Original Article

Retinal Vascular Changes and Prospective Risk of Disabling Dementia: the Circulatory Risk in Communities Study (CIRCS)

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Aim: To investigate the association of retinal vascular changes with a risk of dementia in longitudinal population-based study.

Methods: We performed a nested case-control study of 3,718 persons, aged 40−89 years, enrolled between 1983 and 2004. Retinal vascular changes were observed in 351 cases with disabling dementia (average period before the onset, 11.2 years) and in 702 controls matched for sex, age, and baseline year. Incidence of disabling dementia was defined as individuals who received cares for disabilities including dementia-related symptoms and/or behavioral disturbance. Conditional logistic regression analysis was used to calculate odds ratio (OR) and multivariable adjusted OR (Models 1 and 2) for incidence of disabling dementia according to each retinal vascular change. Regarding confounding variables, Model 1 included overweight status, hypertension, hyperglycemia, dyslipidemia, and smoking status, whereas Model 2 also included incidence of stroke prior to disabling dementia for further analysis.

Results: The proportion of cases (controls) with retinal vascular changes was 23.1 (15.7)% for generalized arteriolar narrowing, 7.7 (7.5)% for focal arteriolar narrowing, 15.7 (11.8)% for arteriovenous nicking, 10.5 (9.3)% for increased arteriolar wall reflex, and 11.4 (9.8)% for any other retinopathy. Generalized arteriolar narrowing was associated with an increased risk of disabling dementia: crude OR, 1.66 (95% confidence interval, 1.19−2.31); Model 1: OR, 1.58 (1.12−2.23); Model 2: OR, 1.48 (1.04−2.10). The number of retinal abnormalities was associated in a dose−response manner with the risk.

Conclusion: Generalized arteriolar narrowing and total number of retinal abnormalities may be useful markers for identifying persons at higher risks of disabling dementia.

> ### See editorial vol. 24: 675-676

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Introduction

Dementia has become a major burden in disabled elderly individuals[1, 2]. Microvascular brain damage, such as microinfarction, microhemorrhage, and macrohemorrhage[3, 4], as well as peripheral arterial stiffness[5, 6], heighten the risk of cognitive impairment.
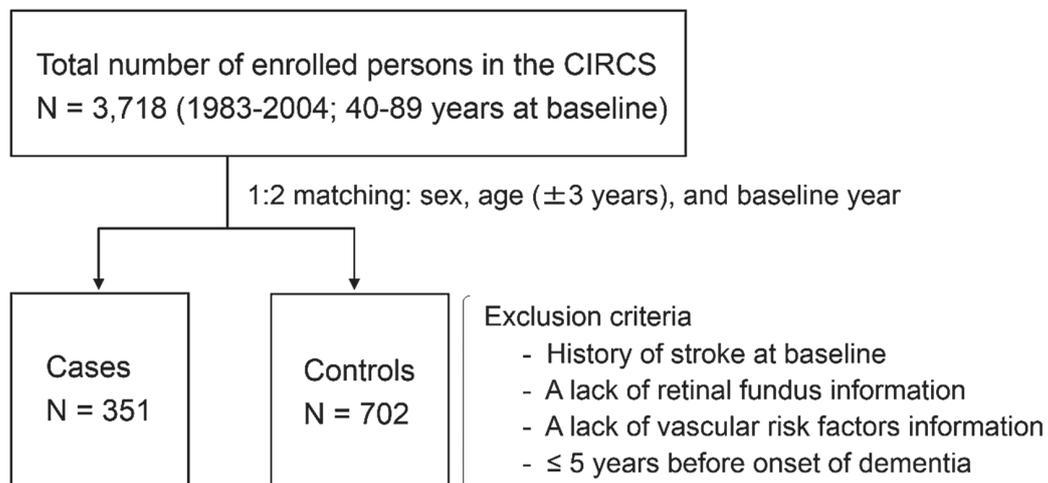
Fig. 1. Diagram of the present study.

Flow diagram of participant enrollment and selection for nested case-control study.

Previous studies have suggested that such brain abnormalities may be associated with retinal vascular changes due to shared embryological, anatomical, and physiological features[7-9]. In addition, retina is the only location in which it is possible to macroscopically diagnose microvascular abnormalities. Retinal vascular changes, therefore, may serve as risk markers for dementia, but the epidemiological evidence has been limited[10].

Several longitudinal population-based studies have investigated the associations between retinal vascular changes and incidence of dementia[11], or indicators of dementia such as brain imaging abnormalities[12-15], cognitive decline[16], and disability[17], but these results have been inconsistent. In addition, most of these studies investigated the association of retinal vascular changes with the risk of dementia and/or cognitive decline without taking into account incidence of stroke before the onset of dementia. Nevertheless, retinal vascular changes have been shown to be risk markers for incidence of stroke[18-20]. Therefore, further longitudinal population-based studies are becoming increasingly important in order to confirm these associations while also considering mediation by incidence of stroke.

Our hypothesis was that retinal vascular changes would be associated with an increased risk of disabling dementia and that this association would persist after further adjustment for incidence of stroke before the onset of disabling dementia.
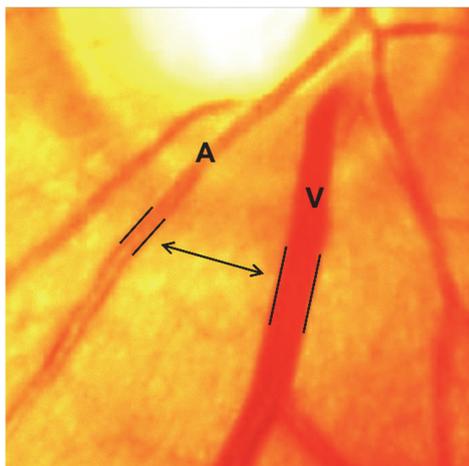
Methods

Case and Control Identification

We performed a nested case-control study of 3,718 people, ranging in age from 40 to 89 years, who lived in the Ikawa community in Japan and were enrolled in the Circulatory Risk in Communities Study (CIRCS) between 1983 and 2004 (**Fig. 1**). Details of the CIRCS protocol have been described elsewhere[21-23]. Briefly, this cohort was followed via annual cardiovascular risk surveys and surveillance for incidence and mortality of stroke. Surveillance for disabling dementia was also conducted from October 1999 until March 2014.
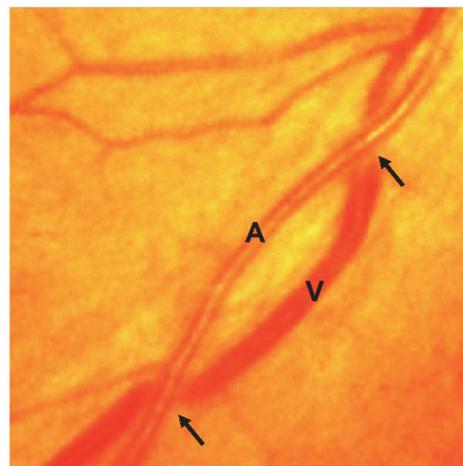
The criteria of disabling dementia were the same as those of our previous studies[21, 24-26]. Incidence of disabling dementia was defined as individuals who received cares for disability including dementia-related symptoms and/or behavioral disturbance and who were ranked as II or greater on the standardized physicians' classification in Long-Term Care Insurance in Japan. These criteria were validated by comparing with neuropsychiatrists' diagnoses as defined by the International Psychogeriatric Association[27], which examine five domains of cognitive function: attention, memory, visuospatial function, language, and reasoning. A total of 622 people, aged 65 years or older, were evaluated by neuropsychiatrists and 123 persons were diagnosed with disabling dementia. The calculated sensitivity and specificity values for disabling dementia were 82.9% and 95.8%, respectively[26].

We identified 351 cases with disabling dementia and matched two controls with each case based on sex, age (±3 years), and baseline year. We excluded
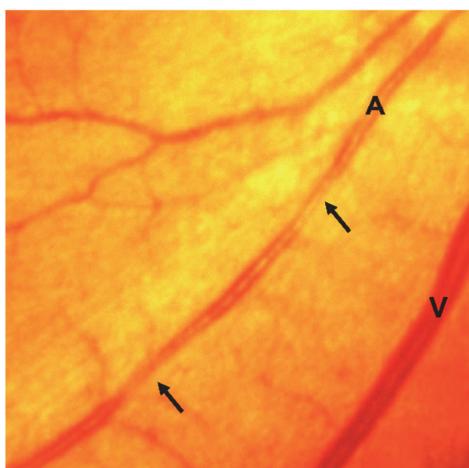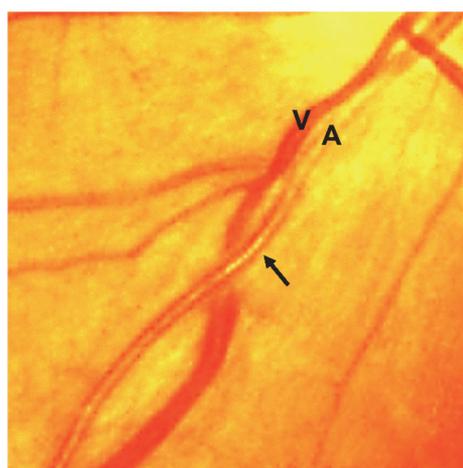
(A) Generalized arteriolar narrowing

(C) Arteriovenous nicking

(B) Focal arteriolar narrowing

(D) Increased arteriolar wall reflex

Fig. 2. Example photographs of retinal vascular changes.

A, retinal arteriole; V, retinal venule; Example photographs of retinal vascular changes: (A) Generalized arteriolar narrowing: arteriolar-to-venular diameter ratio of 2:3 or lower; (B) Focal arteriolar narrowing: localized constrictions along the course of arterioles; (C) Arteriovenous nicking: narrowing of a venule as an arteriole crosses over it; and (D) Increased arteriolar wall reflex: an increased light reflex from the central portion of the retinal arteriolar surface; All photographs were modified from Iida and Kitamura (2009) with the authors' permission[28].

persons with a history of stroke at baseline or lack of retinal fundus information and/or vascular risk factors information. We also excluded cases that developed disabling dementia within 5 years from their baseline. The Ethics Committees of the Osaka Center for Cancer and Cardiovascular Disease Prevention and Osaka University approved this study.

Retinal Vascular Changes

All participants underwent retinal fundus photography of their right eye using a retinal camera at least once every 2 years. When a photograph of the right eye was not obtained due to anterior segment or media opacity (e.g., corneal opacity or cataracts), a photograph of the left eye was taken; photographs of the right eye were used in 96% of participants. Two well-trained physicians and/or medical technologists evaluated retinal findings and identified the presence of generalized arteriolar narrowing, focal arteriolar narrowing, arteriovenous nicking, increased arteriolar wall reflex, and any other retinopathy. As shown in **Fig. 2**, we graded retinal vascular change as "present"

when the following criteria were found: (A) for generalized arteriolar narrowing, an arteriolar-to-venular ratio of 2:3 or lower; (B) for focal arteriolar narrowing, localized constrictions along the course of arterioles; (C) for arteriovenous nicking, narrowing or invisibility of a vein as an arteriole crossed over it; and (D) for increased arteriolar wall reflex, the presence of an increased light reflex from the central portion of the retinal arteriolar wall surface[28]. The presence of other retinopathies was based on the observation of any of the following lesions: blot or flame-shaped hemorrhages, microaneurysms, exudates (soft or hard), optic disc swelling, new vessels at the disk or elsewhere, intra retinal microvascular abnormalities, vitreous hemorrhage, or laser photocoagulation scars[28]. Additionally, the overall impact of retinal microvascular changes was estimated based on the total number of retinal abnormalities, including generalized arteriolar narrowing, focal arteriolar narrowing, arteriovenous nicking, increased arteriolar wall reflex, and the other retinopathies. We previously calculated intergrader prevalence- and bias-adjusted Kappa scores in a preliminary validation study of 116 eyes, and the principal major results were 0.52 for generalized arteriolar narrowing, 0.48 for focal arteriolar narrowing, 0.59 for arteriovenous nicking, and 0.98 for hemorrhages.

Vascular Risk Factors

We calculated body mass index as body weight (kg) divided by body height squared (m^2), and overweight was defined as 25 kg/m^2 or higher. Blood pressures were measured by trained physicians using standard mercury sphygmomanometers and standardized epidemiological methods. We defined hypertension as systolic blood pressure of 140 mmHg or higher and/or diastolic blood pressure of 90 mmHg or higher and/or antihypertensive medication use. We also identified hyperglycemia as fasting serum glucose of 110 mg/dl or higher or casual serum glucose 140 mg/dl or greater and/or antidiabetic medication use and hypercholesterolemia as serum total cholesterol of 220 mg/dl or higher and/or lipid-lowering medication use. A standard 12-lead resting electrocardiogram was obtained in supine position, and we noted atrial fibrillation (Minnesota Codes, 8-3-1 or 8-3-2) and ST-T changes (Minnesota Code, 4-1 to 4-3 and/or 5-1 to 5-3). We identified current smokers as those who reported smoking one or more cigarettes per day, past smokers as those who had quit smoking for 3 months or more, current drinkers as those who reported drinking 1 or more times per week, and ex-drinkers as those who had not drunk for 3 months or more.

Ascertainment of Incidence of Stroke

From 1981 to the present, we obtained information on incidence of stroke from death certificates, national insurance claims, annual cardiovascular risk surveys, and reports by local physicians, public health nurses, and health volunteers. To confirm the diagnoses, all living patients were telephoned, visited, or invited to participate in the risk surveys, or alternatively, a medical history was obtained from their families. In addition, medical records and findings of imaging studies such as CT and/or MRI from local clinics and hospitals were reviewed. In cases of death, histories were obtained from families and/or attending physicians and medical records were reviewed. The definition of incidence of stroke was a focal neurological disorder with rapid onset that persisted for at least 24 h or until death (International Classification of Diseases, 9 th Revision, code 430-438). Final diagnoses of stroke were made by a panel of three to four epidemiologists who were blinded to the data from the risk surveys.

Statistical Analysis

The analysis of covariance was used to test for differences in means and proportions of baseline characteristics between cases and controls. We calculated the conditional odds ratios (ORs) and 95% confidence intervals (95% CIs) for incidence of disabling dementia associated with generalized arteriolar narrowing, focal arteriolar narrowing, arteriovenous nicking, increased arteriolar wall reflex, any other retinopathy, and the total number of retinal abnormalities (one, two, or more). Two models were constructed. Model 1 included adjustments for vascular risk factors: overweight status (yes, no), hypertension (yes, no), hyperglycemia (yes, no), hypercholesteremia (yes, no), electrocardiogram abnormality (yes, no), current smoking status (current, past, never), and drinking status (current, ex-, never). Model 2 incorporated full covariate adjustment, specifically adding an intermediate variable, namely the presence of incidence of stroke before the onset of disabling dementia (yes, no). SAS9.3 (SAS Institute Inc., Cary, NC) was used for analyses, and a two-tailed p value of < 0.05 denoted the presence of a statistically significant difference.

Results

The baseline characteristics of the 351 cases and 702 controls are shown in **Table 1**. Cases and controls showed no differences in overweight status, hypertension, hypercholesterolemia, or electrocardiogram abnormalities, but differed in terms of proportions of

Table 1. Comparison of baseline characteristics between cases with disabling dementia and controls

	Case (N = 351)	Control (N = 702)	P-value
At baseline			
Age, years	67.9 (0.4)	67.8 (0.3)	0.873
Male, %	35.6 (2.6)	35.6 (1.8)	1.000
Body mass index, kg/m²	24.1 (0.2)	24.4 (0.1)	0.196
Overweight status, %	15.7 (1.9)	15.2 (1.4)	0.856
Systolic blood pressure, mmHg	135.0 (0.9)	134.5 (0.7)	0.676
Diastolic blood pressure, mmHg	78.9 (0.5)	78.5 (0.4)	0.499
Hypertension, %	58.7 (2.6)	59.1 (1.9)	0.894
Antihypertensive medication use, %	45.0 (2.6)	42.5 (1.9)	0.429
Hyperglycemia, %	24.2 (2.1)	17.8 (1.5)	0.014
Glucose-lowering medication use, %	6.0 (1.3)	6.1 (0.9)	0.927
Total cholesterol, mg/dl	202.0 (1.8)	204.3 (1.3)	0.304
Hypercholesterolemia, %	35.0 (2.6)	38.0 (1.8)	0.344
Lipid-lowering medication use, %	9.7 (1.6)	10.7 (1.2)	0.617
Electrocardiogram abnormality, %	11.1 (1.6)	8.5 (1.1)	0.179
Current smoker, %	17.7 (2.0)	16.2 (1.4)	0.560
Past smoker, %	11.1 (1.7)	12.0 (1.2)	0.684
Current drinker, %	30.0 (2.4)	28.1 (1.7)	0.550
Ex-drinker, %	5.4 (1.1)	4.0 (0.8)	0.296
In followed-up period			
Incidence of stroke, %	23.9 (1.9)	12.1 (1.4)	< 0.001

Mean values (standard error); Body mass index, body weight (kg) divided by squared body height (m); Overweight status, Body mass index, ≥25 kg/m²; Hypertension, systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or antihypertensive medication use; Hypercholesterolemia, serum total cholesterol ≥220 mg/dl and/or lipid-lowering medication use; Hyperglycemia, fasting serum glucose ≥110 mg/dl or casual serum glucose ≥140 mg/dl and/or glucose-lowering medication use; Electrocardiogram abnormality, atrial fibrillation (Minnesota Codes, 8-3-1 or 8-3-2) and/or ST-T changes (Minnesota Code, 4-1 to 4-3 and/or 5-1 to 5-3); Current smoking status (current, past, never) and drinking status (current, ex-, never).

hyperglycemia and incidence of stroke before the onset of disabling dementia.

The proportion of subjects with each retinal finding was as follows: generalized arteriolar narrowing, 18.0%; arteriovenous nicking, 13.1%; any other retinopathy, 10.3%; increased arteriolar wall reflex, 9.6%; and focal arteriolar narrowing, 7.9%. As shown in **Table 2**, generalized arteriolar narrowing (case: 23.1% vs control: 15.7%, P=0.003) and two or more retinal abnormalities (case: 18.2% vs control: 13.4%, P=0.038) were more frequent in cases compared with controls. While arteriovenous nicking tended to be more frequent in cases than in controls (case: 15.7% vs control: 11.8%, P=0.081), the other conditions occurred at similar rates in cases and controls.

As shown in **Table 3**, we tested the associations between each retinal vascular change and disabling dementia using conditional logistic regression models. Generalized arteriolar narrowing was associated with an increased risk of disabling dementia: crude OR, 1.66 (95% CI, 1.19−2.31), P=0.003. The positive association remained statistically significant after adjustment for vascular risk factors: OR, 1.58 (1.12−2.23), P=0.010 in Model 1, and after further adjustment for incidence of stroke before the onset of disabling dementia: OR, 1.48 (1.04−2.10), P=0.029 in Model 2. Arteriovenous nicking was associated with borderline increased risk of disabling dementia: crude OR, 1.39 (0.96−2.01), P=0.081; OR, 1.39 (0.95−2.03), P=0.087 in Model 1; OR, 1.32 (0.90−1.95), P=0.154 in Model 2. Compared with no retinal abnormality, two or more retinal abnormalities were associated in a dose−response manner with an increased risk of disabling dementia even after adjustment for both vascular risk factors and incidence of stroke before the onset of disabling dementia. Other retinal vascular changes were not associated with increased risk.

Discussion

In this population-based nested case-control

Table 2. Comparison of proportions of retinal microvascular abnormalities between cases with disabling dementia and controls at baseline

	Case (N=351)	Control (N=702)	*P*-value
Generalized arteriolar narrowing, %	23.1 (2.1)	15.7 (1.4)	0.003
Focal arteriolar narrowing, %	7.7 (1.4)	7.5 (1.0)	0.935
Arteriovenous nicking, %	15.7 (1.8)	11.8 (1.3)	0.081
Increased arteriolar wall reflex, %	10.5 (1.6)	9.3 (1.1)	0.508
Any other retinopathy, %	11.4 (1.6)	9.8 (1.2)	0.432
Hemorrhages, %	7.1 (1.3)	6.6 (0.9)	0.728
Microaneurysms, %	2.6 (0.7)	1.4 (0.5)	0.191
Exudates, %	2.8 (0.9)	2.6 (0.6)	0.787
New vessels, %	1.1 (0.5)	0.9 (0.4)	0.654
Laser photocoagulation scars, %	0.9 (0.5)	1.0 (0.4)	0.822
Total number of retinal abnormalities			
1 finding, %	26.8 (2.3)	22.8 (1.6)	0.154
≥2 findings, %	18.2 (1.9)	13.4 (1.3)	0.038

In parentheses, standard error; Optic disc swelling, which is one of any other retinopathy, was not observed in this study population.

study, we found that a retinal vascular change, specifically generalized arteriolar narrowing i.e., a low ratio of arteriolar-to-venular diameter (2:3 or lower), was associated with an increased risk of disabling dementia, and the risk was unchanged after adjustment for vascular risk factors. While arteriovenous nicking showed a nonsignificant association with the risk, the other retinal abnormalities demonstrated no association. The total number of retinal abnormalities was also associated with the risk in a dose−response manner.

Previous longitudinal population-based studies have shown similar results linking retinal vascular changes to various indicators of incidence of dementia[11-13, 17]. According to an 11.6-year follow-up of men and women aged 55 years and older in the Rotterdam Study, generalized arteriolar narrowing and venular dilation tended to be associated with incidence of dementia[9], although the study did not report arteriolar-to-venular ratios, which we used as a criterion for the diagnosis of generalized arteriolar narrowing. Their findings seem to be consistent with those of the present study because small arteriolar diameter and the venular dilation led to small arteriolar-to-venular ratio. In the Rotterdam Study, Ikram *et al.* found that venular dilation and arteriolar-to-venular ratio were associated with the progression of brain abnormalities detected by imaging, namely periventricular white matter lesions and lacunar infarcts over 3 years, whereas only venular dilation was strongly associated with the progression of subcortical white matter lesions[12]. Schrijvers *et al.* also reported a positive association between retinopathy (hemorrhages, microan-

eurysms, cotton wool spots, and laser photocoagulation scars) and the prevalence of dementia in a cross-sectional analysis, but no association with the risk of dementia in a prospective analysis[13]. In a 5-year follow-up of men and women aged 65 years and older of the Cardiovascular Health Study, they reported dose−response relationships between the total number of retinal vascular changes and incidence of disability, defined by executive dysfunction, slow gait, and depressive symptoms[17]. These results support the present finding that retinal vascular changes, represented by a small arteriolar-to-venular ratio, may help predict the risk of incidence of disabling dementia.

A 14-year follow-up of men and women aged 45−64 years of the Atherosclerosis Risk in Communities (ARIC) study did not investigate the association between retinal vascular changes and the risk of dementia, but it did examine the association between this risk and cognitive decline[16]. The ARIC study found that cognitive decline was associated with focal arteriolar narrowing and retinopathy but not generalized arteriolar narrowing. They did not state the reason for the lack of correlation with generalized arteriolar narrowing. However, cognitive decline is not always a preclinical sign of dementia, and these two outcomes likely have different predictors[10].

As previous studies have reported the associations of hypertension with generalized arteriolar narrowing[29] and incidence of dementia[30], hypertension could be one of the most important risk factors in the present study. However, we found no association between hypertension and incidence of disabling dementia among the subjects (average age=68 years).

Table 3. Conditional odds ratios for incidence of disabling dementia according to each retinal microvascular abnormality

	N	N of case	Crude OR (95% CI)	Multivariable OR[†] (95% CI)	Multivariable OR[‡] (95% CI)
Generalized arteriolar narrowing					
Absent	862	270	1.00	1.00	1.00
Present	191	81	1.66 (1.19-2.31)	1.58 (1.12-2.23)	1.48 (1.04-2.10)
P-value			0.003	0.010	0.029
Focal arteriolar narrowing					
Absent	973	324	1.00	1.00	1.00
Present	80	27	1.02 (0.63-1.65)	1.01 (0.62-1.65)	0.98 (0.60-1.62)
P-value			0.934	0.960	0.946
Arteriovenous nicking					
Absent	915	296	1.00	1.00	1.00
Present	138	55	1.39 (0.96-2.01)	1.39 (0.95-2.03)	1.32 (0.90-1.95)
P-value			0.081	0.087	0.154
Increased arteriolar wall reflex					
Absent	951	314	1.00	1.00	1.00
Present	102	37	1.16 (0.75-1.80)	1.11 (0.71-1.73)	1.11 (0.71-1.75)
P-value			0.498	0.638	0.649
Any other retinopathy					
Absent	944	311	1.00	1.00	1.00
Present	109	40	1.19 (0.75-1.88)	1.17 (0.73-1.88)	1.20 (0.74-1.94)
P-value			0.472	0.523	0.465
Total number of retinal abnormalities					
Absent	641	193	1.00	1.00	1.00
1 finding	254	94	1.33 (0.97-1.83)	1.31 (0.95-1.82)	1.20 (0.86-1.67)
≥ 2 findings	158	64	1.62 (1.12-2.34)	1.52 (1.04-2.23)	1.50 (1.02-2.22)
P-value for trend			0.005	0.016	0.035

OR, conditional odds ratio; 95% CI, 95% confidence interval; Case-control matching variables: sex, age (± 3 years), and baseline-year.
[†] Adjustment for vascular risk factors included overweight status, hypertension, hyperglycemia, hypercholesterolemia, electrocardiogram abnormality, current smoking status (current, past, never) and drinking status (current, ex-, never).
[‡] Further adjustment for incidence of stroke before the onset of disabling dementia.

The contribution of hypertension to the development of dementia may be weakened among the elderly. Ninomiya *et al.* reported the association of hypertension with incidence of all-cause dementia among middle-aged adults (average age = 57 years), but not among older adults (average age = 72 years)[30]. In addition, generalized arteriolar narrowing, associated with the risk of incidence of disabling dementia in our study, was likely to be caused by long-term hypertension[31]. On the other hand, focal arteriolar narrowing, which was not associated with the risk of incidence of disabling dementia in our study, was reported to be caused by short-term hypertension[31]. Thus, long-term hypertension from young to middle age may cause generalized arteriolar narrowing, and it may lead to incidence of disabling dementia in the elderly.

The most important strength of our study was the longitudinal population-based design. No other studies in Asia have shown the associations between comprehensive retinal vascular changes and the risk of disabling dementia. Some further methodologic issues should be discussed. We used a subjective grading system to evaluate retinal vascular changes. Such methods generally show lower reproducibility than computer-assisted systems[32]. However, the significant associations in the present study indicate that standardized qualitative grading is also useful in identifying persons at higher risks of disabling dementia.

Conclusion

We found that retinal vascular changes were positively associated with the risk of disabling dementia, even after adjustment for vascular risk factors and incidence of stroke before the onset of disabling dementia. Generalized arteriolar narrowing and total

number of retinal abnormalities may be useful markers for identifying persons at higher risks of disabling dementia.

CIRCS Investigators

Acknowledgements

Sources of Funding

Conflict of Interest

None.

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