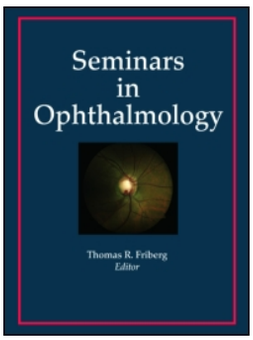

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Prevalence and Risk Factors for Polypoidal Choroidal Vasculopathy in a General Japanese Population: The Hisayama Study

Kohta Fujiwara[1,2,3], Miho Yasuda[2], Jun Hata[1,4], Yuji Oshima[2], Sawako Hashimoto[1,2], Takeshi Yoshitomi[3], Yutaka Kiyohara[5], Tatsuro Ishibashi[2], Toshiharu Ninomiya[1,4], and Koh-Hei Sonoda[2]

[1]Department of Epidemiology and Public Health, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, [2]Department of Ophthalmology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, [3]Department of Ophthalmology, Graduate School of Medical Sciences, Akita University, Akita, Japan, [4]Center for Cohort Studies, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, and [5]Hisayama Research Institute for Lifestyle Diseases, Fukuoka, Japan

ABSTRACT

Purpose: To estimate the prevalence and risk factors for polypoidal choroidal vasculopathy (PCV) in a general Japanese population. *Methods*: This population-based, cross-sectional study was conducted in 2007 with subjects from the Hisayama Study. Of the 3,648 residents in Hisayama, Japan, 2,663 who were ≥ 50 years old were enrolled in this study. The characteristics of PCV were determined by fundus examination or based on indocyanine green and fluorescein angiographic findings. We evaluated the contributions of the risk factors for PCV. *Results*: Among the 207 participants with age-related macular degeneration (AMD), 174 (6.5%) had early AMD, and 33 (1.2%) had late AMD, including 10 participants with PCV (0.4%). Male and smoking habit were significant risk factors for the development of PCV. *Conclusions*: The prevalence of PCV is higher among Japanese subjects than Caucasians in Western countries. Male gender and smoking habit were significant risk factors for PCV in a general Japanese population.

Keywords: Polypoidal choroidal vasculopathy, age-related macular degeneration, population-based study, risk factors, prevalence

INTRODUCTION

Age-related macular degeneration (AMD) is a major cause of irreversible visual impairment and blindness in older people in developed countries.[1] We have reported that the 5- and 9-year incidences of early and late AMD in the general Japanese population have increased[2,3] and could reach the same level as that for Caucasian populations. Further, by its very nature, the incidence of AMD is likely to increase as the numbers of aged individuals increase worldwide.

Among Japanese and other Asian populations, more men than women suffer from AMD, and the frequency of patients with polypoidal choroidal vasculopathy (PCV) is higher in individuals with late AMD.[4–6] Moreover, the prevalence of neovascular AMD and geographic atrophy (GA) among patients with late AMD increases with advancing age.[7,8] Because information on the prevalence of PCV in a general population is scarce,[9] it is worthwhile to clarify the prevalence and risk factors of PCV. These data are necessary to better understand the mechanism and prevention of PCV. We conducted the present study to examine the prevalence

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Correspondence: Miho Yasuda, Department of Ophthalmology, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. E-mail: miho-m@info.med.kyushu-u.ac.jp

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and risk factors of PCV in a general Japanese population.

METHODS

Study Population

The Hisayama Study is an ongoing, long-term, cohort study on cardiovascular disease and its risk factors in the town of Hisayama, which adjoins Fukuoka City, a metropolitan area in southern Japan.[10] As a part of the present study, we performed a cross-sectional survey of eye diseases. In 2007, among the 3,648 residents of Hisayama, 2,663 individuals (1,158 men, 1,505 women, aged ≥ 50 years, 73.0% of the original cohort) were enrolled in the present study.

Ophthalmic Examination and Definition of Age-Related Maculopathy

The methods used for the eye examination have been described in detail.[11,12] Briefly, each participant underwent an ophthalmic examination after pupil dilatation with 1.0% tropicamide and 10% phenylephrine. Fundus photographs (45°) were taken using a Topcon TRC NW-6SF fundus camera (Topcon, Tokyo), and 35-mm color transparencies were made using Fujichrome slide film (Sensia II; Fujifilm, Tokyo). One field per eye was photographed. Both examinations used a similar, masked photographic grading technique based on the International Age-related Maculopathy Epidemiological Study Group grading protocol and the grids of the Wisconsin Age-related Maculopathy Grading System.[13,14] The grid system was adapted to the magnification of the camera.

This protocol divided AMD into early and late stages. Early-stage AMD was defined by the presence of large drusen (soft distinct and indistinct) or retinal pigment epithelium pigmentary abnormalities (hyperpigmentation or hypopigmentation)[13] within the grid in the absence of late AMD in either eye. Late-stage AMD was defined as the presence of neovascular AMD, GA, or PCV. Neovascular AMD included serous or hemorrhagic detachment of the retinal pigment epithelium or sensory retina, and the presence of subretinal pigment epithelium hemorrhages or subretinal fibrous scar tissue.[14] GA was characterized by sharply edged, roughly round or oval areas of retinal pigment epithelium hypopigmentation, with clearly visible choroidal vessels.[14] The minimum area of GA was a circle ≥ 175 μm in diameter.

Figure 1 shows the flow of participants through the study and the diagnostic process. A total of 2,663 residents underwent the screening eye examinations including the fundus photograph, and 207 of them had features of some form of AMD. Among these 207 subjects, 164 subjects were diagnosed with early AMD because they had no features of late AMD. The remaining 43 subjects underwent the fundus photograph examination using fluorescein angiography/indocyanine green angiography (FA/ICGA) because one or both of their eyes were suspected to have the features of late AMD. The FA/ICGA examination was performed at Kyushu University Hospital using the Heidelberg Retina Angiograph 2 (HRA 2; Heidelberg Engineering, Heidelberg, Germany).

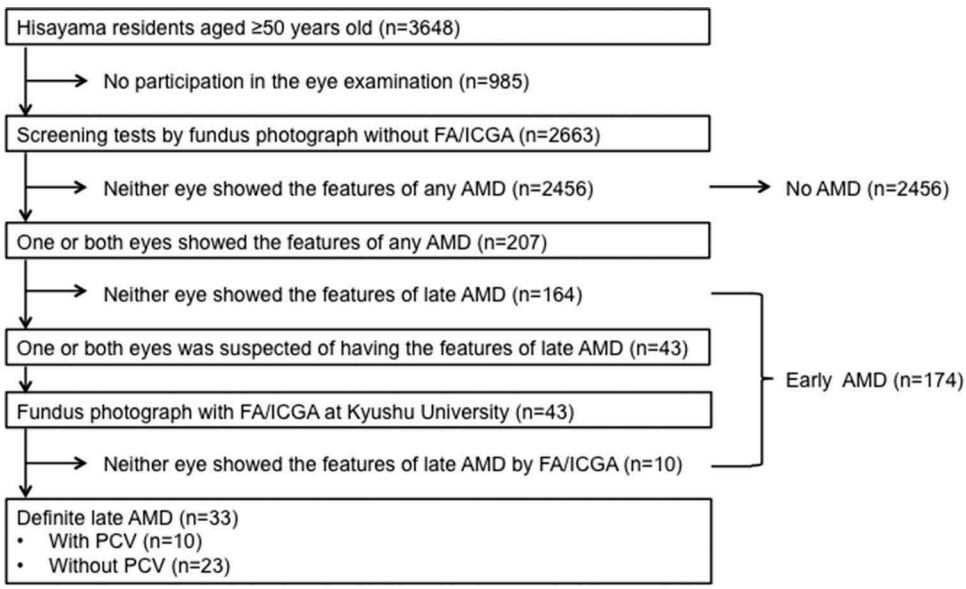

FIGURE 1. Flow of participants through the Hisayama Study.

Finally, 33 patients were diagnosed as having definite late AMD and the remaining 10 were diagnosed as having early AMD because they had no features of late AMD by the FA/ICGA examination.

We diagnosed PCV based on the presence of elevated orange-red lesions (excluding pigment epithelial detachment, choroidal hemangioma, and subretinal blood) observed in the fundus examination or on the indocyanine green and fluorescein angiographic findings.[15] Three experienced graders (authors MY, TI, OY), masked to the subject information, assessed the AMD. Interobserver and intraobserver variability were analyzed, and the levels of agreement among the graders were 0.80 and 0.86 for most features. Finally, for cases in which there was disagreement in diagnosis, discussion among the graders was used to resolve the disagreement.

Data Collection

Blood pressure was measured three times after the participant had rested for ≥ 5 min in the sitting position. The average of the three measurements was used for the analysis. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg, diastolic blood pressure (DBP) ≥ 90 mmHg, or current use of antihypertensive medication. Blood samples were collected from an antecubital vein after an overnight fast of ≥ 12 hr. After the fasting blood specimen was obtained, an oral glucose tolerance test was performed with a 75-g glucose equivalent carbohydrate load (Trelan G; Shimizu Pharmaceutical, Shimizu, Japan) for most of the participants. Diabetes was defined as a fasting plasma glucose level ≥ 7.0 mmol/L, a 2-hr postloading glucose level or postprandial glucose level ≥ 11.1 mmol/L, or a medical history of diabetes.

Serum total cholesterol and high-density lipoprotein (HDL) cholesterol levels were determined enzymatically using an autoanalyzer (TBA-80S; Toshiba, Tokyo). Information on smoking habit and alcohol intake was obtained by trained interviewers using a standard questionnaire at the initial examination. Smoking habit and alcohol intake were classified as current habitual use or non-habitual use. Each participant's body height and weight were measured when the participant was in light clothing without shoes, and the body mass index (BMI; kg/m^2) was calculated.

Statistical Methods

The SAS software package (ver. 9.4, SAS, Cary, NC, USA) was used to perform all statistical analyses. Two-sided values of $P < 0.05$ were considered significant. We determined the prevalence of pigmentary abnormalities, drusen, GA, neovascularization, and PCV, and then analyzed the risk factors for each subtype of AMD. We considered the following 13 possible risk factors for PCV: age, sex, SBP, DBP, hypertension, diabetes, total cholesterol, HDL cholesterol, waist circumference, BMI, smoking habit, alcohol intake, and history of cardiovascular disease. Age, SBP, DBP, total cholesterol, HDL cholesterol, waist circumference, and BMI were treated as continuous variables and the others as categorical variables. Each categorical variable was coded as either 1 or 0 depending on the presence or absence of the factor. Mean values were compared by Student's *t*-test and frequencies were compared by the chi-square test.

The comparison of mean values between the healthy participants (i.e., those without AMD) and each lesion of the participants with early and late AMD was done by the Dunett's test for multiple comparisons. Differences in frequencies were compared using the chi-square test or Fisher's exact test with Bonferroni's correction for multiple comparisons. We estimated the age- and sex-adjusted odds ratio (OR) and 95% confidence interval (CI) of each potential risk factor by performing a logistic regression analysis.

Ethical Considerations

This study was approved by the Human Ethics Review Committee of the Kyushu University Graduate School of Medical Sciences, and was carried out in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

RESULTS

The mean values or frequencies of potential risk factors for AMD categorized by the sex of the participants were assessed (Table 1). The values for DBP, BMI, waist circumference, and frequencies of hypertension, diabetes, current smoking, current drinking, and history of cardiovascular disease were significantly higher for the men compared to the women. Total cholesterol and HDL cholesterol were higher for the women compared to the men. There were no significant differences in the mean values of age or SBP between the men and women.

A total of 207 of the 2,663 participants had AMD (Table 2). Late AMD was present in 33 participants (1.2%), including 10 participants with PCV (0.4%). Early AMD was present in 174 participants (6.5%). There was no significant difference in the prevalence of early AMD between the men and women; nor was there a gender difference in the prevalence of drusen. However, the prevalence of retinal pigmentary abnormalities was significantly higher in the men than the women.

TABLE 1. Characteristics of the Hisayama study (2007) subjects by sex.

Variable	Men (n = 1,158)	Women (n = 1,505)	P-Value
Age, years	66 ± 10	67 ± 11	0.09
Systolic blood pressure, mmHg	134 ± 18	133 ± 19	0.08
Diastolic blood pressure, mmHg	81 ± 10	79 ± 10	< 0.001
Hypertension, no. (%)	651 (56.2)	784 (52.1)	0.04
Diabetes, no. (%)	249 (21.5)	207 (13.8)	< 0.001
Total cholesterol, mmol/L	5.1 ± 0.9	5.7 ± 0.9	< 0.001
HDL-cholesterol, mmol/L	1.6 ± 0.4	1.8 ± 0.5	< 0.001
Body mass index, kg/m^2	23.2 ± 3.1	22.9 ± 3.8	0.04
Waist circumference, cm	86 ± 8	85 ± 10	0.003
Current smoking, no. (%)	370 (32.0)	98 (6.5)	< 0.001
Current drinking, no. (%)	785 (67.9)	423 (28.1)	< 0.001
History of cardiovascular disease, no. (%)	250 (21.6)	199 (13.2)	< 0.001

Values are given as means ± standard deviations or as percentages; HDL, high-density lipoprotein.

TABLE 2. Prevalence by sex of early and late age-related macular degeneration.

	All subjects (n = 2,663)	Men (n = 1,158)	Women (n = 1,505)	
	Prevalence n (%)	Prevalence n (%)	Prevalence n (%)	P-Value
Early AMD	174 (6.5)	76 (6.6)	98 (6.5)	0.96
Pigmentary abnormalities	46 (1.7)	28 (2.4)	18 (1.2)	0.02
Soft distinct and indistinct drusen	128 (4.8)	48 (4.2)	80 (5.3)	0.19
Late AMD	33 (1.2)	25 (2.2)	8 (0.5)	< 0.001
Geographic atrophy	1 (0.04)	1 (0.1)	0 (0.0)	0.43
Neovascular AMD	22 (0.8)	15 (1.3)	7 (0.5)	0.03
Polypoidal choroidal vasculopathy	10 (0.4)	9 (0.8)	1 (0.1)	0.003

AMD, age-related macular degeneration.

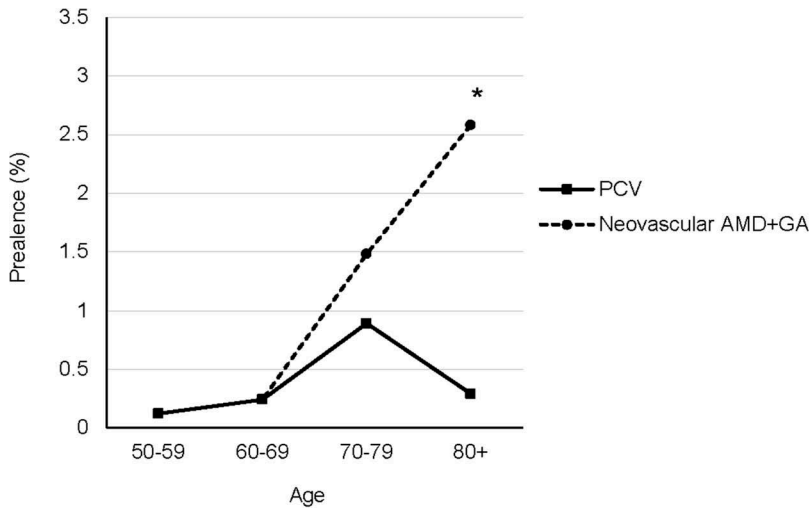

FIGURE 2. Age-specific prevalence of polypoidal choroidal vasculopathy (PCV), neovascular age-related macular degeneration (AMD), and geographic atrophy (GA). Solid line: PCV; broken line, neovascular AMD and GA. *P < 0.01 for trend.

Regarding late AMD, there were significantly more cases among the men compared to the women, and both neovascular AMD and PCV occurred more frequently among the men.

TABLE 3. Age- and sex-adjusted odds ratios of risk factors for polypoidal vasculopathy and neovascular age-related macular degeneration and geographic atrophy.

	PCV			Neovascular AMD+ GA		
Risk factor	OR	(95%CI)	*P*-Value	OR	(95%CI)	*P*-Value
Age, years	1.06	(0.99–1.12)	0.08	1.10	(1.05–1.14)	< 0.001
Men, %	12.53	(1.58–99.31)	0.02	3.45	(1.40–8.50)	0.01
Systolic blood pressure, mmHg	0.75	(0.52–1.08)	0.13	0.91	(0.73–1.14)	0.40
Diastolic blood pressure, mmHg	0.58	(0.30–1.10)	0.09	0.77	(0.51–1.17)	0.22
Hypertension, %	0.41	(0.11–1.48)	0.17	0.48	(0.21–1.11)	0.09
Diabetes, %	0.39	(0.05–3.10)	0.37	1.14	(0.41–3.06)	0.83
Total cholesterol, mg/dL	0.92	(0.44–1.91)	0.82	1.03	(0.65–1.65)	0.90
HDL-cholesterol, mg/dL	0.69	(0.14–3.36)	0.64	1.28	(0.51–3.24)	0.60
Body mass index, kg/m^2	1.14	(0.94–1.38)	0.19	0.90	(0.79–1.03)	0.14
Waist circumference, cm	1.07	(0.99–1.15)	0.06	0.98	(0.94–1.03)	0.45
Current smoking, %	3.79	(1.01–14.28)	0.049	3.13	(1.22–8.02)	0.02
Current drinking, %	0.70	(0.19–2.65)	0.60	0.94	(0.37–2.39)	0.90
History of cardiovascular disease, %	1.88	(0.49–7.19)	0.36	0.86	(0.32–2.28)	0.76

PCV, polypoidal choroidal vasculopathy; GA, geographic atrophy; AMD, age-related macular degeneration; OR, odds ratio; CI, confidence interval.

Figure 2 demonstrates the age-specific prevalence of PCV, neovascular AMD and GA. In contrast to PCV, the prevalence of neovascular AMD+ GA increased significantly with age.

We determined the mean values or frequencies of potential risk factors for early and late AMD (supplementary table S1). Compared to the healthy participants, the age and frequency of cardiovascular disease history were significantly higher for the participants with soft drusen in early AMD, whereas the total cholesterol values of the latter participants were lower. In late AMD, the participants with neovascular AMD+ GA were significantly older than the healthy participants, and a significantly greater percentage of men with late AMD had PCV.

The results of our logistic regression analyses of risk factors for PCV and neovascular AMD + GA are shown in Table 3. Since we focused on PCV rather than late AMD and the number of subjects with GA was few, we combined the data on neovascular AMD and GA and analyzed the risk factors. After adjusting for age and sex, male gender (OR 12.53; 95% CI 1.58–99.31) and smoking habit (OR 3.79; 95% CI 1.01–14.28) were significant risk factors for the onset of PCV and neovascular AMD + GA. Although older age was significantly associated with neovascular AMD + GA, there was no significant association between that variable and PCV.

DISCUSSION

This study demonstrated that the prevalence of PCV was approx. 30.3% among the study participants with late AMD, and it did not significantly increase with advancing age. In the age- and sex-adjusted analysis, male gender and smoking habit were significant risk factors for PCV.

Several hospital-based studies reported the prevalence of PCV in different populations. Yannuzzi et al. found a PCV prevalence of 7.8% in Caucasian populations in the USA,[16] whereas Wen et al. reported a 22.3% prevalence in a Chinese population.[6] In Japan, a clinical study reported that the prevalence of PCV in 2003 was 23.0%, and in 2007 it was reported to be 53.7%.[4,5] Thus, the prevalence of PCV among Asians with AMD appears to be higher than the corresponding values in Western countries. Our results are in concordance with these reports. The reason(s) for the difference in the reported prevalences of PCV between Asian and Caucasian populations are unclear but could be associated with lifestyle differences, genetic factors, and the methodologies used in the studies. Further investigations are needed to address this issue.

Li Y. et al reported that the prevalence of PCV was 0.5% in their population-based study in China.[9] Although this was a higher prevalence than we observed in the present study, their diagnosis of PCV was based on fundus photographs and OCT images, an approach that yields more presumptive than definitive results. In addition, they showed that older age, thicker subfoveal choroid, and thicker central cornea were significantly associated with PCV after multivariable adjustment. Smoking was not a significant risk factor in the univariable analysis. These differences between their study and our results were likely due to the small numbers of PCV patients enrolled in both studies.

We reported that the incidence of early and late AMD increases significantly with advancing age in both men and women.[2] Although age is a major risk factor for the development of AMD, the etiology and

pathogenesis of AMD are largely unknown. Our present study's results indicate that the prevalence of PCV did not increase with advancing age, whereas neovascular AMD + GA did increase with age. In the participants older than 80 years, the prevalence of PCV was significantly lower than that of neovascular AMD + GA. There are several reasons that may explain this phenomenon. Being male is a major risk factor for PCV development. It, along with age and smoking, also increases the risk of cardiovascular disease and death compared to women. The loss of males (who are at high risk for PCV development) through death due to gender, age, and smoking could reduce the prevalence of PCV in the population of individuals over 70 years old.

The results of this study provide evidence that cigarette smoking increases the risk of developing PCV, as it does for AMD in general. Our participants who were currently smoking had an approx. 3.8 times higher risk of developing PCV compared to those who were not currently smoking. These findings are consistent with other studies showing that cigarette smoking was related to the development of AMD.[17–19] Smoking is a well-recognized and modifiable risk factor for AMD, suggesting that smoking cessation can reduce the development of AMD.[2]

There are several possible mechanisms by which smoking could increase the likelihood of AMD and PCV development. First, smoking causes oxidative stress by an activation of phagocytic cells in the retina.[20–22] Second, the reduction of choroid outflow through a smoking-induced adhesion of platelets to vessel walls contributes to the development of ischemic conditions that can induce degenerative changes in the macula.[23,24] Last, inflammatory mediators that accompany cigarette smoking may be involved in the development of AMD.[25] Increased levels of circulating leukocytes in the serum are associated with retinal vasculitis and dysfunction of the blood-retinal barrier in the process of AMD development.[16] These mechanisms could explain the strong association between smoking and the high prevalence PCV in late AMD.

Our results are significant because of the large sample size and the high response rate (73.0%). Nevertheless, there is a limitation that should be taken into consideration. Because this was a cross-sectional study, the interpretation of the causal relationship between risk factors and PCV is limited. However, we believe that the risk factors that we have analyzed for the potential to promote PCV development are reasonable because PCV itself is unlikely to induce these systemic risk factors. Second, the definition of PCV in our study was not based on OCT findings. Therefore, there is a possibility that we underestimated the prevalence of PCV. Thus, taking this limitation into account, the association between risk factors and PCV may have been even stronger than suggested.

In conclusion, our present findings suggest that PCV is more common among Japanese patients compared to Caucasians in Western countries. Further, it is likely that male gender and smoking habit are significant risk factors for the development of PCV in general Japanese populations.

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CONFLICT OF INTEREST

The authors state that they have no conflicts of interest associated with this study.

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed here.

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