［Ⅲ］研究成果の刊行に関する一覧表

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C-reactive protein levels and risk of disabling dementia with and without stroke in Japanese: The Circulatory Risk in Communities Study (CIRCS)

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ABSTRACT

Objective: Studies have shown that elevated high-sensitivity C-reactive protein (hs-CRP) predicts stroke, which is a risk factor for dementia. It remains, however, unclear whether hs-CRP increases risk of dementia.

Methods: A prospective nested case–control study of Japanese 40–69 years of age was conducted using frozen serum samples collected from approximately 7531men and women who participated in cardiovascular risk surveys from 1984 to 1994 in one community and 1989–1995 in another community under the Circulatory Risk in Communities Study (CIRCS). Two control subjects per case were matched by sex, age, community, and year of serum storage. The hs-CRP was measured using a latex particle-enhanced immunonephelometric assay.

Results: Between 1999 and 2013, we identified 275 disabling dementia cases (96 cases with history of stroke and 179 without it). There was a positive association between hs-CRP levels and risk of dementia with history of stroke. No significant association was observed between hs-CRP levels and risk of dementia without history of stroke. After adjustment for hypertension, diabetes and other confounding variables, the positive association remained statistically significant. The multivariable odds ratios associated with 1-SD increment of log hs-CRP were 1.02 (0.87–1.20) for total dementia, 1.35 (1.02–1.79) for dementia with history of stroke, and 0.89 (0.72–1.10) for dementia without history of stroke.

Conclusion: Elevated hs-CRP levels were associated with increased risk of disabling dementia in individuals with history of stroke but not in those without it.

1. Introduction

As a consequence of a rapidly growing elderly population, the number and proportion of individuals with dementia is dramatically expanding worldwide. In Japan, where the elderly population has been increasing faster than in other countries, it is projected that the number of elderly with dementia will increase from 30 million in 2010 to 36 million in 2020 [1]. This has led to intense efforts to identify factors that distinguish persons who are at higher or lower risk for developing dementia.

Cardiovascular diseases are the leading cause of disability and death in Japan [2,3] and Japanese populations have a higher incidence of stroke compared to western populations [4]. Patients with history of stroke have a 5 fold increased risk of developing dementia compared with patients without it [5]. Cardiovascular risk factors profiles for dementia with history of stroke and dementia

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without it may be different. The pooled results from a meta-analysis study revealed that midlife total cholesterol was positively associated with risk of dementia without history of stroke, but not dementia with it [6]. However, follow-up studies of elderly (65 years or older) found that low-density lipoprotein (LDL) cholesterol was associated with risk of dementia with history of stroke (with a relative risk range from 2.5 to 2.6) for the highest compared with the lowest quartile of LDL cholesterol but not in dementia without it [7,8]. Elevated high sensitive C-reactive protein (hs-CRP), an acute-phase reactant and a marker of systemic inflammation, has been associated with risk of stroke in western [9,10] and Japanese populations [11,12]; however, the connection between elevated serum hs-CRP levels and risk of developing dementia still remains controversial.

In the Honolulu-Asia Aging study [13], 1050 Japanese American men (mean age = 54–58 years) were followed-up for 25 years, those with elevated serum hs-CRP in midlife were associated with higher risk of developing dementia in later life (OR:2.8, 95% CI 1.6–5.1). The Rotterdam study [14] and the Conselice Study of Brain Aging [15] also found an association between elevated hs-CRP levels and increased risk of dementia. The pooled hazard ratio from meta-analysis for hs-CRP and the incidence of dementia was 1.5 (95% CI 1.1–1.9) [16]. However, in the Women's Health Study [17], hs-CRP levels were not associated with cognitive function in older women (age 60–90 years) and in the 90 + Study [18], hs-CRP was not associated with dementia in the oldest elderly individuals. Other prospective studies [19,20] also failed to find such an association. In contrast, in the Framingham Heart Study [21] elevated serum hs-CRP levels were associated with reduced risk of dementia, however, after adjusting for additional risk factors such as *APOE4* allele, the results were no longer statistically significant. To date, age-stratified analysis on the association between hs-CRP levels and risk of dementia with history of stroke and without it has not been undertaken with a large Japanese cohort.

Inflammatory process may directly or indirectly relate to dementia risk via their role in initiation of athero- and arteriolesclerotic lesions in the cerebral vascular system, and may contribute to the development of dementia. Our hypothesis is that elevated hs-CRP levels, a biomarker of inflammation, increased risk of dementia with history of stroke. We measured hs-CRP from stored serum samples of two Japanese communities of the Circulatory Risk in Communities Study (CIRCS), and examined the association between hs-CRP levels and risk of disabling dementia with history of stroke and without it.

2. Materials and methods

2.1. Subjects

The present study was an ancillary study of the CIRCS. The details of this study have been described previously [22]. Participants in the present study were recruited from all residents who participated in cardiovascular risk surveys in two communities of CIRCS. The surveyed populations comprised approximately 7531 men and women 40–69 years old who participated in the surveys between 1984 and 1994 in a mid-eastern rural community (Kyowa; n = 5349) and between 1989 and 1995 in northeastern rural community (Ikawa; n = 2182). These two cohorts have been followed up with annual cardiovascular surveys and surveillance for incidence and mortality of stroke and coronary heart disease systematically, as described elsewhere. We excluded persons aged 70 old or older at baseline, since serum hs-CRP is likely to be an indicator of advanced age rather than inflammatory process for the elderly [23–25]. Within these two cohorts, elderly persons aged ≥ 65 years with disabling dementia requiring care were identified under the national long-term care insurance program, between 1999 and 2005 in Kyowa, and between 1999 and 2013 in Ikawa. We did not have information on cognitive function prior to dementia. The mean duration of follow-up was 14 years, with 6 being the minimum and 24 the maximum. Informed consent was obtained by community leaders and by individual participants verbally, which was common practice in Japanese communities at that time. The Ethics Committees of the Osaka Center for Cancer and Cardiovascular Disease Prevention and University of Tsukuba approved the study procedures.

2.2. Long-term care insurance program for elderly aged ≥65

Details of the national long-term care insurance program for elderly aged ≥65 have been reported elsewhere [26,27]. In brief, the insurance program began in Japan from April 2000. This program was essentially an extension of the national health insurance system, and partially relied on subsidies from general revenue from the national government, prefectures and municipalities. All individuals aged ≥40 are required to pay a supplement to their health insurance, which is transferred to a long-term care fund. The payment is directly withdrawn from their monthly income, shared with the employer or deducted from their public pension. All individuals are able to receive long-term care through their resided municipalities when they turn 65 and also if they have disabling dementia and/or reduced capacity for daily living.

2.3. Case selection

The cases were selected among subjects aged ≥65 years between 1999 and 2005 in Kyowa, between 1999 and 2013 in Ikawa, who were regarded as suffering from dementia under the long-term insurance program. The dementia status was classified into six ranks (0–V) and was reported by their primary care physicians according to a standardized physicians' manual issued by the Health and Welfare Bureau for the Elderly of Japan [28]. The dementia status was usually updated annually and was reviewed until the patients were withdrawn due to death or move out of the study area. Individuals without dementia were classified as rank 0. Individuals who were diagnosed with mild cognitive dysfunction, but who had no dementia-related symptoms or behavioral disturbance and were capable of living independently, were classified as rank I. Individuals who had moderate dementia-related behavioral disturbance and cognitive impairment with slight dependence were classified as rank II. Individuals who had moderate to severe dementia-related behavioral disturbance and cognitive impairment with moderate dependence were classified as rank III. Individuals who had severe dementia-related behavioral disturbance and cognitive impairment with heavy dependence were classified as rank IV. Finally, individuals with severe dementia-related behavioral disturbance and cognitive impairment who required medical treatment were classified as rank V. Individuals who were ranked II or greater for the first time were regarded as incident disabling dementia cases in the present analysis. The validation for the cut-off point was determined by neuropsychiatrists of the subjects' cognitive functions (attention, memory, visuospatial function, language and reasoning) based on their aging-associated cognitive decline, as defined by the International Psychogeriatric Association [29]. The calculated sensitivity and specificity values were 36% and 90%, respectively, from the preliminary validation study of 34 disabling subjects. [30].

2.4. History of stroke identification

The history of stroke was obtained from the annual cardiovascular surveys and/or surveillance of the cardiovascular disease

registration system [11] from 1981 to the present. In the present study, 90% of stroke occurrence was confirmed based on CT or MRI using standardized criteria [11,31]. The determination of stroke without imaging studies was conducted based on the clinical criteria [32]. Stroke was defined as rapid-onset focal neurological disorder persisting for ≥ 24 h, or until death. Transient ischemic attack was not included.

2.5. Control selection

We employed risk set sampling [33] of controls, i.e. matching each case of dementia randomly with two of all other individuals with no diagnosis of dementia in the study cohort who were alive and resident within the same community on the date of diagnosis of dementia for the case, age (±2 years) and who had the same gender as the control. The vital status of controls was assessed before control selection.

2.6. Determination of serum high-sensitivity C-reactive protein

Non-fasting venous blood was collected in a 7- to 10- mL plain tube and allowed to stand for <30 min for serum separation. The serum samples were aliquoted immediately and placed on dry ice at the survey sites and then stored at −80 °C until analysis. Serum hs-CRP was measured using latex particle-enhanced immunonephelometric assays on the BN Prospec nephrometer Behring II (Dade Behring). In this method, monoclonal anti-CRP antibodies coated with polystyrene particles formed a complex with CRP present in the measured study sample. The amount of scattered light was directly proportional to the size of the antigen–antibody complex and reflected the hs-CRP concentration present in the study sample [34]. For results under the measurement limit of hs-CRP; hs-CRP>0.500 mg/dL or hs-CRP< 0.004 mg/dL, the values of 0.500 mg/dL or 0.004 mg/dL were used respectively.

2.7. Determination of confounding variables

Confounding variables were collected in the same year of blood collection. An interview was conducted to ascertain histories of cigarette smoking, ethanol intake and medication use for hypertension and diabetes. Height in stocking feet and weight in light clothing were measured. Body mass index (BMI) was calculated as weight (kg)/height (m^2). Systolic and diastolic blood pressures were measured by trained observers using a standard mercury sphygmomanometer on the right arm of seated participants after a 5-min rest. Use of antihypertensive medication was defined as systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg and as taking antihypertensive medication. Serum total cholesterol was measured by enzymatic method. Serum glucose was measured by the hexokinase method. Borderline diabetes was defined as a fasting glucose of 6.1–6.9 mmol/L and/or a non-fasting glucose level of 7.8–11.0 mmol/L, without medication use for diabetes. Diabetes was defined as a fasting glucose level of ≥7.0 mmol/L and/or a non-fasting glucose level of ≥11.0 mmol/L and/or use of medication for diabetes. Atrial fibrillation was defined using Minnesota Codes 8-3-1 or 8-3-2 in electrocardiogram.

2.8. Statistical analysis

The unpaired student's *t* test and Wilcoxon rank sum test were used to compare the mean values of baseline dementia risk factors and median variables of hs-CRP between incident cases and control subjects. The χ^2 test was used to compare proportions between cases and control subjects. Potential confounding factors according to hs-CRP quartiles were investigated using the analysis of variance for continuous variables and χ^2 test for categorical variables. The conditional odds ratios (OR) and 95% confidence intervals (CI) for disabling dementia, dementia with stroke and dementia without stroke were estimated according to quartiles of hs-CRP levels and 1-SD increment of log transformed hs-CRP (antilog of SD = 3.3 mg/dL) of control subjects with conditional logistic regression models. Adjustment was made for systolic blood pressure (mmHg), use of antihypertensive medication (yes and no), BMI (kg/m^2), ethanol intake (never, former, current: less than 46 g/day, and 46 g/day or more ethanol), cigarette smoking status (never, ex-, and current smokers; 20 cigarettes/day or less, and more than 20 cigarettes/day), serum total cholesterol levels (mmol/L), borderline diabetes (yes and no) and diabetes (yes and no). Linear regression was employed to test for linear trends across the hs-CRP categories by using a median variable of hs-CRP for each hs-CRP category. The significance of the interactions for sex, use of antihypertensive medication (yes and no) and diabetes (yes and no) were tested using cross-product terms of sex, use of antihypertensive medication and diabetes with hs-CRP levels. All probability values of statistics were two- tailed, and values of $P < 0.05$ were regarded as statistically significant. The SAS statistical package version 9.1.3 (Statistical Analysis System Inc., Cary, NC) was used for analyses.

3. Results

Table 1 shows the risk characteristics of total dementia cases, dementia cases with history of stroke and dementia cases without history of stroke compared with control subjects. The average age for both cases and control of total dementia and dementia subtypes was 63 years. The proportion of men was higher in dementia with history of stroke (46%) than dementia without it (27%). Mean systolic blood pressure levels, diastolic blood pressure levels and median hs-CRP levels were higher in dementia with history of stroke than in controls; however this trend was not observed in dementia without it. The prevalence of diabetes was higher in total dementia than in controls, and these cases-controls differences were more evident in dementia with history of stroke than dementia without it.

During the follow-up period, we identified 275 dementia cases, comprising 96 dementia cases with a history of stroke and 179 dementia cases without such history.

Table 2 shows age-, sex-, community-, and survey year-matched and multivariable-adjusted odds ratios (95% CI) for total and subtypes of dementia according to quartiles of hs-CRP levels and 1-SD increment in log transformed hs-CRP levels. There was a significant association between elevated hs-CRP levels and dementia with history of stroke. After adjustment for hypertension, diabetes and other confounding variables, these positive associations remained statistically significant. The multivariable odds ratios associated with 1-SD increment of hs-CRP were 1.02 (0.87–1.20) for total dementia, 1.35 (1.02–1.79) for dementia with history of stroke, and 0.89 (0.72–1.10) for dementia without history of stroke. The multivariable odds ratios of dementia with history of stroke for the highest vs. lowest quartiles of hs-CRP levels were 0.99 (0.61–1.60) for total dementia, 2.72 (1.12–6.64) for dementia with history of stroke, and 0.63 (0.34–1.14) for dementia without history of stroke.

We examined potential effect modification by stratifying the analyses for use of antihypertensive medication (yes and no) and diabetes (yes and no) (data not shown) for dementia with history of stroke. There were no statistically significant interactions between hs-CRP levels and use of antihypertensive medication (p for interaction = 0.48) or diabetes (p for interaction = 0.12).

Table 1
Risk characteristics among cases and control subjects of total dementia stratified by the presence of stroke history.

	No	Age y	Men, %	Systolic BP, mm Hg	Diastolic BP, mm Hg	Antihypertensive medication use, %	BMI, kg/m2	Ethanol intake, g/d	Current smokers, %	Serum cholesterol mmol/L	Impaired glucose tolerance %	Diabetes mellitus %	Atrial fibrillation %	Median hs-CRP (mg/dL)
Total dementia														
Cases	275	62.8 ± 5.2	33.8	137.2 ± 18.4‡	79.9 ± 10.8*	32.4	23.9 ± 3.5	0.48 ± 0.90	23.3	200.1 ± 32.9	16.7	10.2*	0.4	0.041
Control subjects	550	62.6 ± 5.2	33.8	132.7 ± 16.7	78.1 ± 10.5	30.9	23.9 ± 3.2	0.43 ± 0.84	19.1	198.2 ± 33.3	15.6	5.3	0.4	0.042
Dementia with history of stroke														
Cases	96	62.4 ± 4.3	45.8	140.8 ± 19.9‡	82.5 ± 10.5‡	39.6	23.7 ± 3.3	0.65 ± 0.97	29.2	198.2 ± 32.8	16.7	9.4*	1.1	0.050*
Control subjects	192	62.2 ± 4.4	45.8	132.1 ± 16.1	78.0 ± 11.4	32.3	23.8 ± 3.1	0.57 ± 0.97	26.0	193.0 ± 32.8	17.7	2.6	0.5	0.036
Dementia without history of stroke														
Cases	179	63.1 ± 5.6	27.4	135.4 ± 17.3	78.6 ± 10.8	28.5	24.0 ± 3.6	0.39 ± 0.85	20.1	201.1 ± 32.4	16.8	10.6	0	0.037
Control subjects	358	62.8 ± 5.6	27.4	132.9 ± 17.1	78.1 ± 10.0	30.2	24.0 ± 3.2	0.35 ± 0.75	15.4	201.0 ± 33.2	14.5	6.7	0.3	0.044

Data are shown as mean ± SD, frequency as a number (%).
hs-CRP levels are expressed as median (interquartile range).
P values for differences from control subjects : *$P < 0.05$, ‡$P < 0.001$.

4. Discussion

The present study is the first study to provide evidence that elevated hs-CRP levels were associated with increased risk of disabling dementia in individuals with history of stroke. These associations remained unchanged even after adjustment for risk factors of dementia and the matching variable of age, sex, years of serum storage, and community. In addition, this association does not vary according to use of antihypertensive medication or whether a person has diabetes. However, no significant association was observed between hs-CRP levels and risk of disabling dementia in individuals without history of stroke.

The most important findings in the present study were that elevated hs-CRP in midlife was associated with the increased risk of developing dementia in individuals with history of stroke but not in individuals without such history. The evidence from Honolulu—Asia Aging study [13] indicated that elevated hs-CRP levels in midlife increased the risk of developing dementia in later life. That study, however, did not stratify individuals with dementia by stroke history but included stroke as a mediating variable in their model. Previous prospective studies [13–15] of hs-CRP and dementia showed a 1.5–2.8-fold increased risk of dementia with elevated hs-CRP levels whereas other studies [20,21] failed to find such associations. Again, those studies did not stratify individuals with dementia by stroke history. The inconsistent results across previous studies may suggest that the interaction effect of hs-CRP and cardiovascular disease on developing dementia was often insufficiently considered. One reason to explain our findings is the fact that Japan populations have the higher incidence of stroke compared to Western countries [4]. The comparatively larger number of stroke cases in our sample could account for the positive association we found between hs-CRP levels and dementia in individuals with history of stroke, and a result not found in studies conducted in Western countries.

Inflammatory process may directly or indirectly relate to dementia risk via their role in the initiation of athero- and arteriolesclerotic lesions in cerebrovascular system [25], which subsequently may increase risk of developing dementia in individuals with stroke history. High CRP facilitates the formation of foam cells in the process of atherogenesis [25] and also impairs endothelial function by attenuating the production of nitric oxide [35]. Both processes contribute the cognitive decline in older adults [36]. In addition, increased myo-inositol signal is a neurochemical abnormality associated with cognitive decline and Alzheimer's disease [37]. A recent cross-sectional study found that higher serum CRP was associated with higher ratio of cerebral myo-inositol/creatine concentrations in cognitively normal middle-aged adults, suggesting the linkage of high CRP to neurochemical changes [38].

Previous cohort studies reported that CRP levels were positively associated with risk of vascular dementia [13–15] but not associated with risk of Alzheimer's disease [13–15,21,39]. These findings corresponded to our present result that CRP levels were positively associated with risk of dementia with history of stroke, but not with dementia without history of stroke, presumably Alzheimer's disease. Although the carrying of *APOE4 allele* is a major risk factor for Alzheimer's disease [40] and *APOE4* carriers had lower levels of CRP compared to non *APOE4 allele* carriers [41–43], the effect of *APOE4 allele* to the association between CRP levels and Alzheimer's disease still remains murky. In the ULSAM-study [39] CRP levels were not associated with Alzheimer's disease after accounted for *APOE* genotype (*APOE4* allele carriers *versus* non carries). However, in a cohort study of Mexican Americans aged 60-101, CRP levels were found inversely associated with the risk of Alzheimer's disease (HR:0.74 (95% CI 0.35–0.90)) in *APOE4* carriers (13% of total subjects) and were positively associated with

Table 2
Odd ratios (95% confidence intervals) of total dementia, stratified by the presence of stroke history according to quartiles of serum hs-CRP levels of control subjects.

	Quartiles of hs-CRP, mg/dL					OR for 1SD increment of log hs-CRP
	1 (low)	2	3	4 (high)	*P* for trend	
Serum hs-CRP						
Median (mg/L)	0.01	0.03	0.06	0.152		
Range (mg/L)	0.002–0.016	0.017–0.041	0.042–0.088	0.090–3.11		
Total dementia						
No. of case	55	83	74	63		
No. of control	134	141	138	137		
Age-, sex, and community-matched OR	1.00	1.44 (0.95–2.18)	1.32 (0.86–2.04)	1.13 (0.73–1.74)	0.69	1.06 (0.92–1.22)
Multivariable OR[a]	1.00	1.34 (0.86–2.07)	1.16 (0.73–1.85)	0.99 (0.61–1.60)	0.82	1.02 (0.87–1.20)
Dementia with history of stroke						
No. of case	11	34	24	27		
No. of control	49	56	44	43		
Age-, sex, and community-matched OR	1.00	2.71 (1.22–6.03)*	2.43 (1.06–5.60)*	2.72 (1.21–6.10)*	0.02	1.33 (1.04–1.71)*
Multivariable OR[a]	1.00	2.15 (0.90–5.15)	2.06 (0.82–5.21)	2.72 (1.12–6.64)*	0.04	1.35 (1.02–1.79)*
Dementia without history of stroke						
No. of case	44	49	50	36		
No. of control	85	85	94	94		
Age-, sex, and community-matched OR	1.00	1.10 (0.66–1.83)	1.04 (0.62–1.74)	0.74 (0.44–1.27)	0.27	0.94 (0.78–1.12)
Multivariable OR[a]	1.00	1.08 (0.64–1.84)	0.93 (0.54–1.62)	0.63 (0.34–1.14)	0.11	0.89 (0.72–1.10)

*$P < 0.05$.
[a] Adjusted for systolic blood pressure, antihypertensive medication use, borderline diabetes, diabetes, BMI, alcohol intake categories, cigarette smoking status, serum total cholesterol levels as well as matching for sex, age, community, year of serum stored, and fasting status.

the risk of Alzheimer's disease (HR 1.24 (95% CI 1.29–1.40)) in non *APOE4* carriers [43].

The strengths of the present study were its prospective design, the comprehensive nature of cardiovascular surveys, storage of serum blood samples and the large number of strokes confirmed by imaging studies. These allowed us to investigate the association between hs-CRP levels and risk of dementia with history of stroke and without such history and to adjust for important potential confounding variables. Moreover, because we used annual cardiovascular surveys that were carried out at least 5 years before the endpoint determination, severe dementia was unlikely to be present at the time of the risk factor assessment. This would enhance our confidence that elevated hs-CRP was not influenced by subclinical dementia.

There are some limitations of the current study. First, we did not have the data of *APOE* genotype, and could not examine an effect modification by *APOE4* allele. Further studies are required to confirm the potential effect of CRP levels on Alzheimer's disease in the presence and absence of *APOE4* allele. Second, we did not assess the cognitive functions of studied subjects at baseline. Therefore, we cannot completely exclude the effects of co-existing subclinical dementia at the time of blood serum collection. However, participants were presumed fit and able to attend the annual cardiovascular checkup for data collection. We conducted another analysis that excluded 6 cases that attended the annual cardiovascular survey within at least 5 years of the diagnosis of dementia, and the results remained unchanged (data not shown). Third, we had a systematic survey and surveillance for stroke incidence, but did not obtain the imaging study results for 10% of the stroke cases because CTs and MRIs were not common at local hospitals in the early 1980s. However, the diagnosis for stroke based only on clinical evidence (excluding medical imaging) was found to be in agreement with 97% of the autopsy results in a previous Japanese study [32]. Therefore, false-negative stroke cases were less likely to exist in our dementia cases. Fourth, we used frozen serum to estimate hs-CRP levels and we did not examine long-term changes in hs-CRP levels in stored serum samples. However, hs-CRP levels were reported to be stable at −70 °C which were stored for 8–11years [44]. Finally, these findings are based on a single measure of hs-CRP. CRP levels of subjects in the general population tend to be stable, although CRP levels may spike occasionally in the presence of minor or subclinical infections, inflammation or trauma [45].

In conclusion, elevated hs-CRP levels were associated with increased risk of dementia among those with history of stroke. No significant association was observed among those without history of stroke. The current study highlights that the risk of developing dementia in the elderly could be predicted in part through CRP measures.

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Disclosure

None.

Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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Appendix I

The Circulatory Risk in Communities Study (CIRCS) is a collaborative study managed by the Osaka Center for Cancer and Cardiovascular Disease Prevention, University of Tsukuba, Osaka

University, and Ehime University. The CIRCS investigators who contributed to this study are as follows: Masahiko Kiyama, Masakazu Nakamura, Takeo Okada, Kenji Maeda, Masatoshi Ido, Masayuki Yao, Mitsugu Kajiura, Yoshinori Ishikawa, Masamitsu Konishi, Takashi Shimamoto, Hideki Ozawa, Minoru Iida, and Yoshio Komachi, Osaka Center for Cancer and Cardiovascular Disease Prevention, Osaka; Yoshihiko Naito, Mukogawa Women's University, Nishinomiya; Shinichi Sato, Chiba Prefectural Institute of Public Health, Chiba; Masakazu Nakamura, National Cerebral and Cardiovascular Center, Suita; Tomoko Sankai, Kazumasa Yamagishi, Mitsumasa Umesawa, ChoyLye Chei and Minako Tabata, University of Tsukuba, Tsukuba; Hiroyasu Iso, Akihiko Kitamura, Hironori Imano, Renzhe Cui, Hiroyuki Noda, Satoyo Ikehara, Yuji Shimizu, Isao Muraki, Masanori Nagao and Minako Maruyama, Osaka University, Suita; Takeshi Tanigawa and Ai Ikeda, Juntendo University, Tokyo; Tetsuya Ohira, Fukushima Medical University, Fukushima; Isao Saito, Susumu Sakurai, Shinichi Hitsumoto, Kotatsu Maruyama, and Eri Eguchi, Ehime University, Tōon.

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Serum coenzyme Q10 and risk of disabling dementia: The Circulatory Risk in Communities Study (CIRCS)

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ABSTRACT

Objective: To examine whether coenzyme Q10, a potent antioxidant, is associated with risk of dementia, which has not yet been elucidated. **Approach and results**: We performed a case–control study nested in a community-based cohort of approximately 6000 Japanese aged 40–69 years at baseline (1984–1994). Serum coenzyme Q10 was measured in 65 incident cases of disabling dementia with dementia-related behavioral disturbance or cognitive impairment incident between 1999 and 2004, and in 130 age-, sex- and baseline year-matched controls. Serum coenzyme Q10 was inversely associated with dementia: the multivariate odds ratios (95% confidence intervals) were 0.68 (0.26–1.78), 0.92 (0.33–2.56), and 0.23 (0.06–0.86) for individuals with the second, third, and highest quartiles of coenzyme Q10, respectively, as compared with the lowest quartile (P for trend = 0.05). A similar association was found for the coenzyme Q10/total cholesterol ratio: the respective ORs were 0.67 (0.25–1.78), 0.73 (0.28–1.92), and 0.21 (0.05–0.90) (P for trend = 0.04). **Conclusions**: Serum coenzyme Q10 levels were inversely associated with risk of disabling dementia.

1. Introduction

Coenzyme Q10 (CoQ10), or ubiquinone, is a vitamin-like substance synthesized by animal cells. CoQ10 largely exists in the myocardium and plays a role in mitochondrial energy production. It also has an antioxidant function and is widely consumed as a supplement in the United States [1]. In addition to the prescription of CoQ10 as an orphan drug for mitochondrial encephalomyopathy, some evidence exists for a beneficial effect of CoQ10 on several neurologic diseases such as Parkinson disease [2], Huntington disease [3], and Friedreich ataxia [4,5] as well as on improved physical exercise capacity [6] and lowered blood pressure [6,7]. Animal studies have shown a potential benefit of CoQ10 on cognitive function [8–11]. A randomized controlled trial, however, has shown that the supplementation of CoQ10 did not influence cerebrospinal fluid biomarkers in patients with mild-to-moderate Alzheimer disease [12]. Yet, evidence on this issue is still limited, and no prospective study has been performed on the preventive effect of CoQ10 on risk of incident dementia in the general population.

In the present study, we hypothesized that because of its antioxidant effect, serum level of CoQ10 is inversely associated with disabling dementia. To test this hypothesis, we conducted a nested case–control study in the Circulatory Risk in Communities Study (CIRCS), a large community-based cohort study of Japanese population.

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2. Materials and methods

The CIRCS is an ongoing dynamic community cohort study involving 5 communities in Japan. Details of the CIRCS protocol have been described elsewhere [13]. In this study, we included only 1 community, Kyowa, where disabling dementia surveillance is being carried out, and serum CoQ10 values have been measured. A total of 65 cases of patients who were diagnosed between 1999 and 2004 as having disabling dementia, participated in annual health checkups (baseline) at least 5 years before receiving the dementia diagnosis (ie, between 1984 and 1994), were aged 40–69 years at baseline, and provided sera for storage at baseline were identified. The criteria of disabling dementia were the same as those of our previous study [14], which also includes the validation of the criteria and the details of the study protocol. As supplemental analysis, we further classified the dementia cases into cases with and without history of stroke on the basis of the systematic stroke registration system described elsewhere [14]. We excluded individuals aged 70 years or older at baseline, because serum CoQ10 would be likely affected by the baseline age, and residents aged 70 years and over were not invited systematically to the baseline examination. One hundred thirty randomly selected controls whose age (±3 years), sex, and follow-up time were matched at a ratio of 2:1 with the cases were also identified from the risk set. Venous blood was collected at baseline, and sera were prepared from the blood samples as soon as possible after the blood collection at the checkup sites. The serum samples were collected in 0.3 mL tubes and stored at −80 °C until measurement in 2005. Serum CoQ10 was measured using high-performance liquid chromatography (HPLC) at the Public Health Institute of Kochi Prefecture with modification of the reported methods [15]. Briefly, a 10 μL serum sample was pretreated with 380 μL of 2-propanol. After centrifugation at 7000 g for 5 min, 10 μL of supernatant was applied to the HPLC system (L-7000 series; Hitachi High-Technologies Corporation, Tokyo, Japan) using a SUPELCOSIL LC-8 HPLC Column (Sigma–Aldrich Japan, Tokyo, Japan), an RC-10 reduction column (Shiseido Company, Tokyo, Japan), and an electrochemical detector (SI-2; Shiseido Company). The oxidation potential for the electrochemical detector was 600 mV. The mobile phase consisted of 50 mmol/L sodium perchlorate in methanol/2-propanol (100/10, v/v) with a flow rate of 1 mL/min. Serum total cholesterol was measured at baseline using the Liebermann-Burchard direct method at the Osaka Medical Center for Cancer and Cardiovascular Disease, an international member of the US National Cholesterol Reference Method Laboratory Network (CRMLN) [16].

For statistical analyses, we conducted conditional logistic analyses using SAS 9.1.3. Service Pack 4 (SAS Institute, Cary, NC, USA) with adjustments for body mass index, smoking status, alcohol consumption, diastolic blood pressure, total cholesterol, diabetes mellitus, and use of medication for hypertension or hypercholesterolemia. Since CoQ10 and total cholesterol were strongly correlated (Spearman $r = 0.34$), we also examined the association of the CoQ10/total cholesterol ratio with risk of disabling dementia. All probability values for the statistical tests were 2-tailed, and probability values below 0.05 were considered significant. Informed consent was obtained from community leaders and, verbally, from individual participants according to the guidelines of the Council for International Organizations of Medical Science [17]. The study was approved by the institutional review boards of the Osaka Center for Cancer and Cardiovascular Disease Prevention and of the University of Tsukuba.

3. Results

As shown in Table 1, the baseline characteristics did not differ materially between the cases and the non-cases, although diastolic blood pressure levels tended to be higher, and prevalence of cholesterol-lowering medication use, lower for cases than for non-cases.

Table 1
Baseline characteristics of dementia cases and non-cases, CIRCS aged 40–69 years.

	Dementia cases	Non-cases	*P* for difference
Number	65	130	
Age, y	64.5	64.1	0.64
Male gender, %	34	34	1.00
Body mass index, kg/m^2	24.3	24.1	0.77
Current smokers, %	26	22	0.47
Current drinkers, %	28	28	1.00
Systolic blood pressure, mm Hg	137	136	0.43
Diastolic blood pressure, mm Hg	81	79	0.08
Antihypertensive medication, %	28	33	0.45
Diabetes mellitus, %	14	7	0.12
Serum total cholesterol, mg/dL	205	201	0.53
Cholesterol-lowering medication, %	3	10	0.09
Serum coenzyme Q10,[a] nmol/L	731	762	0.32
Coenzyme Q10/total cholesterol ratio,[a] 10^{-6}	138.5	151.4	0.15

[a] Median values and *P* values for differences tested by the Wilcoxon rank sum test.

Serum coenzyme Q10 was inversely associated with risk of incident dementia (Table 2). The multivariate odds ratios and 95% confidence intervals were 0.68 (0.26–1.78), 0.92 (0.33–2.56), and 0.23 (0.06–0.86), for individuals with the second, third, and highest quartiles of CoQ10, respectively, compared with the lowest quartile (*P* for trend = 0.05). A similar association was observed for the CoQ10/total cholesterol ratio. The respective odds ratios were 0.67 (0.25–1.78), 0.73 (0.28–1.92), and 0.21 (0.05–0.90) (*P* for trend = 0.04).

As supplemental analysis, we stratified dementia cases into those with history of stroke and those without it. Although the number of cases was limited, the associations were stronger for dementia without stroke for both serum CoQ10 and the CoQ10/total cholesterol ratio. The unadjusted odds ratios and 95% confidence intervals of dementia without stroke were 1.18 (0.37–3.75), 0.50 (0.15–1.70), and 0.46 (0.12–1.74) for individuals with the second, third, and highest quartiles of CoQ10 (*P* for trend = 0.13), and were 0.47 (0.15–1.48), 0.34 (0.11–1.09), and 0.24 (0.06–0.98) for respective quartiles of CoQ10/total cholesterol ratio (p for trend = 0.04). The corresponding odds ratios and 95% confidence intervals of dementia with stroke were 0.82 (0.26–2.57), 2.24 (0.63–7.96) and 0.35 (0.06–2.05) according to quartiles of CoQ10 (p for trend = 0.45), and were 1.68 (0.45–6.29), 2.05 (0.51–8.30) and 0.43 (0.06–2.97) according to quartiles of CoQ10/total cholesterol ratio (p for trend = 0.43).

4. Discussion

We found a strong inverse association between serum CoQ10 concentration and risk of disabling dementia in the Japanese population. To date, this is the first prospective study to examine the association between CoQ10 and incident dementia in a general setting.

Several animal studies have shown that CoQ10 may have a beneficial effect on dementia progression. In transgenic mice, dietary supplementation with CoQ10 reduced brain oxidative stress and deposition of amyloid plaque or amyloid-β and improved behavioral performance [11]. Rats with damaged hippocampi and cerebral cortices showed an adverse alteration in the markers of oxidative damage, but with supplementation with CoQ10, this alteration was reversed [8]. Thus, CoQ10 has been considered a

Table 2
Age and sex-matched and multivariate adjusted conditional odds ratios and 95% confidence intervals of incident dementia according to quartiles of serum coenzyme Q10 and coenzyme Q10/total cholesterol ratio.

	Men and women				
	Quartiles of serum coenzyme Q10 (nmol/L)				
	Q1	Q2	Q3	Q4	Trend *P*
	228–558	559–765	766–1015	1016–2353	
Median, nmol/L	459	635	850	1253	
Total disabling dementia					
Number of cases	18	20	18	9	
Number of non-cases	32	33	32	33	
Matched OR (95%CI)[a]	1.0	1.03 (0.47–2.29)	0.94 (0.41–2.14)	0.43 (0.16–1.19)	0.10
Multivariable OR (95%CI)[c]	1.0	0.68 (0.26–1.78)	0.92 (0.33–2.56)	0.23 (0.06–0.86)	0.05
	Quartiles of serum coenzyme Q10/total cholesterol ratio (10^{-6})				
	Q1	Q2	Q3	Q4	Trend *P*
	54.1–107.5	107.6–151.3	151.4–203.6	203.7–489.1	
Median, 10^{-6}	91.2	127.3	173.6	230.7	
Total disabling dementia					
Number of cases	21	19	17	8	
Number of non-cases	32	33	33	32	0.02
Matched OR (95%CI)[a]	1.0	0.80 (0.35–1.81)	0.72 (0.31–1.67)	0.28 (0.09–0.84)	
Multivariable OR (95%CI)[b]	1.0	0.67 (0.25–1.78)	0.73 (0.28–1.92)	0.21 (0.05–0.90)	0.04

[a] Matched with age (±3 years), sex and baseline-year.
[b] Multivariable model further includes body mass index, smoking status, alcohol consumption, diastolic blood pressure, diabetes mellitus and medication of hypertension and hypercholesterolemia.
[c] Further includes serum total cholesterol.

promising treatment for Alzheimer disease. However, a recent randomized control trial of patients with mild-to-moderate Alzheimer disease did not show that antioxidant treatment, including supplementation with high-dose CoQ10, improved the indices of markers of oxidative stress or of neurodegeneration in the cerebrospinal fluid [12]. Although this finding warrants confirmation by replication studies, when it is taken together with the findings of the present study, we assume that CoQ10 could have a more prominent impact on prevention, rather than on treatment, of dementia.

The limitations of this study include (1) the relatively small number of cases, although the associations were strong enough to be detected; (2) the diagnoses of disabling dementia conducted by attending physicians, although such diagnosis by attending physicians was previously validated [14]; and (3) the use of long-stored sera, although a previous study showed that the plasma CoQ10 value was unchanged after being deep-frozen and stored for 3 years [18]. When we excluded the serum samples collected before 1989 (23 cases and 46 matched controls excluded), the results were similar (not shown). Fourth limitation is that we did not classify dementia into Alzheimer type and vascular type. Instead, we have information on dementia with and without history of stroke. The associations seemed stronger for dementia without history of stroke, which needs to be confirmed by further studies. Last, we did not survey the dementia at baseline. However, we constructed the baseline at least 5 years prior to the beginning of dementia survey, so the possibility of reverse causation may be small.

The inverse association between serum CoQ10 levels and incident dementia did not directly assure that dietary intake of CoQ10 would prevent dementia. Furthermore, CoQ10 supplements were not generally available in Japan at the era of the baseline period (1984–1994). The impact of dietary or supplementary intake of CoQ10 was not tested in the present study, which must be examined by a randomized control trial in the future.

In conclusion, the serum level of CoQ10 was inversely associated with disabling dementia in this Japanese general population, which suggests that higher serum CoQ10 levels may have a beneficial effect on prevention of dementia.

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