1.3% and 0.6%, respectively. Clearly demonstrated was the effect of age on the prevalence for both PAC including PACG and suspected PACG, and PACG, but the effect of gender was only evident for the former category. The prevalence of PACG was numerically 3 times higher in females than in males (0.9% vs. 0.3%) in the present study, but the intergender difference did not reach a statistically significant level because of relatively small numbers of PACG diagnoses. Compared with other reports conducted in other Asian countries, the prevalence of PACG or PAC in Japanese tended to be lower, especially relative to the Mongolia or Andhra Pradesh study, but was still higher than in Caucasians or African Americans.

In a previous epidemiological study conducted between 1988 and 1989 in Japan, it had been reported that the prevalence of PACG, defined as a closed or occludable angle and IOP $\geq$ 21 mmHg, was 0.34%.[25] If the same definition were adopted, the prevalence in the present study would be 0.23%, being comparable to the previous figure. However, there was no information regarding the prevalence of suspected PACG or occludable angles in the previous study.

In the present study, the overall prevalence of SG including exfoliation glaucoma was 0.5%. Exfoliation glaucoma was found to be the principal contributor to the prevalence of SG. However, the detection method in the present study included observation of only the pupillary margin and lens surface through undilated pupils. Because it was previously reported that exfoliation material may be missed in 10% to 20% of undilated eyes with exfoliation syndrome,[41,42] the prevalence of exfoliation glaucoma may have been underestimated in the present study. We also found that uveitic glaucoma is a common type of SG, and we confirmed that pigmentary glaucoma is rarely seen in Japan.[43] The epidemiology of SGs differs among various regions and races. Also, it is almost certain that the reported prevalence is affected by the accessibility to medical care and the prevalence of underlying conditions. The Egna–Neumarkt Study reported a 0.2% prevalence for aphakic glaucoma and 0.1% for SG.[10] In a Hispanic population 40 years or older, a 0.02% prevalence of SG was reported.[27] In Africans, the SG prevalence was reported as 0.15% in Tanzania[38] and 1.7% in South Africa, being mainly exfoliative and aphakic glaucoma.[28] In Asian countries, the Andhra Pradesh Eye Disease Study found a 0.28% prevalence for SG,[6,44] whereas, in the Aravind Comprehensive Eye Survey,[7] a higher prevalence for SGs was found: 0.4%, 0.06%, and 0.3% for pseudoexfoliation, absolute glaucoma, and other types of SGs, respectively. The Tanjong Pagar Study[5] in Singapore found a 0.5% prevalence for SGs (i.e., secondary pathologic process and glaucomatous optic neuropathy) in Chinese, in whom neovascular and lens-related forms were predominant and no exfoliation glaucoma cases were found. In Mongolia,[4] a 0.3% prevalence for SG comprised of exfoliation and uveitic glaucoma was reported. Thus, the prevalence and underlying conditions of SG vary even among the Asian regions and ethnicities.

Early-onset developmental or congenital glaucoma was not found in the present study. Because the prevalence of this type of glaucoma is 1 of 10 000 to 100 000 births,[45] this

Table 5. Age-Specific Prevalence of Exfoliation Syndrome Excluding Exfoliation Glaucoma and Suspected Cases

Age Groups (yrs)	Exfoliation Syndrome Excluding Exfoliation Glaucoma and Suspected Cases (Percentage, 95% CI)		
	Male	*Female*	*All*
40–49	0/338 (0.0, 0.0–0.0)	0/445 (0.0, 0.0–0.0)	0/783 (0.0, 0.0–0.0)
50–59	0/427 (0.0, 0.0–0.0)	2/532 (0.4, 0.0–0.90)	2/959 (0.2, 0.0–0.50)
60–69	3/324 (0.9, 0.0–1.98)	4/360 (1.1, 0.03–2.19)	7/684 (1.0, 0.27–1.77)
70–79	4/190 (2.1, 0.07–4.15)	4/238 (1.7, 0.05–3.31)	8/428 (1.9, 0.59–3.15)
≥80	2/55 (3.6, 0.0–8.59)	3/112 (2.7, 0.0–5.67)	5/167 (3.0, 0.41–5.57)
All subjects	9/1334 (0.6, 0.18–1.06)	13/1687 (0.9, 0.46–1.29)	22/3021 (0.8, 0.47–1.07)

CI = confidence interval.

Table 6. Standardized Prevalence of Glaucoma and Suspected Cases in Patients over 40 Years (%)

	Male (95% CI)	Female (95% CI)	Overall (95% CI)
Glaucoma			
Primary open-angle*	4.1 (3.0–5.2)	3.7 (2.8–4.6)	3.9 (3.2–4.6)
Primary angle-closure	0.3 (0.0–0.7)	0.9 (0.5–1.3)	0.6 (0.4–0.9)
Secondary†	0.6 (0.2–1.0)	0.4 (0.1–0.7)	0.5 (0.2–0.7)
Early-onset developmental	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
All	5.0 (3.9–6.2)	5.0 (4.0–6.0)	5.0 (4.2–5.8)
Glaucoma including suspected cases			
Primary open-angle*	6.3 (5.0–7.6)	5.8 (4.7–6.9)	6.0 (5.1–6.8)
Primary angle-closure	0.5 (0.1–0.9)	1.1 (0.6–1.6)	0.8 (0.5–1.2)
Secondary†	0.7 (0.2–1.2)	0.6 (0.3–1.0)	0.7 (0.4–1.0)
Early-onset developmental	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
All	7.5 (6.1–8.9)	7.5 (6.3–8.7)	7.5 (6.5–8.4)

CI = confidence interval.
*Regardless of intraocular pressure.
†Including exfoliation glaucoma.

may be due to the relatively small number of subjects (3021) in the present study, and life expectancy, expected to be shorter with some forms of congenital glaucoma with systemic anomalies, might be also a contributing factor.

The present study and our study group's previous report[24] revealed that prevalences of all cases of glaucoma and glaucoma/suspected glaucoma are 5.0% (95% CI, 4.2%–5.8%) and 7.5% (95% CI, 6.5%–8.4%), respectively, in those 40 years or older in Japan. The prevalence of PACG or SG increased with age significantly. This, along with the similar trend for POAG,[24] means that glaucoma is an important health issue in the elderly population. The subtypes of various glaucomas differ among various ethnic groups. The ratio of the prevalence of POAG with normal IOP (i.e., normal-tension glaucoma) to that of all glaucoma was 72% (3.6%/5.0%) in our population. This high prevalence of normal-tension glaucoma is the most distinctive feature of glaucoma epidemiology in Japanese. Further research is needed to elucidate the cause of glaucomatous optic neuropathy in Japanese eyes with apparently normal IOP.

Acknowledgments. The authors thank Tajimi City, the Japanese Ophthalmological Society, and the Japanese Association of Certified Orthoptists for their support and cooperation in this project.

References

1. Thylefors B, Nègrel AD, Pararajasegaram R, Dadzie KY. Global data on blindness. Bull World Health Organ 1995;73: 115–21.
2. Thylefors B, Nègrel AD. The global impact of glaucoma. Bull World Health Organ 1994;72:323–6.
3. Foster PJ, Johnson GJ. Glaucoma in China: how big is the problem? Br J Ophthalmol 2001:85:1277–82.
4. Foster PJ, Baasanhu J, Alsbirk PH, et al. Glaucoma in Mongolia. A population-based survey in Hövsgöl province, northern Mongolia. Arch Ophthalmol 1996;114:1235–41.
5. Foster PJ, Oen FT, Machin D, et al. The prevalence of glaucoma in Chinese residents of Singapore: a cross-sectional population survey of the Tanjong Pagar district. Arch Ophthalmol 2000;118:1105–11.
6. Dandona L, Dandona R, Mandal P, et al. Angle-closure glaucoma in an urban population in southern India. The Andhra Pradesh Eye Disease Study. Ophthalmology 2000;107: 1710–6.
7. Ramakrishnan R, Nirmalan PK, Krishnadas R, et al. Glaucoma in a rural population of southern India: the Aravind Comprehensive Eye Survey. Ophthalmology 2003;110:1484–90.
8. Wensor MD, McCarty CA, Stanislavsky YL, et al. The prevalence of glaucoma in the Melbourne Visual Impairment Project. Ophthalmology 1998;105:733–9.
9. Cedrone C, Culasso F, Cesareo M, et al. Prevalence of glaucoma in Ponza, Italy: a comparison with other studies. Ophthalmic Epidemiol 1997;4:59–72.
10. Bonomi L, Marchini G, Marraffa M, et al. Prevalence of glaucoma and intraocular pressure distribution in a defined population. The Egna-Neumarkt Study. Ophthalmology 1998; 105:209–15.
11. Hillman JS. Acute closed-angle glaucoma: an investigation into the effect of delay in treatment. Br J Ophthalmol 1979; 63:817–21.
12. Drance SM. Angle closure glaucoma among Canadian Eskimos. Can J Ophthalmol 1973;8:252–4.
13. Cox JE. Angle closure glaucoma among the Alaskan Eskimos. Glaucoma 1984;6:135–7.
14. Hollows FC, Graham PA. Intra-ocular pressure, glaucoma, and glaucoma suspects in a defined population. Br J Ophthalmol 1966;50:570–86.
15. Hu Z, Zhao JL, Dong FT, et al. An epidemiologic investigation of glaucoma in Beijing City and Shun-yi County [in Chinese]. Zhonghua Yan Ke Za Zhi 1988;25:115–8.
16. Lemoine AN Jr. Glaucoma: a statistical review of 816 patients with 1,112 glaucomatous eyes. Am J Ophthalmol 1950;33: 1353–73.
17. Lowe RF. Comparative incidence of angle-closure glaucoma among different national groups in Victoria, Australia. Br J Ophthalmol 1963;47:721–7.
18. Smith R. The incidence of the primary glaucomas. Trans Ophthal Soc U K 1958;78:245–57, discussion 257-9.
19. Alsbirk PH. Primary angle-closure glaucoma. Oculometry, epidemiology, and genetics in a high risk population. Acta Ophthalmol Suppl 1976;(127):5-31.
20. Luntz MH. Primary angle-closure glaucoma in urbanized South African caucasoid and negroid communities. Br J Ophthalmol 1973;57:445–56.

21. Gorin G. Shortening of the angle of the anterior chamber in angle-closure glaucoma. Am J Ophthalmol 1960;49:141–6.
22. Lowe RF. Primary angle-closure glaucoma. A review of provocative tests. Br J Ophthalmol 1967;51:727–32.
23. Pollack IP. Chronic angle-closure glaucoma: diagnosis and treatment in patients with angles that appear open. Arch Ophthalmol 1971;85:676–89.
24. Iwase A, Suzuki Y, Araie M, et al, Tajimi Study Group, Japan Glaucoma Society. The prevalence of primary open-angle glaucoma in Japanese: the Tajimi Study. Ophthalmology 2004;111:1641–8.
25. Shiose Y, Kitazawa Y, Tsukahara S, et al. Epidemiology of glaucoma in Japan: a nationwide glaucoma survey. Jpn J Ophthalmol 1991;35:133–55.
26. van Herick W, Shaffer RN, Schwarz A. Estimation of width of angle of anterior chamber: incidence and significance of the narrow angle. Am J Ophthalmol 1969;68:626–9.
27. Anderson DR, Patella VM. Automated Static Perimetry. 2nd ed. St. Louis: Mosby; 1999:152-3.
28. Quigley HA, West SK, Rodriguez J, et al. The prevalence of glaucoma in a population-based study of Hispanic subjects. Proyecto VER. Arch Ophthalmol 2001;119:1919–26.
29. Rotchford AP, Johnson GJ. Glaucoma in Zulus: a population-based cross-sectional survey in a rural district in South Africa. Arch Ophthalmol 2002;120:471–8.
30. Wolfs RC, Borger PH, Ramrattan RS, et al. Changing views on open-angle glaucoma: definitions and prevalences—the Rotterdam Study. Invest Ophthalmol Vis Sci 2000;41:3309–21.
31. Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. Br J Ophthalmol 2002;86:238–42.
32. Friedman DS. Who needs an iridotomy? Br J Ophthalmol 2001;85:1019–21.
33. Thomas R, George T, Braganza A, Muliyil J. The flashlight test and van Herick's test are poor predictors for occludable angles. Aust N Z J Ophthalmol 1996;24:251–6.
34. Okabe I, Tomita G, Sugiyama K, Taniguchi T. An epidemiological study on the prevalence of the narrow chamber angle in Japanese [in Japanese]. Nippon Ganka Gakkai Zasshi 1991;95:279–87.
35. Kondo Y, Yamamoto T, Sato Y, et al. A frequency-doubling perimetric study in normal-tension glaucoma with hemifield defect. J Glaucoma 1998;7:261–5.
36. Wu LL, Suzuki Y, Kunimatsu S, et al. Frequency doubling technology and confocal scanning ophthalmoscopic optic disc analysis in open-angle glaucoma with hemifield defects. J Glaucoma 2001;10:256–60.
37. Bowd C, Zangwill LM, Berry CC, et al. Detecting early glaucoma by assessment of retinal nerve fiber layer thickness and visual function. Invest Ophthalmol Vis Sci 2001;42:1993–2003.
38. Patel KH, Javitt JC, Tielsch JM, et al. Incidence of acute angle-closure glaucoma after pharmacologic mydriasis. Am J Ophthalmol 1995;120:709–17.
39. Buhrmann RR, Quigley HA, Barron Y, et al. Prevalence of glaucoma in a rural East African population. Invest Ophthalmol Vis Sci 2000;41:40–8.
40. Arkell SM, Lightman DA, Sommer A, et al. The prevalence of glaucoma among Eskimos of northwest Alaska. Arch Ophthalmol 1987;105:482–5.
41. Aasved H. Mass screening for fibrillopathia epitheliocapsularis, so-called senile exfoliation or pseudoexfoliation of the anterior lens capsule. Acta Ophthalmol (Copenh) 1971;49:334–43.
42. Forsius H, Sveinesson K, Als E, Luukka H. Pseudoexfoliation of the lens capsule and depth of anterior chamber in northern Iceland. Acta Ophthalmol (Copenh) 1974;52:421–8.
43. Campbell DG, Schertzer RM. Pigmentary glaucoma. In: Ritch R, Shields MB, Krupin T, eds. The Glaucomas. 2nd ed. Vol. 2. Clinical Science. St. Louis: Mosby; 1996:975–6.
44. Dandona L, Dandona R, Srinivas M, et al. Open-angle glaucoma in an urban population in southern India. The Andhra Pradesh Eye Disease Study. Ophthalmology 2000;107:1702–9.
45. Etienne R. Congenital glaucoma [in French]. J Genet Hum 1986;34:27–36.

Jpn J Ophthalmol 2005;49:469–476
© Japanese Ophthalmological Society 2005
DOI 10.1007/s10384-005-0248-2

LABORATORY INVESTIGATION

Topographic Characteristics of the Optic Nerve Head Measured with Scanning Laser Tomography in Normal Japanese Subjects

Hideya Uchida[1,2], Tetsuya Yamamoto[1], Makoto Araie[3], Goji Tomita[3], Motohiro Shirakashi[4], Keiji Yoshikawa[5], and the HRT Study Group

[1]Department of Ophthalmology, Gifu University Graduate School of Medicine, Gifu, Japan; [2]Uchida Eye Clinic, Gifu, Japan; [3]Department of Ophthalmology, Tokyo University Graduate School of Medicine, Tokyo, Japan; [4]Division of Ophthalmology and Visual Sciences, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; [5]Yoshikawa Eye Clinic, Tokyo, Japan

Abstract

Purpose: Few studies have been performed regarding the topographic information obtained with the Heidelberg retina tomograph (HRT) in normal Japanese. In this study, we examined the factors influencing optic disc parameters and hemisphere symmetry obtained with the HRT in normal Japanese subjects.

Methods: Mean values and the standard deviation range for the main HRT parameters were evaluated in 223 eyes of 223 normal Japanese subjects. The influence of age, sex, and disc size on HRT topographic data was analyzed. The superior and inferior hemisphere topographic parameters were compared.

Results: Disc area showed a significant difference by sex ($P = 0.0493$). Rim volume ($r = -0.208$, $P = 0.019$), height variation contour ($r = -0.275$, $P = 0.001$), and mean retinal nerve fiber layer (RNFL) thickness ($r = -0.366$, $P = 0.001$) declined with age. All parameters except height variation contour and mean RNFL thickness showed a clinically significant correlation with disc size ($-0.159 < r < 0.719$, $P < 0.01$). Cup parameters in the superior hemisphere were significantly greater than those in the inferior hemisphere. In contrast, rim parameters in the superior hemisphere were significantly smaller than those in the inferior hemisphere.

Conclusions: Some factors, namely, sex, age, and disc size, affected the optic disc parameters in the HRT measurements. Possible parameter asymmetry between the two hemispheres should be considered in normal eyes. **Jpn J Ophthalmol** 2005;49:469–476 © Japanese Ophthalmological Society 2005

Key Words: influence factors, normal Japanese, optic nerve head, scanning laser ophthalmoscopy

Introduction

Recognition of optic disc changes is essential for diagnosing and monitoring glaucoma. The optic nerve head characteristics of normal eyes are known to be highly variable and usually reflect the subject's background and the techniques used to measure the optic disc.

Previous studies have suggested that factors such as age, race, and sex might affect optic disc characteristics in normal eyes.[1–3] Several semiquantitative or quantitative techniques of optic disc measurement have been employed in clinical practice and the laboratory. Evaluation of the cup/disc ratio using an ophthalmoscopic lens with slit-lamp biomicroscopy is subjective, and, although it is the most popular method, there is disagreement among glaucoma experts regarding the reliability of this technique.[4]

Received: August 5, 2004 / Accepted: April 27, 2005
Correspondence and reprint requests to: Hideya Uchida, Uchida Eye Clinic, 4-18 Tetsumei-dori, Gifu 500-8879, Japan
e-mail: gifhu@aol.com

See Appendix for the Heidelberg retina tomograph (HRT) study group members

Jpn J Ophthalmol
Vol 49: 469–476, 2005

The quantitative methods used in research include planimetric evaluation of stereoscopic photographs, digitized optic nerve image analyzers (e.g., the Rodenstock optic nerve head analyzer), and, more recently, the confocal scanning laser ophthalmoscope. These methods have markedly improved the consistency of the measurements. Results of semiquantitative evaluation of the cup/disc ratio differ from those of quantitative methods, especially in normal subjects,[5] and a previous study revealed an inconsistency between two different quantitative methods.[6]

The Heidelberg retina tomograph, a confocal scanning laser ophthalmoscope, has now become popular in glaucoma clinics because of its potential use in obtaining an objective and quantitative evaluation of the optic nerve head.[7–11] An accurate disc and nerve fiber layer complex measurement with the HRT enables the clinician to track glaucomatous changes during routine examinations. The latest version, ver.1.12 or later, of the HRT employs a classification program that enables the clinician to distinguish between normal and glaucomatous eyes using discriminant analysis.[12] To improve potential early glaucoma recognition with the HRT, we require detailed information about the characteristics of disc topography, cup/disc ratio side differences,[13] and hemispherical and segmental analyses[14] of normal eyes.

Racial differences in the normal optic disc have also been demonstrated by several previous studies.[1,15] Although several studies have described the optic nerve head topography obtained with the HRT in normal white subjects,[15,16] little is known about the topographic characteristics of optic discs of normal Japanese subjects. Moreover, little is known regarding the factors contributing to the characteristics of the optic disc or the symmetry of the disc sectors in the Japanese population. In the present study, we examined HRT images in a large number of normal Japanese, and studied the distribution pattern of each HRT parameter and the factors contributing to the parameters and hemisphere symmetry of the normal Japanese optic disc.

Subjects and Methods

Normal subjects were recruited from hospital staff members and their friends or family members, retired staff members, and visiting patients who met the inclusion criteria. All subjects were examined at Gifu University, Tokyo University, Niigata University, Hiroshima University, Nihon University, or the Yoshikawa Eye Clinic. The institutional review board of each institution approved this study. Informed consent was obtained from each subject.

The inclusion criteria for normal subjects were as follows: (1) no history of eye diseases except incipient age-related cataract; (2) no history of systemic diseases such as diabetes mellitus or hypertension; (3) no family history of glaucoma; (4) no history of intraocular surgery or neurological disease; (5) intraocular pressure less than 22 mmHg; (6) best-corrected visual acuity of 0.7 or better; (7) a spherical refraction between –5.0 D and +3.0 D and a cylinder correction within ±2.5 D; and (8) normal visual field with the Central 30-2 program of the Humphrey Field Analyzer 630 or Humphrey Field Analyzer II (Zeiss-Humphrey Systems, San Leandro, CA, USA) or program G1 or G2 of the Octopus perimeter (Interzeag, Schlieren, Switzerland).

Optic disc measurements were obtained with a Heidelberg retina tomograph (HRT version 2.11; Heidelberg Engineering, Heidelberg, Germany), the details of which have been reported elsewhere.[4–9] After the optic disc margin was outlined by an operator, stereometric disc and retinal nerve fiber layer (RNFL) parameters were calculated automatically. The reference plane, which was defined as being 50 μm below the retinal surface within the temporal 350°–356° sector, was used for determination of the two- and three-dimensional optic disc parameters.

Trained operators in each institution obtained HRT images three times through undilated pupils. Mean HRT topographic images having less than 30 μm of average variability were used for the analysis. One operator (HU) drew a contour line to determine the optic disc margin on all HRT images obtained. A contour line was drawn as coincident with the inner border of the scleral ring (the Elschnig ring), or with the outer border rim edge when the Elschnig ring was unclear. Data from deformed discs (e.g., markedly tilted, morning glory-like, disc drusen, microdiscs, megalodiscs) or poor-quality images were excluded from the database. For each subject, if both eyes met the inclusion criteria, one eye was randomly selected for the analyses, except for the side difference analysis.

We determined the following HRT stereometric parameters: disc area, cup area, cup-to-disc area ratio, cup volume, rim volume, height variation contour, cup shape measure, mean RNFL thickness, and RNFL cross-sectional area. The mean ± SD and range of each disc parameter were calculated, and the distribution pattern was evaluated using the Kolomogorov-Smirnov test.

Influences on the main HRT parameters, sex, age, and optic disc size, were evaluated using the Bonferroni-Dunn test for sex and Spearman's rank correlation test for age and optic disc size. Comparison between the superior and inferior hemisphere symmetry of the HRT parameters was carried out using the Wilcoxon signed-ranks test. The interocular difference in HRT parameters was also calculated in 174 subjects in whom good-quality HRT images had been obtained in both eyes.

A P value of less than 0.05 was considered statistically significant.

Results

From the initial database of 248 subjects (448 eyes), 223 subjects (124 women, 99 men) (223 eyes) were selected for this study. Twenty-five subjects were excluded because of their poor-quality images or unsatisfied inclusion criteria. The mean (±SD) age was 45 years ± 17.5 years (range, 15 to 76 years), and the mean refractive error (spherical equivalent) was –1.8 D ± 2.8 D (range, –4.75 D to +2.5 D).

Morphometric Data for the Optic Disc

The normal optic disc parameters obtained with HRT are shown in Table 1. Histograms of all HRT parameters, except cup volume, show a normal distribution curve (Fig. 1) by the Kolomogorov-Smirnov test. The histogram for cup volume is positively skewed.

Influence of Sex, Age, and Optic Disc Size on HRT Parameters

Disc area was larger in men than in women ($P = 0.049$). Other HRT disc parameters showed no significant intersex differences (Table 2). The rim volume ($r = -0.208$, $P = 0.019$), height variation contour ($r = -0.275$, $P = 0.0011$), RNFL cross-sectional area ($r = -0.348$, $P = 0.006$), and mean RNFL thickness ($r = -0.366$, $P = 0.001$) declined with age. The cup shape measure showed a significant positive correlation with age ($r = 0.153$, $P = 0.023$). No other parameters significantly correlated with age (Table 3).

All parameters, except the height variation contour and the mean RNFL thickness, showed significant correlations with disc size (Table 4). Cup area showed the strongest correlation ($r = 0.72$, $P = 0.01$) with disc size in normal eyes.

Symmetry Analysis Between Superior and Inferior Disc Hemispheres

HRT parameters in the superior and inferior disc hemispheres are summarized in Table 5. The cup area, cup-to-disk area ratio, cup volume, mean RNFL thickness, and

Table 1. Summary of Heidelberg retina tomograph (HRT) disc parameters in the present study (number of eyes = 223)

Parameter	Mean ± SD	Range
Disc area (mm^2)	2.167 ± 0.485	0.896–4.086
Cup area (mm^2)	0.595 ± 0.362	0.009–2.073
Cup/disc area ratio	0.261 ± 0.121	0.007–0.595
Rim area (mm^2)	1.567 ± 0.328	0.403–2.814
Height variation contour (mm)	0.401 ± 0.110	0.177–0.850
Cup volume (mm^3)	0.144 ± 0.156	0–1.330
Rim volume (mm^3)	0.416 ± 0.138	0.141–0.784
Mean cup depth (mm)	0.225 ± 0.093	0.044–0.600
Maximum cup depth (mm)	0.628 ± 0.199	0.137–1.211
Cup shape measure	−0.209 ± 0.078	−0.446–0.001
Mean RNFL thickness (mm)	0.266 ± 0.081	0.050–0.505
RNFL cross-sectional area (mm^2)	1.362 ± 0.417	0.151–2.488

RNFL, retinal nerve fiber layer.

Table 3. Effect of age on HRT parameters

Parameter	*R*	*P**
Disc area (mm^2)	0.053	0.434
Cup area (mm^2)	0.057	0.394
Cup/disc area ratio	0.069	0.302
Rim area (mm^2)	0.004	0.953
Height variation contour (mm)	−0.275	0.001
Cup volume (mm^3)	0.069	0.301
Rim volume (mm^3)	−0.208	0.019
Mean cup depth (mm)	−0.004	0.994
Maximum cup depth (mm)	−0.101	0.131
Cup shape measure	0.153	0.023
Mean RNFL thickness (mm)	−0.366	0.001
RNFL cross-sectional area (mm^2)	−0.348	0.006

* Spearman's coefficient of rank correlation.

Table 4. Influence of optic disc size on HRT parameters

Parameter	Correlation	*P**
Cup area (mm^2)	0.719	0.010
Cup/disc area ratio	0.504	0.001
Rim area (mm^2)	0.601	0.001
Height variation contour (mm)	−0.081	0.231
Cup volume (mm^3)	0.636	0.001
Rim volume (mm^3)	0.214	0.001
Mean cup depth (mm)	0.457	0.001
Maximum cup depth (mm)	0.309	0.001
Cup shape measure	0.418	0.001
Mean RNFL thickness (mm)	−0.159	0.018
RNFL cross-sectional area (mm^2)	0.180	0.076

* Spearman's coefficient of rank correlation.

Table 2. Comparison of optic disc morphometry by sex

Parameter	Men (99 eyes)	Women (124 eyes)	*P**
Disc area (mm^2)	2.239 ± 0.505	2.110 ± 0.463	0.049
Cup area (mm^2)	0.615 ± 0.382	0.579 ± 0.346	0.467
Cup/disc area ratio	0.260 ± 0.120	0.262 ± 0.122	0.896
Rim area (mm^2)	1.613 ± 0.334	1.531 ± 0.319	0.056
Height variation contour (mm)	0.402 ± 0.122	0.399 ± 0.100	0.858
Cup volume (mm^3)	0.153 ± 0.174	0.137 ± 0.141	0.455
Rim volume (mm^3)	0.428 ± 0.146	0.408 ± 0.132	0.267
Mean cup depth (mm)	0.224 ± 0.089	0.227 ± 0.097	0.795
Maximum cup depth (mm)	0.629 ± 0.191	0.628 ± 0.205	0.978
Cup shape measure	−0.212 ± 0.074	−0.207 ± 0.081	0.691
Mean RNFL thickness (mm)	0.263 ± 0.087	0.267 ± 0.075	0.709
RNFL cross-sectional area (mm^2)	1.375 ± 0.439	1.352 ± 0.399	0.691

Values represent mean ± SD.
* Bonferroni-Dunn test.

Jpn J Ophthalmol
Vol 49: 469–476, 2005

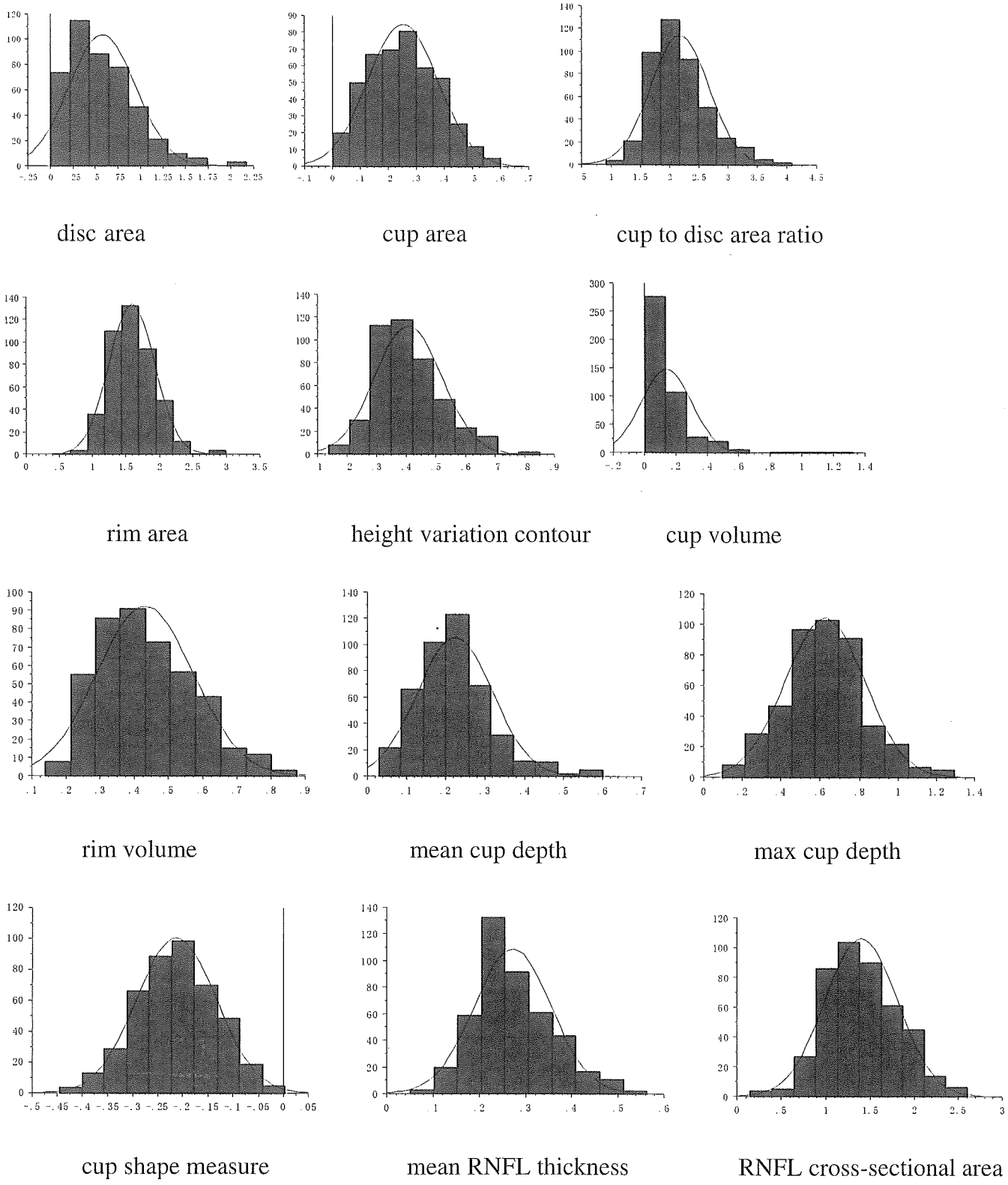

Figure 1. Distribution patterns of Heidelberg retina tomograph (HRT) parameters in normal Japanese were analyzed using the Kolomogorov-Smirnov test. All HRT parameters except cup volume show a normal distribution. Cup volume skews to the left.

Table 5. Symmetry analysis between superior and inferior disc hemispheres in HRT

Parameter	Superior hemisphere	Inferior hemisphere	P*
Disc area (mm^2)	1.084 ± 0.243	1.087 ± 0.244	0.049
Cup area (mm^2)	0.310 ± 0.197	0.289 ± 0.185	0.006
Cup/disc area ratio	0.271 ± 0.133	0.251 ± 0.127	0.005
Rim area (mm^2)	0.774 ± 0.158	0.794 ± 0.186	0.003
Height variation contour (mm)	0.368 ± 0.115	0.372 ± 0.113	0.351
Cup volume (mm^3)	0.081 ± 0.095	0.065 ± 0.070	0.001
Rim volume (mm^3)	0.205 ± 0.073	0.211 ± 0.076	0.029
Mean cup depth (mm)	0.237 ± 0.107	0.213 ± 0.088	0.001
Maximum cup depth (mm)	0.634 ± 0.215	0.574 ± 0.191	0.001
Cup shape measure	−0.193 ± 0.090	−0.186 ± 0.108	0.461
Mean RNFL thickness (mm)	0.269 ± 0.086	0.259 ± 0.089	0.037
RNFL cross-sectional area (mm^2)	0.694 ± 0.218	0.674 ± 0.206	0.038

* Wilcoxon signed-rank test.

Table 6. HRT parameter interocular differences (absolute values)

	Disc area	Cup area	C/D ratio	Rim area	HVC	Cup volume	Rim volume	MCD	MXCD	CSM	MRNFLT	RNFLCSA
Mean	0.117	0.164	0.070	0.164	0.064	0.056	0.098	0.045	0.093	0.056	0.051	0.271
SD	0.132	0.146	0.055	0.148	0.055	0.057	0.079	0.039	0.082	0.048	0.045	0.242
Minimum	0.001	0.002	0.000	0.002	0.000	0.000	0.000	0.000	0.001	0.000	0.000	0.002
Maximum	1.012	1.046	0.230	1.009	0.304	0.304	0.411	0.208	0.418	0.216	0.227	1.424
95% C.I.	0.375	0.450	0.178	0.454	0.172	0.168	0.253	0.121	0.254	0.145	0.139	0.745

C, cup; D, disc; HVC, height variation contour; MCD, mean cup depth; MXCD, maximum cup depth; CSM, cup shape measure; MRNFLT, mean retinal nerve fiber layer thickness; RNFLCSA, retinal nerve fiber layer cross-sectional area; C.I., confidence interval.

RNFL cross-sectional area in the superior hemisphere were significantly larger than those in the inferior hemisphere. In contrast, the rim area and rim volume in the superior hemisphere were significantly smaller than those in the inferior hemisphere.

Intraocular Differences of HRT Parameters

The intraocular differences in disc areas ranged from 0.001 to 1.012 mm^2, and the 95% confidence interval was 0.375 mm^2. Side differences in other HRT parameters are shown in Table 6.

Discussion

There is a considerable interindividual variability in optic disc morphometry in normal eyes. Many previous studies[1–3,14–26] have attempted to analyze normal optic disc parameters using various methods.

A recent population-based study[2] demonstrated optic disc characteristics using stereoscopic photographs obtained by using a simultaneous stereoscopic fundus camera (TRC-SS2; Topcon Optical, Tokyo, Japan) and IMAGEnet (Topcon) in 5114 subjects who were 55 years of age or older, 98% of whom were white. The population mean (±SD) of the disc area, neural rim area, and cup area were reported as 2.42 ± 0.47 mm^2, 1.85 ± 0.39 mm^2, and 0.57 ± 0.34 mm^2, respectively.

Mean optic disc areas in normal eyes varied among different studies (range, 1.70 mm^2 to 2.89 mm^2)[17,18]. These different results may reflect the inherent great interindividual variability in the appearance of the normal optic disc or differences in the inclusion criteria for normal eyes among the studies, different measurement methods, such as different fundus magnifications, or different definitions of disc and cup borders used by the various investigators.

It should be kept in mind that differences exist between indirect clinical image analysis methods such as the Rodenstock optic nerve head analyzer, computer-aided planimetry, and confocal scanning laser ophthalmoscopy and direct disk measurements,[26] in addition to the variability inherent in the various image analysis devices.[27–29] Dichtl et al.[27] examined the neuroretinal rim area differences between HRT and stereoscopic optic disc photograph measurements (planimetric technique) in 25 normal eyes and 32 glaucomatous eyes. They reported that the neural rim area obtained with HRT was larger, especially in the nasal region, than that obtained with photographs. These differences also increase with increasing glaucomatous optic disc damage. By contrast, another study[3] showed very similar disc measurement values, obtained by two different methods. One study[26] suggested that actual optic disc measurements were larger than those based on clinical imaging methods. Thus, we should always take into account the mea-

Jpn J Ophthalmol
Vol 49: 469–476, 2005

surement method and be aware of the characteristic differences among the various imaging methodologies used in optic disc analysis.

We used a confocal scanning laser ophthalmoscope (HRT) to obtain measurements of various optic disc parameters in the present study. The HRT was recently developed to measure two- and three-dimensional parameters of the optic nerve head with excellent test and retest consistency.[9] A previous study demonstrated that disc measurements obtained with the HRT corresponded to direct optic disc measurements made in phakic eyes.[30] Recently reported mean optic disc areas in normal eyes using HRT ranged from 1.801 mm^2 to 2.67 mm^2.[3,8,9,16] In the present study, the mean (±SD) disc area measured with the HRT was 2.167 ± 0.485 mm^2 with an interindividual variability of 1:4.3. Knowledge of the distribution pattern of each HRT parameter is necessary to determine which statistical methods should be employed. All HRT parameters except cup volume were normally distributed. Cup volume distribution in the normal Japanese in this study was skewed to the right, which is concordant with previous studies in normal white subjects.[16] Compared to recent investigations using HRT, our disc measurement results in Japanese were numerically larger than those in white races[3,8,16] and smaller than those in Hispanics and blacks,[15] although no statistical comparisons between ethnic groups were carried out.

The current study was not designed to be population-based; hence topographic measurements in our study do not represent the normal optic disc of all Japanese. However, this is the first study to describe a large number of normal Japanese optic discs using multiple-center data. Furthermore, all HRT topographic data were analyzed at one institution, and all contour lines were outlined by a single operator in a masked fashion to minimize the operator bias at each institution.

Many previous studies[1–3,17,19,22,24] have suggested that factors such as sex, age, and optic disc size might influence the morphometry of the optic disc. The influence of sex and age on optic disc characteristics remains controversial. Some studies have reported no significant differences in the optic disc area between the sexes,[1,14,20] while others have reported that men have a larger disc area than women.[2,25] The Rotterdam Study[2] demonstrated that the disc area and rim area were 3.2% and 4.3% larger in men than in women, respectively; and the Baltimore Eye Study[1] demonstrated that men had a disc area that was 2%–3% larger than that in women. The present study found that men had numerically larger HRT topographic measurements than did women, although the differences were not statistically significant except for disc area.

Some investigators found no relationship between disc characteristics and age cross-sectionally[1,2,14,16] or longitudinally,[23] whereas others found age-related optic disc changes cross-sectionally.[3,24] An age-related decline in the number of optic nerve axons has previously been shown histologically, with the number of optic nerve fibers lost with age reported to be about 4000–5000/year.[31,32] The present findings suggest that there is an aging effect on several HRT parameters. The rim volume, height variation contour, mean RNFL thickness, and RNFL cross-sectional area declined with age in our HRT analysis. Although mean RNFL thickness and RNFL cross-sectional area by HRT measurement do not represent actual nerve fiber layer (NFL) thickness, our current result is concordant with a recent investigation evaluating the aging effect on nerve fiber thickness using optical coherence tomography (OCT).[33] Additionally, the cup shape measure showed a positive correlation with age. Such stereometric measurements as rim volume, height variation contour, and mean RNFL thickness might represent the number of optic nerve fibers more accurately than conventional two-dimensional parameters, that is, cup area, cup-to-disc area ratio, and rim area. The cup shape measure is a unique HRT parameter that measures the overall three-dimensional slope of the cup. This parameter summarizes in one number the structure of the cup and takes into account its depth variation and the steepness of the cup wall. Its value is typically negative in normal eyes and usually less negative or even positive in steep cups, that is, in the glaucomatous eye. The cup shape measure is also reported to be a sensitive marker of glaucomatous optic disc changes, especially at an early stage.[12,34] This finding suggests that optic discs in elderly subjects may be more susceptible to change and more similar to those seen in glaucoma than is the case in younger subjects. Thus, distinction of age-related deterioration of disc parameters from pathological changes still seems problematic in HRT analysis.

Several studies[17,20,21] concluded that the optic disc size might influence the intrapapillary morphometry. In normal eyes, the larger the optic disc area, the larger the cup area,[20,21] and it may be the case that disc area affects many intrapapillary parameters. Britton et al.[20] demonstrated a linear correlation between disc area and both the neuroretinal rim area ($r = 0.75$) and the cup area ($r = 0.83$). Caprioli et al.[17] reported positive correlations between disc area and cup area and rim area and cup volume using computerized image analysis with the Rodenstock optic nerve head analyzer.

The present study confirms the relationship between the optic disc area and all intrapapillary parameters, except the height variation contour. The height variation contour represents the difference in height between the most elevated point and the most depressed point of the corrected contour line and, theoretically, is independent of the disc area and circumference.

It is important to know the detailed rim shape configuration in normal eyes if we are to make an early detection of a glaucomatous change. In the present study, we compared HRT parameter symmetries between the superior and inferior hemispheres. The HRT rim area and rim volume in the inferior hemispheres were significantly larger than those in the superior hemispheres. This agrees with a previous study that showed the neural rim is broadest in the inferior sector, followed by the superior, nasal, and temporal sectors, in normal eyes, according to a planimetry analysis.[35] Conversely, the NFL parameters of HRT in the inferior hemisphere were significantly smaller than those in the

superior hemisphere. This result also agrees with recent studies that measured NFL thickness with OCT[33] or scanning laser polarimetry (GDx).[36] These findings of NFL characteristics may explain the fact that inferior light sensitivity usually is functionally more predominant than that of the superior hemisphere in normal eyes.[37]

Careful observation of the interocular differences in the optic disc parameters is helpful for early glaucoma detection.[25] The 95% confidence interval of interocular differences of the cup-to-disc area ratio and rim area in this study were 0.178 and 0.454 mm^2, respectively. Our current data are similar to those of a previous study using HRT in a white population.[16] On the other hand, another study[14] showed larger interocular differences in rim area than our data because of the different measurement method employed. The information on side differences in normal eyes seems to have important implications for the early deterioration of the optic nerve head in glaucoma patients.

In conclusion, the present study reported the topographic measurements of the normal Japanese optic disc obtained with HRT. Several HRT parameters seem to be affected by age and disc size. Disc topographic asymmetry between the two hemispheres was present. These topographic characteristics in Japanese are in accordance with the results of previous studies;[3,19,22,24,34] hence, it should be emphasized that several factors can affect the normal individual disc and must be taken into account in evaluating glaucomatous optic neuropathy. Further studies are needed to construct an effective glaucoma classification system based on a normative database considering the above-mentioned, potential influencing factors involved with the use of the confocal scanning laser.

Appendix: Members of the HRT Study Group

Hideya Uchida[1,2], Tetsuya Yamamoto[1], Makoto Araie[3], Goji Tomita[3], Keiji Yoshikawa[4], Yoshiaki Kitazawa[5], Aiko Iwase[1], Reiko Shiraki[1], Yasuyuki Suzuki[3], Atsuo Tomidokoro[3], Shiho Kunimatsu[3], Haruki Abe[6], Motohiro Shirakashi[6], Shigeo Funaki[6], Kiyoshi Yaoeda[6], Hiromu Mishima[7], Koji Okada[7], Hiroki Nii[7], Yoshio Yamazaki[8], Yuko Ohno[9].

[1]Department of Ophthalmology, Gifu University Graduate School of Medicine, Gifu, Japan; [2]Uchida Eye Clinic, Gifu, Japan; [3]Department of Ophthalmology, University of Tokyo Graduate School of Medicine, Tokyo, Japan; [4]Yoshikawa Eye Clinic, Tokyo, Japan; [5]Akasaka Kitazawa Eye Clinic, Tokyo, Japan; [6]Division of Ophthalmology and Visual Sciences, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; [7]Hiroshima University Graduate School of Biomedical Sciences, Hiroshima, Japan; [8]Nihon University School of Medicine, Tokyo, Japan; [9]Osaka University Faculty of Medicine, Osaka, Japan.

References

1. Varma R, Tielsch JM, Quigley HA, et al. Race-, age-, gender-, and refractive error-related differences in the normal optic disk. Arch Ophthalmol 1994;112:1068–1076.
2. Ramrattan RS, Wolfs RC, Jonas JB, Hofman A, de Jong PT. Determinants of optic disk characteristics in a general population: the Rotterdam Study. Ophthalmology 1999;106:1588–1596.
3. Garway-Heath DF, Wollstein G, Hitchings RA. Aging changes of the optic nerve head in relation to open angle glaucoma. Br J Ophthalmol 1997;81:840–845.
4. Lichter PR. Variability of expert observers in evaluating the optic disk. Trans Am Ophthalmol Soc 1976;74:532–572.
5. Zangwill LM, Shakiba S, Caprioli J, Weinreb RN. Agreement between clinicians and a confocal scanning laser ophthalmoscope in estimating cup/disk ratios. Am J Ophthalmol 1995;119:415–421.
6. Jonas JB, Mardin CY, Gründler AE. Comparison of measurements of neuroretinal rim area between confocal scanning tomography and planimetry of photographs. Br J Ophthalmol 1998;82:362–366.
7. Wollstein G, Garway-Heath DF, Hitchings RA. Identification of early glaucoma cases with the scanning laser ophthalmoscope. Ophthalmology 1998;105:1557–1563.
8. Bathija R, Zangwill LM, Berry CC, Sample PA, Weinreb RN. Detection of early glaucomatous structural damage with confocal scanning laser tomography. J Glaucoma 1998;7:121–127.
9. Rohrschneider K, Burk RO, Kruse FE, Volcker HE. Reproducibility of the optic nerve head topography with a new laser tomographic scanning device. Ophthalmology 1994;101:1044–1049.
10. Brigatti L, Caprioli J. Correlation of visual field with scanning confocal laser optic disc measurements in glaucoma. Arch Ophthalmol 1995;113:1191–1194.
11. Zangwill LM, van Horn S, de Souza Lima M, Sample PA, Weinreb RN. Optic nerve head topography in ocular hypertensive eyes using confocal scanning laser ophthalmoscopy. Am J Ophthalmol 1996;122:520–525.
12. Mikelberg FS, Parfitt CM, Swindale NV, Graham SL, Drance SM, Gosine R. Ability of the Heidelberg retina tomograph to detect early glaucomatous field loss. J Glaucoma 1995;4:242–247.
13. Armaly MF. Genetic determination of cup/disc ratio of the optic nerve. Arch Ophthalmol 1967;78:35–43.
14. Jonas JB, Gusek GC, Naumann GO. Optic disc, cup and neuroretinal rim size, configuration and correlations in normal eyes. Invest Ophthalmol Vis Sci 1988;29:1151–1158.
15. Tsai CS, Zangwill L, Gonzalez C, et al. Ethnic differences in optic nerve head topography. J Glaucoma 1995;4:248–4257.
16. Saruhan A, Orgul S, Kocak I, Prunte C, Flammer J. Descriptive information of topographic parameters computed at the optic nerve head with the Heidelberg retina tomograph. J Glaucoma 1998;7:420–429.
17. Caprioli J, Miller JM. Optic disc rim area is related to disc size in normal subjects. Arch Ophthalmol 1987;105:1683–1685.
18. Jonas JB, Gusek GC, Guggenmoos-Holzmann I, Naumann GO. Variability of the real dimensions of normal human optic discs. Graefes Arch Clin Exp Ophthalmol 1988;226:332–336.
19. Budde WM, Jonas JB, Martus P, Grundler AE. Influence of optic disc size on neuroretinal rim shape in healthy eyes. J Glaucoma 2000;9:357–362.
20. Britton RJ, Drance SM, Schulzer M, Douglas GR, Mawson DK. The area of the neuroretinal rim of the optic nerve in normal eyes. Am J Ophthalmol 1987;103:497–450.
21. Bengtsson B. The variation and covariation of cup and disk diameters. Acta Ophthalmol 1981;59:1–14.
22. Funk J, Dieringer T, Grehn F. Correlation between neuroretinal rim area and age in normal subjects. Graefes Arch Clin Exp Ophthalmol 1989;227:544–548.
23. Moya FJ, Brigatti L, Caprioli J. Effect of aging on optic nerve appearance: a longitudinal study. Br J Ophthalmol 1999;83:567–572.
24. Tsai CS, Ritch R, Shin DH, Wan JY, Chi T. Age-related decline of disc rim area in visually normal subjects. Ophthalmology 1992;99:29–35.
25. Leibowitz HM, Krueger DE, Maunder LR. The Framingham Eye Study monograph. Surv Ophthalmol 1980;24(suppl):335–610.

26. Quigley HA, Brown AE, Morrison JD, Drance SM. The size and shape of the optic disc in normal human eyes. Arch Ophthalmol 1990;108:51–57.
27. Dichtl A, Jonas JB, Mardin CY. Comparison between tomographic scanning evaluation and photographic measurement of the neuroretinal rim. Am J Ophthalmol 1996;121:494–501.
28. Rohrschneider K, Burk RO, Volcker HE. Comparison of two laser scanning tomography systems for three-dimensional analysis of the optic papilla. Ophthalmology 1993;90:613–619.
29. Hatch WV, Trope GE, Buys YM, Macken P, Etchells EE, Flanagan JG. Agreement in assessing glaucomatous discs in a clinical teaching setting with stereoscopic disc photographs, planimetry, and laser scanning tomography. J Glaucoma 1999;8:99–104.
30. Bartz-Schmidt KU, Weber J, Heimann K. Validity of two-dimensional data obtained with the Heidelberg Retina Tomograph as verified by direct measurements in normal optic nerve heads. Ger J Ophthalmol 1994;3:400–405.
31. Mikelberg FS, Drance SM, Schulzer M, Yidegiligne HM, Weis MM. The normal human optic nerve. Axon count and axon diameter distribution. Ophthalmology 1989;96:1325–1328.
32. Jonas JB, Schmidt AM, Muller-Bergh JA, Schlotzer-Schrehardt UM, Naumann GO. Human optic nerve fiber count and optic disc size. Invest Ophthalmol Vis Sci 1992;33:2012–2018.
33. Kanamori A, Escano MFT, Eno A, et al. Evaluation of the effect of aging on retinal nerve fiber layer thickness measured by optical coherence tomography. Ophthalmologica 2003;217:273–278.
34. Uchida H, Brigatti L, Caprioli J. Detection of structural damage from glaucoma with confocal laser image analysis. Invest Ophthalmol Vis Sci 1996;37:2393–2401.
35. Jonas JB, Fernandez MC, Sturmer J. Pattern of glaucoma neuroretinal rim loss. Ophthalmology 1993;100:63–68.
36. Funaki S, Shirakashi M, Yaoeda K, et al. Sensitivity and specificity of glaucoma detection in the Japanese population using scanning laser polarimetry. Br J Ophthalmology 2002;86:70–74.
37. Iwase A, Kitazawa Y. Ohno Y. On age-related norms of the visual field. Jpn J Ophthalmol 1988;32:429–437.