Showa Univ J Med Sci **22**(4), 229～237, December 2010

Original

Age-Specific Prevalence of Glaucoma is Determined by the Presence of Refractive Errors Among Japanese Workers

AkiraYAMAZAKI[1], Masayuki TATEMICHI[2], Tadashi NAKANO[3], Miho ARATAKE[1], Toshio NAKADATE[2] and Minoru SUGITA[1]

Abstract: To develop appropriate glaucoma mass screening programs for occupational health among Japanese workers, we estimated the prevalence of glaucoma and the increase rate by age. A total of 10,579 Japanese general workers (men / women = 9292 / 1287) underwent frequency doubling technology (FDT) perimetry testing. Visual field abnormalities (VFA) were identified by the FDT-based glaucoma screening protocol (FDT-VFA). Subjects with FDT-VFA were ophthalmologically diagnosed and classified as "normal," "glaucomatous VFA" (preperimetric, suspicious, and definitive glaucoma) or "other ocular diseases." Prevalence of FDT-VFA and positive predictive values for "glaucomatous VFA" and "definitive glaucoma" were calculated by five-year age intervals, and then the prevalence of "glaucomatous VFA" and "definitive glaucoma" in each age interval was estimated. Prevalence of "glaucomatous VFA" and "definitive glaucoma" in workers younger than 30 years old was approximately 1.5% and 0.5%, respectively. Interestingly, the increase in prevalence of glaucoma by age was significantly different between workers with and without refractive errors (RE). From ages 30 to 55 years, the estimated prevalence of "definitive glaucoma" linearly increased with a regression coefficient (% / age in years) that was 2.5-fold higher in subjects with RE than in those without RE {regression coefficient = 0.131 [95% confidence interval (CI) = 0.109, 0.152; $R^2 = 0.980$] vs. 0.047 [95% CI = 0.026, 0.068; $R^2 = 0.869$] for subjects with RE vs. those without RE, respectively}. Further, among workers older than 55 years, the prevalence of glaucoma continued increasing in workers with RE, whereas it plateaued in those without RE. From these estimates, we propose that FDT testing should be conducted as follows: 1) once in workers under the age of 30 years, 2) according to both age and the presence of RE in 30–55 years old, and 3) by age only in those over 55 years old.

Key words: glaucoma, screening, FDT, visual field abnormality, refractive errors

[1] *Department of Environmental and Occupational Health, Toho University School of Medicine,* 5-21-16 Omorinishi, Ota-ku, Tokyo 143-8540, Japan.
[2] *Department of Hygiene and Preventive Medicine, Showa University, School of Medicine.*
[3] *Department of Ophthalmology, Jikei University School of Medicine.*

Introduction

Glaucoma is a common disease, for which the prevalence increases with age. Prevention of visual field defects is thus an important public health issue among aging societies. However, the majority (approximately 50%–90%) of glaucoma sufferers remain untreated, particularly those with primary open angle glaucoma (POAG)[1–3]. likely due to the lack of obvious symptoms or screening[4]. Most public health specialists consider that mass screening programs should be implemented, however, the suitable ages and proper interval have not been clearly defined.

Indications for mass screening appear clearer among Japanese, as a large portion of Japanese patients have normal tension glaucoma (NTG). A large-scale survey for NTG showed that further reductions in ocular pressure via medication could prevent the development of visual field abnormalities (VFA)[5]. Nevertheless, although the value of mass screening programs for NTG appears stronger in Japan than in other countries, information is still lacking about optimum age and interval of the screening.

It is estimated that at least 2–3% of workers in the occupational health field have glaucoma[3, 6]. We demonstrated in a previous study that screening using visual field testing with frequency doubling technology (FDT) perimetry is very effective at detecting glaucoma among Japanese general workers[6], with a positive predictive value (PPV) for detecting definitive glaucoma or glaucoma including a preperimetric stage of approximately 40% and $>70\%$, respectively, indicating a high sensitivity for definitive glaucoma when prevalence is considered. These values reflect that the test subjects were relatively young, healthy workers with a lower general prevalence of illnesses such as diabetes mellitus and cataracts. This in turn raises the question of the optimum age at which FDT testing should be performed.

To facilitate the development of a mass-screening program by FDT testing, we analyzed data from our previous large-scale study to estimate the prevalence of glaucoma and the correlation of increased incidence with age among Japanese workers.

Materials and Methods

Study design

Details of our study population and protocols for the FDT test and diagnosis for glaucoma have been described in our previous study[6]. Briefly, FDT-VFAs were determined using the FDT glaucoma screening protocol (FDT-GSP). This protocol consisted of two algorithms, reproducibility and decision. Reproducibility was determined by immediately conducting a retest upon detection of any VFA in the initial FDT test. A positive result was noted in the reproducibility algorithm if the VFAs ascertained in the retest were the same as or close to those identified in the initial test. A positive result was noted in the decision algorithm if the FDT results showed one or more VFAs with a mild relative loss located within the four central spots on the nasal side of the eye, two or more VFAs in

any location, or one or more VFAs with moderate or severe relative loss in any location. The presence of refractive errors (RE) (use of eyeglasses or contact lenses) was based on self-reporting. The study was approved by the Ethics Committee of Showa University.

Study subjects

The dataset of our previous study[6] provided both RE information and FDT perimetry testing results of 11,010 people (mean age ± SD : 44.7 ± 10.4 years ; men / women = 9683 / 1327) who were mainly workes for electronics and steel industries. Of these, 431 subjects had either another ocular disease or unreliable FDT test results and were not used for this study. Among the remaining 10,579 people (mean age ± SD : 44.6 ± 10.4 years ; men / women = 9292 / 1287), 10138 had normal FDT test results and 441 had FDT-VFAs.

Ophthalmologic diagnosis

Subjects with FDT-VFAs were ophthalmologically examined and classified into one of four categories for glaucoma : "normal", "preperimetric", "suspicious", or "definitive". If a patient had a non-glaucoma ocular disease, based on results of a complete ophthalmologic examination and perimetric results, they were classified under "other ocular diseases". In this study, "glaucomatous VFA" was defined in subjects who were "preperimetric", "suspicious", or who had "definitive" glaucoma. Subjects with abnormal glaucomatous disk findings (cup-to-disk ratio >0.7, presence of disk hemorrhage, notching in the disk, nerve fiber bundle defects, or peripapillary atrophy), but without VFAs as assessed by standard perimetric tests, were classified as "preperimetric". In principle, VFAs are defined based on the results of the Humphrey Field Analyzer 30-2 test (HFA ; Carl Zeiss Meditec Dublin, CA, USA). The present study, however, included subjects diagnosed by Octopus perimetry (Interzeag, Schlieren, Switzerland). "Suspicious" glaucoma was diagnosed using the HFA, according to Anderson's modified criteria[7], under any of the following situations : when the pattern deviation probability plot showed a cluster of three or more non-edge points ; when the pattern standard deviation or corrected pattern standard deviation was less than 0.05, or when the results of a glaucoma hemi-field test fell outside the normal limits. If HFA results satisfied all three of the above criteria, the subject was diagnosed with "definitive" glaucoma. With regard to the Octopus perimetry test, "suspicious" glaucoma was diagnosed under any of the following situations : when three adjacent points were depressed by 5 dB, with one point depressed by at least 10 dB ; when two adjacent points were depressed by 10 dB ; or, when a 10 dB difference across the nasal horizontal meridian was demonstrated for two adjacent points[8]. If Octopus perimetry results satisfied all three of these criteria, a subject was diagnosed with "definitive" glaucoma.

Statistical analysis

The chi-squared test was used to determine statistical significance among categorized data.

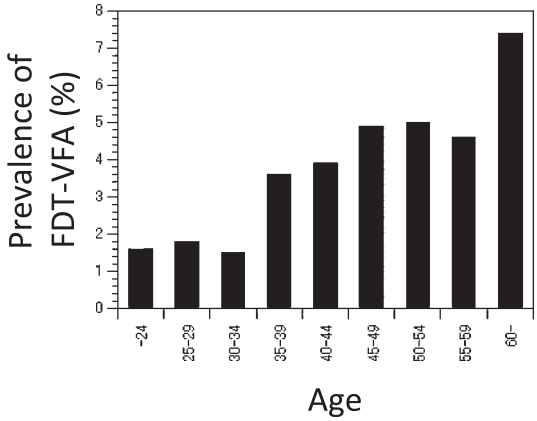

Fig. 1. Prevalence of visual field abnormalities by frequently doubling technology perimetry testing separated into five-year age intervals. FDT-VFA (visual field abnormalities by frequently doubling technology perimetry test) was determined by the FDT-glaucoma screening protocol.

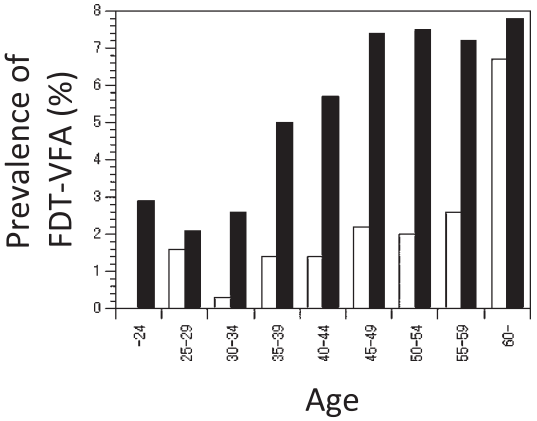

Fig. 2. Prevalence of visual field abnormalities by the frequently doubling technology perimetry test (FDT-VFA) separated into five-year age intervals and the presence of refractive errors (RE). ■; RE+, □; RE−

Student's-t test was used to determine statistical significance between subjects with and without RE. Regression coefficients and 95% confidence intervals were calculated for subjects from ＞25 to 54 years old and for those from 50 to over 60 years old. All statistical analyses were performed using SPSS version 17.0 (SPSS Inc, Tokyo, Japan). Values were considered statistically significant at $P < 0.05$.

Results

The rate of FDT-VFA by stratification of age into five-year intervals is shown in Fig. 1. The rate of FDT-VFA remained about 2% among workers under 35 years, increased two fold among workers between 35 and 50 years old , and stopped increasing among workers between 50 and 60 years old. Subjects older than 60 years showed the highest rate of FDT-VFA.

Interestingly, the rate of FDT-VFA increased until age 55 only among subjects with RE (n ＝5936), but not among those without RE (n＝4643) (Fig. 2). After age 60, the rate of FDT-VFA did not differ significantly between subjects with and without RE.

The positive predictive value (PPV) of each five-year interval was calculated based on the result of the ophthalmologic examinations (Table 1). The PPV of "glaucomatous VFA" among workers with RE was significantly higher than in those without RE (69.7% vs. 55.8%, $P < 0.05$).

Fig. 3 shows the estimated prevalence of "glaucomatous VFA" and "definitive glaucoma" among subjects separated into those with and without RE. Workers younger than 30 years show a 1.5% and 0.5% rate of "glaucomatous VFA" and "definitive glaucoma", respectively.

Table 1. Distribution of ophthalmologic diagnosis and positive predictive value for "glaucomatous VFA" and "definitive glaucoma"

	Subjects without refractive errors						Subjects with refractive errors					
age	n	Normal (%)	Preperimetric+ Suspicious (%)	Definitive glaucoma PPV(%)	Glaucomatous VFA PPV(%)	Others (%)	n	Normal (%)	Preperimetric+ Suspicious (%)	Definitive glaucoma PPV(%)	Glaucomatous VFA PPV(%)	Others (%)
-24	n.d	n.d	n.d	n.d	n.d	n.d	1	0	0	100	100	0
25-29	3	33.3	33.3	0	33.3	33.3	4	0	50	25	75	25.1
30-34	1	100	0	0	0	0	12	8.3	41.7	41.7	83.4	8.3
35-39	6	33.3	16.7	33.3	50	16.7	35	17.1	22.9	40	62.9	20
40-44	8	12.5	37.5	25	62.5	25	51	11.8	37.3	37.3	74.6	13.7
45-49	16	18.8	6.3	50	56.3	25	63	12.7	20.6	44.4	65	22.2
50-54	15	13.3	6.7	60	56.7	20	56	7.1	25	48.2	73.2	19.6
55-59	15	20	26.7	40	66.7	13.3	40	12.5	30	37.5	67.5	20
60-	22	4.5	13.6	31.8	45.5	50	18	0	27.8	44.4	72.2	27.8
Total	86	16.3	16.3	39.5	55.8	27.9	280	10.7	27.9	41.8	69.7	19.6

VFA, visual field abnormality ; PPV, positive predictive value ; n.d, not determined
Glaucomatous VFA includes "preperimetric", "suspicious," and "definitive" glaucoma

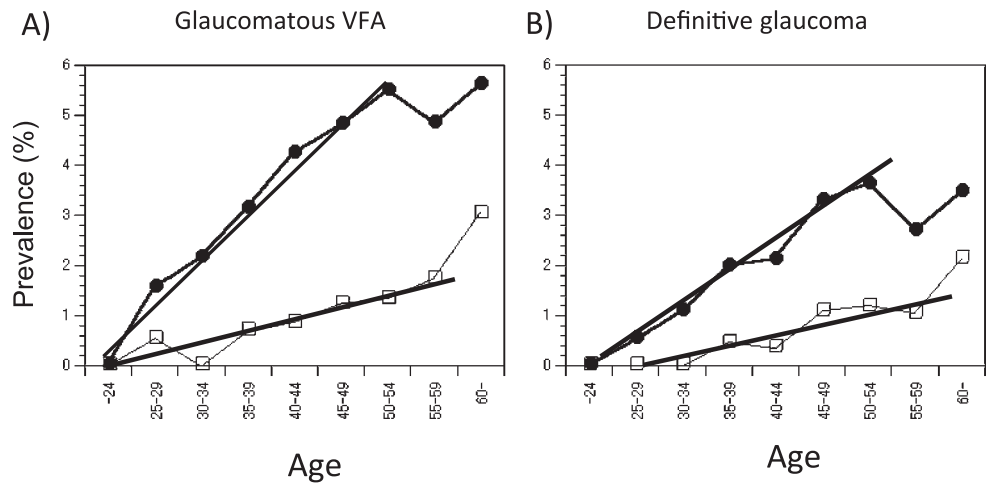

Fig. 3. Prevalence of "glaucomatous visual field abnormalities (glaucomatous VFA)" and "definitive glaucoma" by five-year age intervals and the presence of refractive errors (RE). The prevalence of "glaucomatous VFA" and "definitive glaucoma" were estimated using age-specific positive predictive values for them. "Glaucomatous VFA" includes "preperimetric", " suspicious," and "definitive" glaucoma. ●; RE+, □; RE-

The increasing trend was significantly different between workers with and without RE. Among workers aged 30-55 years, those with RE showed an increasing, strictly linear trend ($R^2 = 0.962$ and 0.980, "glaucomatous VFA" and "definitive glaucoma", respectively). The regression coefficients and 95% CIs were calculated as shown in Table 2. Regression coefficients of "glaucomatous VFA" and "definitive glaucoma" among workers with RE were

Table 2. Increase rate in the prevalence of glaucomatous VFA and definitive glaucoma

	Age	Subjects without refractive errors				Subjects with refractive errors			
		Regression Coefficient (% / years)	95%CI		R^2	Regression Coefficient (% / years)	95%CI		R^2
Glaucomatous VFA	(−24)～(50−54)	0.047	0.021	0.073	0.816	0.186	0.144	0.229	0.962
Definitive glaucoma		0.047	0.026	0.068	0.869	0.131	0.109	0.152	0.980
Glaucomatous VFA	(50−54)～	0.207	−1.194	1.609	0.780	−0.002	−1.368	1.365	0
Definitive glaucoma		0.102	−1.37	1.574	0.436	−0.043	−1.579	1.492	0.115

VFA, visual field abnormality ; CI, confidence interval
Glaucomatous VFA includes "preperimetric", "suspicious", and "definitive" glaucoma

two to three-fold higher than those among workers without RE, with statistical significance (0.186 vs. 0.047 and 0.131 vs. 0.047), respectively. Among workers older than 55 years, only those without RE showed an increasing trend in the prevalence of "glaucomatous VFA" and "definitive glaucoma" with age.

To examine whether RE were myopic, we investigated spherical power among subjects with FDT-VFA. Among subjects with RE and FDT-VFA, 93.3% (249 / 267) showed minus dioptors, and respective mean ± standard deviation (SD) of spherical power in the right / left eye by age was > 40 years : −6.9 ± 3.5 / −6.8 ± 3.5 (n = 48), 40−49 years : −5.9 ± 3.0 / −5.7 ± 3.2 (n = 106), and 50 years : −4.8 ± 4.0 / −4.3 ± 3.8 (n = 113), indicating that RE were mainly myopic.

Discussion

This cross-sectional study indicated that subjects with and without RE show a markedly different trend in the increasing prevalence of glaucoma. In workers with RE, prevalence increased linearly to age 55 and plateaued thereafter. Until age 55, the regression coefficient was two to three times higher among subjects with RE than among those without RE, then, after age 55, the prevalence of glaucoma increased markedly only in subjects without RE.

Based on these trends, we can approximate the optimum age of screening. Because the prevalence of workers with "glaucomatous VFA" and "definitive glaucoma" aged less than 30 years was 1.5% and 0.5%, respectively, workers in this age group require a single FDT testing. In contrast, the frequency of testing should depend on both age and the presence of RE in people aged 30-55 years, given the marked increase in the prevalence of glaucoma in workers of this age with RE. Frequency of testing should depend on age only for people > 55 years of age.

Several large-scale epidemiological studies have shown that myopia is a significant risk factor for POAG[9−13]. The Blue Mountains Eye Study reported that the relative risk for mild

myopia and moderate-severe myopia was 2.3 and 3.3, respectively[14]. In addition, the role of myopia as the most important risk factor for NTG in Japanese has been clearly demonstrated[10]. The result from that study showed that the presence of RE among subjects with FDT-VFA was closely related to myopia, supporting the suggested relationship between myopia and NTG. However, the basic mechanisms underlying such a relationship remain largely unknown. Myopic eyes have anatomically weak discs, reduced blood flow, and low ocular pulse amplitude, possibly resulting in ischemia or damage due to the changes in intraocular pressure. Nonetheless, some studies have reported no significant association between myopia and glaucoma[15-18] and, recently, between myopia and the progression of visual field defects among NTG patients after treatment[19]. We believe that this reflects the mean age of the subjects in these studies (approximately 60 years) at the start of the follow-up. In contrast, the present data suggest that the effect of myopia on glaucoma depends on age, particularly before age 60.

A more comprehensive understanding of the effect of myopia on the progression of glaucomatous VFA may require the investigation of a broader age spectrum and the possible differences among patients in disease pathology. Myopia, for example, may be an important risk factor for some subtypes of glaucoma (myopia-related glaucoma), but not others, while the onset of myopia-related glaucoma might occur earlier than that of myopia-unrelated glaucoma. It is therefore possible that myopia-unrelated glaucoma was more prevalent among our subjects older than 60 years, and increased in an age-dependent manner in workers without RE.

Given the high prevalence and chronicity of glaucoma, and the high associated treatment costs, any evaluation of mass screening should include the medical-economic benefits. Earlier detection of glaucoma raises treatment costs while later detection impairs quality of life, highlighting the importance of appropriate screening levels. Among our subjects with glaucomatous discs, comparison of changes in standard perimetry between those with and without FDT-VFA showed that progression was more rapid among subjects with FDT-VFA (Nakano's unpublished data). In addition, our study population demonstrated a high PPV for glaucoma[6]. Thus, a large portion of the VFA cases determined by FDT testing in Japanese workers were associated with glaucoma. Considering the current medical-economic background and screening capability, detection of severe cases at the early stage of "definitive glaucoma" is crucial. Further, given that the FDT-GSP algorithm has been confirmed to demonstrate the appropriate screening level[6], we consider that glaucoma mass screening using FDT-GSP is beneficial from an occupational health perspective. With regard to VFA of POAG, these are known to progress slowly, highlighting the importance of avoiding false-positive diagnoses. Another study reported that the FDT test has high specificity and moderate sensitivity for glaucoma screening, indicating its suitability for glaucoma mass screening among general Japanese workers[20].

In this study, the prevalence of "definitive glaucoma" could be underestimated, because it

was calculated on the basis of the FDT test results, which did not show 100% sensitivity (early stage = 83.3%, moderate to severe stage = 100%) for detecting "definitive glaucoma"[6]. The true prevalence of "definitive glaucoma" could be obtained by dividing values by the FDT test sensitivity.

Several limitations of this study warrant mention. First, the study was conducted under a cross-sectional design, and determining the optimum frequency of FDT-based screening will require a follow-up study to investigate the needs of affected individuals over time. Second, we were unable to obtain complete information on the ophthalmological diagnosis for all subjects with FDT-VFA, and thus self-selection bias might have resulted in an overestimation of PPV for "definitive glaucoma" Third, we did not determine RE in all subjects using an autorefractometer. Fourth, few female data were available. Considering these limitations, further follow-up studies are warranted.

This study showed that the trend in increasing prevalence of glaucoma differs markedly between subjects with and without RE, and it is particularly rapid in those with RE of 30–55 years of age. FDT testing should be conducted once before age 30, according to age and the presence of myopia from 30 to 55 years old, and according to age only in those aged over 55 years old. In addition, workers with myopia should undergo FDT testing more frequently than those without. These findings highlight the importance of mass screening for VFA as an indicator of glaucoma.

References

1) Quigley HA and Vitale S: Models of open-angle glaucoma prevalence and incidence in the United States. *Invest Ophthalmol Vis Sci* **38**: 83–91 (1997)
2) Bonomi L, Marchini G, Marraffa M, Bernardi P, De Franco I, Perfetti S, Varotto A and Tenna V: Prevalence of glaucoma and intraocular pressure distribution in a defined population. The Egna-Neumarkt Study. *Ophthalmology* **105**: 209–215 (1998)
3) Iwase A, Suzuki Y, Araie M, Yamamoto T, Abe H, Shirato S, Kuwayama Y, Mishima HK, Shimizu H, Tomita G, Inoue Y, Kitazawa Y and Tajimi Study Group, Japan Glaucoma Society: The prevalence of primary open-angle glaucoma in Japanese: the Tajimi Study. *Ophthalmology* **111**: 1641–1648 (2004)
4) Tatemichi M, Nakano T, Hayashi T, Tanaka K, Hiro H, Miyamoto T, Aratake M, Nishinoue N, Yamazaki A, Nakadate T and Sugita M: Symptoms related to glaucomatous visual field abnormalities among male Japanese workers in a population-based setting. *Acta Ophthalmol* (2010) (in press)
5) The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Collaborative Normal-Tension Glaucoma Study Group. *Am J Ophthalmol* **126**: 498–505 (1998)
6) Tatemichi M, Nakano T, Tanaka K, Hayashi T, Nawa T, Miyamoto T, Hiro H, Iwasaki A, Sugita M and Glaucoma Screening Project (GSP) Study Group: Performance of glaucoma mass screening with only a visual field test using frequency-doubling technology perimetry. *Am J Ophthalmol* **134**: 529–537 (2002)
7) Anderson DR and Patella VM: Automated Static Perimetry. 2nd ed, St. Louis, Mosby (1999)
8) Iester M, Mermoud A and Schnyder C: Frequency doubling technique in patients with ocular hypertension and glaucoma: correlation with octopus perimeter indices. *Ophthalmology* **107**: 288–294 (2000)
9) Hyung SM, Kim DM, Hong C and Youn DH: Optic disc of the myopic eye: relationship between refractive errors and morphometric characteristics. *Korean J Ophthalmol* **6**: 32–35 (1992)
10) Suzuki Y, Iwase A, Araie M, Yamamoto T, Abe H, Shirato S, Kuwayama Y, Mishima HK, Shimizu H, Tomita

G, Inoue Y, Kitazawa Y and Tajimi Study Group : Risk factors for open-angle glaucoma in a Japanese population : the Tajimi Study. *Ophthalmology* **113** : 1613-1617 (2006)
11) Quigley HA, Enger C, Katz J, Sommer A, Scott R and Gilbert D : Risk factors for the development of glaucomatous visual field loss in ocular hypertension. *Arch Ophthalmol* **112** : 644-649 (1994)
12) Wong TY, Klein BE, Klein R, Knudtson M and Lee KE : Refractive errors, intraocular pressure, and glaucoma in a white population. *Ophthalmology* **110** : 211-217 (2003)
13) Wu SY, Nemesure B and Leske MC : Refractive errors in a black adult population : the Barbados Eye Study. *Invest Ophthalmol Vis Sci* **40** : 2179-2184 (1999)
14) Mitchell P, Hourihan F, Sandbach J and Wang JJ : The relationship between glaucoma and myopia : the Blue Mountains Eye Study. *Ophthalmology* **106** : 2010-2015 (1999)
15) Leske MC, Heijl A, Hyman L, Bengtsson B, Dong L, Yang Z and EMGT Group : Predictors of long-term progression in the early manifest glaucoma trial. *Ophthalmology* **114** : 1965-1972 (2007)
16) AGIS Investigators : The Advanced Glaucoma Intervention Study (AGIS) : 12. Baseline risk factors for sustained loss of visual field and visual acuity in patients with advanced glaucoma. *Am J Ophthalmol* **134** : 499-512 (2002)
17) Drance S, Anderson DR, Schulzer M and Collaborative Normal-Tension Glaucoma Study Group : Risk factors for progression of visual field abnormalities in normal-tension glaucoma. *Am J Ophthalmol* **131** : 699-708 (2001)
18) Nicolela MT, Walman BE, Buckley AR and Drance SM : Various glaucomatous optic nerve appearances. A color Doppler imaging study of retrobulbar circulation. *Ophthalmology* **103** : 1670-1679 (1996)
19) Sohn SW, Song JS and Kee C : Influence of the extent of myopia on the progression of normal-tension glaucoma. *Am J Ophthalmol* **149** : 831-838 (2010)
20) Iwase A, Tomidokoro A, Araie M, Shirato S, Shimizu H, Kitazawa Y and Tajimi Study Group : Performance of frequency-doubling technology perimetry in a population-based prevalence survey of glaucoma : the Tajimi study. *Ophthalmology* **114** : 27-32 (2007)

[Received October 25, 2010 : Accepted November 30, 2010]