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Ⅳ. 研究成果の刊行物・別刷

Differences in circadian variation of cerebral infarction, intracerebral haemorrhage and subarachnoid haemorrhage by situation at onset

S Omama, Y Yoshida, A Ogawa, T Onoda and A Okayama

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PAPER

Differences in circadian variation of cerebral infarction, intracerebral haemorrhage and subarachnoid haemorrhage by situation at onset

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Background: The precise time of stroke onset during sleep is difficult to specify, but this has a considerable influence on circadian variations of stroke onset.
Aim: To investigate circadian variations in situations at stroke onset—that is, in the waking state or during sleep—and their differences among subtypes.
Methods: 12 957 cases of first-ever stroke onset diagnosed from the Iwate Stroke Registry between 1991 and 1996 by computed tomography or magnetic resonance imaging were analysed. Circadian variations were compared using onset number in 2-h periods with relative risk for the expected number of the average of 12 2-h intervals in the waking state or during sleep in cerebral infarction (CIF), intracerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH).
Results: ICH and SAH showed bimodal circadian variations and CIF had a single peak in all situations at onset, whereas all three subtypes showed bimodal circadian variations of stroke onset in the waking state only. These variations were different in that CIF showed a bimodal pattern with a higher peak in the morning and a lower peak in the afternoon, whereas ICH and SAH had the same bimodal pattern with lower and higher peaks in the morning and afternoon, respectively.
Conclusions: Sleep or status in sleep tends to promote ischaemic stroke and suppress haemorrhagic stroke. Some triggers or factors that promote ischaemic stroke and prevent haemorrhagic stroke in the morning cause different variations in the waking state between ischaemic and haemorrhagic stroke.

Stroke occurrence shows chronobiological variations,[1] such as circannual variations, circaseptan variations and circadian variations. Various patterns have been reported but no conclusions have yet been reached on circadian variations. The circadian variations of stroke onset may differ according to subtype or reporter, and are classified as cerebral infarction (CIF) with a single peak[2–4] or double peaks,[7 8] subarachnoid haemorrhage (SAH) with a single peak[9] or double peaks,[6 10–14] and intracerebral haemorrhage (ICH) with double peaks.[6 10 12] Most previous studies have not treated the three major subtypes simultaneously. Only three reports[6–8] discussed all the three subtypes, but the number of cases of ICH, especially of SAH, was too small for investigation of circadian variation. This may have led to differences in the conceived patterns of circadian variation. Large numbers of cases in population-based samples are required to investigate and compare the circadian variations of stroke onset among subtypes. For investigation of the triggers and risk factors of stroke onset, it is necessary to determine the circadian variations of stroke onset with precise times. The precise time of stroke onset during sleep is difficult to specify, but this has a considerable influence on circadian variations of stroke onset.

We investigated circadian variation in stroke onset by situations at onset in CIF, ICH and SAH in a Japanese population, by using stroke registry data. We also investigated the differences in circadian variations, triggers and risk factors among subtypes.

PATIENTS AND METHODS

Stroke registry

A stroke registration programme has been instigated in the Iwate prefecture in the northern part of Honshu Island, Japan, which has a population of 1.4 million. The government of Iwate prefecture and the Iwate Medical Association have been coordinating this programme with all medical facilities (hospitals, medical offices and nursing homes) since January 1991. Registration forms are submitted to the registration office of the Iwate Medical Association by mail when a patient with stroke leaves the medical facility. All data are checked by trained staff for duplicate registration.

The registration form consists of information such as the patient's name, address, date of birth, stroke subtype, date of onset, situation at onset, symptoms and clinical findings, family history of apoplexy, histories of hypertension, diabetes and hyperlipidaemia, and use of antihypertensive or anticoagulant drugs before stroke onset. The results of computed tomography or magnetic resonance imaging (MRI), surgical treatment and outcome were registered. Stroke diagnostic criteria for CIF, ICH and SAH in this registry are based principally on the criteria established for the Monitoring System for Cardiovascular Disease commissioned by the Ministry of Health and Welfare.[15] These criteria correspond with those published by the World Health Organization[16] and define stroke as the sudden onset of neurological symptoms. Cases of traumatic ICH and SAH are not registered. A total of 16 997 cases (9121 men and 7876 women; average age 66.5 and 70.6 years, respectively) were registered between January 1991 and December 1996: 10 093 cases of CIF, 4603 cases of ICH, 1682 cases of SAH and the remaining 619 cases of other cerebrovascular stroke (transient ischaemic attack, cerebral venous thrombosis and unclassified stroke in the registry data). Registered patients hospitalised with stroke accounted for 97.5% (16 585/16 997) of the total

Abbreviations: CIF, cerebral infarction; ICH, intracerebral haemorrhage; MRI, magnetic resonance imaging; SAH, subarachnoid haemorrhage

number of patients. The patients who were diagnosed using computed tomography or MRI accounted for 95.5% (16 240/16 997) of the total number. For our study, 619 patients with other cerebrovascular stroke were excluded. Furthermore, 649 patients diagnosed without computed tomography or MRI and 2772 patients with recurrent stroke were excluded. Our study was conducted using data for the remaining 12 957 patients (7575 with CIF, 3852 with ICH and 1530 with SAH) of first-ever stroke diagnosed using computed tomography or MRI.

Analysis of onset time

Onset time was registered in hourly intervals in the registry. In patients perceiving the occurrence of stroke on awakening, the time of perception was used as the onset time. When the precise onset time was not clear, whether the stroke occurred in the morning or in the afternoon was registered if possible. When the time of onset could not be identified, only the date of onset was registered.

The situation at stroke onset was registered in detail during exercise, during meals, while working, bathing, defecating or urinating, sleeping, drinking, chatting, watching television or in other situations. These situations were categorised simply as "in the waking state" or "during sleep". The cases in which onset time was not registered were categorised as "unknown situation".

For determination of the time of stroke onset, the day was divided into 12 2-h intervals. The cases in which onset times were registered in the morning or in the afternoon only were redistributed equally between pertinent intervals, and those in which onset time was not registered were redistributed equally into 12 intervals. Data were statistically analysed with χ^2 test for goodness of fit to the null model of equal distribution of stroke to evaluate the circadian variations in stroke onset. To estimate the relative risk (RR) of stroke occurring in a specific time period, the observed number of strokes was compared with the average number of 12 2-h intervals.

RESULTS

Table 1 shows the characteristics of the patients with first-ever stroke having CIF, ICH and SAH, diagnosed using computed tomography or MRI.

In all subtypes of stroke, men were about 5 years younger than women on average (men *v* women: CIF, 68.5 (11.5) *v* 73.1 (11.4); ICH, 62.9 (12.3) *v* 68.9 (12.4); SAH, 56.3 (13.4) *v* 62.8 (13.0)). Some data on the ages at onset were missing because the date of onset was not recorded in the registry.

Table 2 shows the percentages of cases in which the onset time was registered hourly, in the morning or afternoon, and unspecified cases, and the proportions of the categorised situation at onset (in the waking state, during sleep and unknown situation).

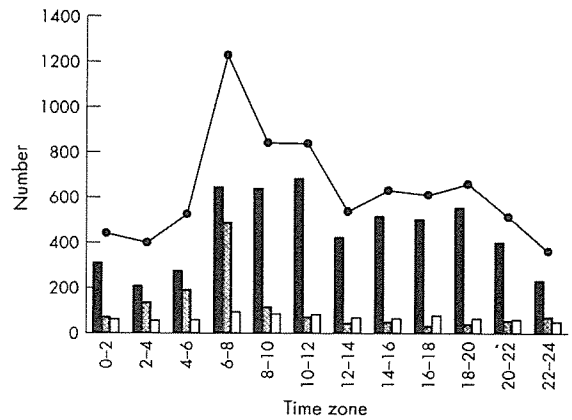

Figure 1 Time-specific onset number for 12 2-h intervals by situation at onset of cerebral infarction. Solid columns, in the waking state; shaded columns, during sleep; empty columns, unknown situation; solid circles, all onset situations.

The percentage of cases of CIF registered hourly was less than those of ICH and SAH (66.8% *v* 82.0% and 85.5%, respectively; $p<0.05$). The percentages of specified cases were not markedly different between the sexes in any subtype. We found no significant differences in age between cases that were specified hourly, in the morning or afternoon, and unspecified cases in any subtype. The percentage of cases of CIF, registered hourly, in which stroke onset occurred while the patient was asleep was more than those of ICH and SAH (14.2% *v* 8.8% and 9.5%, respectively; $p<0.05$). The proportions of categorised situation at onset were similar between cases of ICH and SAH.

Time-specific onset numbers for 12 2-h periods

The time-specific onset numbers by sex were pooled because the characteristics of circadian variation were not markedly different between men and women in all subtypes (table 3).

Figure 1 shows the time-specific onset pattern of cases of CIF. In all onset situations, the circadian variation showed a sharp peak during the period from 06:00 to 07:59 (RR 194.0% (95% confidence interval (CI) 177.2% to 212.4%)), a small dip around noon, a smaller second peak from 18:00 to 19:59 (RR 104.3% (95% CI 94.0% to 115.8%)) and a nadir during the

Table 1 Characteristics of patients with first-ever stroke, diagnosed using computed tomography or magnetic resonance imaging

Variable	CIF, n=7575	ICH, n=3852	SAH, n=1530
Sex, n (%)			
Male	4238 (55.9)	2079 (54.0)	545 (35.6)
Female	3337 (44.1)	1773 (46.0)	985 (64.4)
Mean age (SD), years			
Men	68.5 (11.5)	62.9 (12.3)	56.3 (13.4)
Women	73.1 (11.4)	68.9 (12.4)	62.8 (13.0)
All	70.5 (11.7)	65.6 (12.7)	60.5 (13.5)
Age distribution (years), n (%)			
0–49	313 (4.1)	377 (9.8)	323 (21.1)
50–59	756 (10.0)	751 (19.5)	329 (21.5)
60–69	2007 (26.5)	1165 (30.2)	444 (29.0)
70–79	2433 (32.1)	883 (22.9)	281 (18.4)
Over 80	1574 (20.8)	549 (14.3)	110 (7.2)
Unknown	492 (6.5)	127 (3.3)	43 (2.8)

CIF, cerebral infarction; ICH, intracerebral haemorrhage; SAH, subarachnoid haemorrhage.

Table 2 Cases in which onset time was specified hourly, in the morning or afternoon, or was unspecified

	Cerebral infarction		Intracerebral haemorrhage		Subarachnoid haemorrhage	
	n	%	n	%	n	%
Hourly						
In the waking state	3726	49.2	2668	69.3	1104	72.2
During sleep	1079	14.2	341	8.8	146	9.5
Unknown situation	255	3.4	150	3.9	58	3.8
Morning or afternoon	788	10.4	233	6.1	74	4.8
Unspecified	1727	22.8	460	11.9	148	9.7
All	7575	100.0	3852	100.0	1530	100

night (χ^2 test, $p<0.001$). The cases in which onset occurred in the waking state showed two peaks: one from 10:00 to 11:59 (RR 152.2% (95% CI 136.0% to 170.4%)) and the other from 18:00 to 19:59 (RR 123.7% (95% CI 109.9% to 139.3%)), with a dip around noon and a nadir during the night (χ^2 test, $p<0.001$). The peak in the morning was higher than that in the afternoon. The cases in which onset occurred during sleep showed a single peak during the period from 06:00 to 07:59 (RR 426.6% (95% CI 353.1% to 515.5%); χ^2 test, $p<0.001$).

Figures 2 and 3 show the time-specific onset patterns of ICH and SAH. For all onset situations, two peaks were observed: one from 06:00 to 07:59 (RR 153.1% (95% CI 134.0% to 174.9%) and RR 144.1% (95% CI 116.2% to 178.5%), respectively) and the other from 18:00 to 19:59 (RR 165.8% (95% CI 145.4% to 189.0%) and RR 154.8% (95% CI 125.3% to 191.2%), respectively), with a dip around noon and a nadir during the night (χ^2 test, $p<0.001$). The cases in which onset occurred in the waking state showed variations similar to those seen in all cases. The cases with onset in the waking state showed two peaks: one from 06:00 to 07:59 (RR 133.0% (95% CI 114.3% to 154.8%) and RR 135.7% (95% CI 106.8% to 172.4%), respectively) and the other from 18:00 to 19:59 (RR 179.8% (95% CI 156.0% to 207.2%)) and from 16:00 to 17:59 (RR 168.0% (95% CI 133.7% to 211.1%)), respectively (χ^2 test, $p<0.001$). The cases of ICH and SAH in which onset occurred during sleep showed a single peak in the period from 06:00 to 07:59 (RR 343.4% (95% CI 239.2% to 493.1%)) and from 04:00 to 05:59 (RR 252.8% (95% CI 123.2% to 457.5%)), respectively (χ^2 test, $p<0.001$).

DISCUSSION

Validation of cases in the stroke registry for this study

We used the stroke registry data from the Iwate prefecture. In this registry, the annual registration rates, which were considered to be the annual incidence rates of onset of first-ever stroke per 100 000 people from 1991 to 1996 were

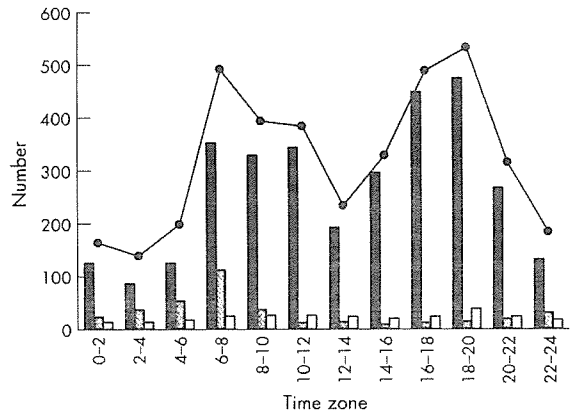

Figure 2 Time-specific onset number for 12 2-h intervals by onset situation of intracerebral haemorrhage. Solid columns, in the waking state; shaded columns, during sleep; empty columns, unknown situation; solid circles, all onset situations.

Table 3 Time-specific onset number by sex

	Cerebral infarction		Intracerebral haemorrhage		Subarachnoid haemorrhage	
Time interval (h)	Men	Women	Men	Women	Men	Women
0–2	112	89	48	51	22	30
2–4	84	74	54	20	10	22
4–6	176	108	81	52	39	43
6–8	529	455	251	175	55	107
8–10	342	256	172	157	45	84
10–12	344	253	180	138	52	77
12–14	217	141	119	64	26	57
14–16	257	194	156	122	39	64
16–18	244	188	212	227	55	127
18–20	267	213	231	251	53	121
20–22	195	140	130	135	25	76
22–24	109	73	72	61	32	47
Morning*	321	260	90	72	24	32
Afternoon†	108	99	45	26	11	7
Unspecified‡	933	794	238	222	57	91
All	4238	3337	2079	1773	545	985

*Onset time registered in the morning.
†Onset time registered in the afternoon.
‡Onset time not registered.

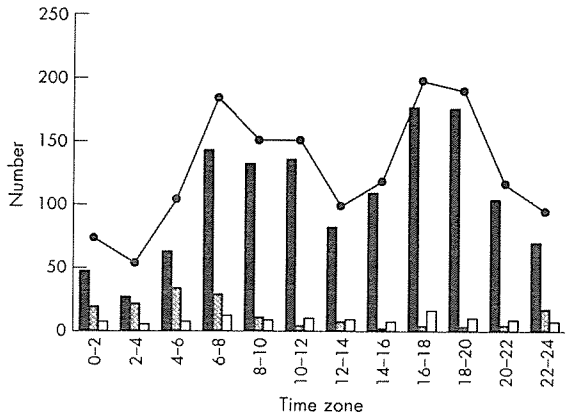

Figure 3 Time-specific onset number for 12 2-h intervals by onset situation of subarachnoid haemorrhage. Solid columns, in the waking state; shaded columns, during sleep; empty columns, unknown situation; solid circles, all onset situations.

88.9, 45.2 and 18.0 per year for CIF, ICH and SAH, respectively. The age-adjusted annual incidence rates of ICH and SAH, estimated using data from the 1985 Japanese population census, were similar to those of previous reports from Japan.[10 17 18] However, the rate for CIF was lower. The percentage of unregistered cases of CIF may be higher than those of ICH and SAH. The average ages of patients with CIF in our study were similar to those of patients in other studies based on the Japanese community.[17 18] The percentages of cases in which onset time was unspecified were similar to those of previous reports.[3 9 13 14 19–21] Therefore, there was probably no bias in the registry with regard to cases with a specific time zone or specific onset category.

Circadian variation of stroke onset

Previous studies showed that the circadian variation of stroke onset in patients with CIF had a single peak,[2–6] whereas those of patients with ICH[9 13 12] and SAH[6 10–14] had double peaks. Only three previous reports have discussed circadian variation of stroke onset separated on the basis of situation at onset—that is, in the waking state or during sleep[1 7 8]—but the numbers of cases included were too few (n = 914, 375 and 675, respectively) for conclusions to be drawn.

In our study, ICH and SAH showed bimodal circadian variations and CIF had a single peak for all cases in all onset situations, whereas all three subtypes showed bimodal circadian variations of stroke onset in the waking state only. This difference was due to the influence of cases of CIF in which onset occurred during sleep, which accounted for about 20% of the cases in all situations and were concentrated at the time of awakening. In contrast, the cases of ICH and SAH occurring during sleep, which accounted for about 10% of the cases in all situations, had a small influence but did not affect bimodal variations. This concentration at the time of wakening corresponded not to the concentration of stroke onset but to that of its recognition. This circadian variation of stroke onset for all cases is actually a sociological variation of stroke onset, and is information that is useful when accepting patients with stroke—for example, for ambulance or hospital services. If all the cases of stroke onset during sleep and with unknown situation occurred equally between midnight and 06:00, circadian rhythm did not lose its nadir during the night in ICH and SAH, but lost it in CIF. Lower blood pressure reduces the incidence of stroke, but nocturnal low blood pressure is a risk factor for ischaemic stroke.[22] Disordered breathing in sleep was reported to be a risk factor for ischaemic stroke onset at night.[23] This shows that sleep or status in sleep tends to promote ischaemic stroke and suppress haemorrhagic stroke.

In the waking state, bimodal circadian variations were different in that CIF showed a bimodal pattern with a higher peak in the morning and a lower peak in the afternoon, whereas ICH and SAH had a bimodal pattern with a lower peak in the morning and a higher peak in the afternoon. Onset time in the waking state was more accurate than those during sleep or with an unknown onset situation. The bimodal circadian variation of stroke onset while awake seems useful for investigation of the trigger for stroke onset. Several previous studies have concluded that arterial blood pressure is a trigger for haemorrhagic stroke onset.[9 11 13 14 20 24 25] Our results on ICH and SAH, showing very similar variations, indicated that the triggers for stroke onset were the same for ICH and SAH. Ischaemic and haemorrhagic stroke were reported previously as having the same trigger.[9] In our study, the results of bimodal circadian variation in the waking state for both ischaemic and haemorrhagic stroke indicated that both types of stroke have a common trigger. However, some other factors are required to explain the difference in heights of the peaks in the morning and afternoon between ischaemic and haemorrhagic stroke. Previous studies indicated increases in the levels of haematocrit, platelet aggregability and hypercoagulability in the morning.[26 27] These factors promote ischaemic events and prevent haemorrhagic events. The triggers for stroke onset seem to consist of two types of factor—that is, blood pressure, which is common to both ischaemic and hemorrhagic stroke and shows a bimodal pattern, and haemostatic functions, which promote ischaemic stroke and prevent haemorrhagic stroke in the morning.

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CRP levels are elevated in smokers but unrelated to the number of cigarettes and are decreased by long-term smoking cessation in male smokers

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Abstract

Background. It is not clear whether there is a dose–response relationship between the number of cigarettes smoked per day and CRP level and whether there is a relationship between the length of smoking cessation and CRP level.

Methods. Geometric mean levels of CRP were compared in smoking status groups for 1926 men aged 40 to 69 years using analysis of covariance.

Results. After adjusting for several confounding factors, geometric mean levels of CRP (mg/L) were significantly different among the three smoking status groups (0.41 in non-smokers, 0.57 in current smokers, 0.48 in past smokers, $P = 0.051$). A linear trend was not found in the relationship between CRP level and number of cigarettes smoked per day. The mean CRP level in the long cessation (>5 years) group was significantly lower than that in the short cessation (≤5 years) group (0.45 vs. 0.58, $P = 0.051$) and similar to that in the non-smokers group (0.45 vs. 0.41, NS).

Conclusions. CRP levels in current smokers are elevated but unrelated to the number of cigarettes smoked per day. In past smokers, long-term smoking cessation may contribute to the reduction in risk of development of cardiovascular diseases through inflammatory mechanisms.

Keywords: Smoking cessation; C-reactive protein; Cross-sectional study; Cardiovascular disease; Iwate-KENCO study

Chronic inflammation plays a pivotal role in the development of atherosclerosis [1]. Traditional risk factors are thought to induce inflammatory reaction and to cause the development of atherosclerosis [2]. Cigarette smoking is thought to be one of the major factors responsible for promotion and progression of atherosclerosis [3–5], although the mechanisms underlying the pathophysiology of atherogenesis have not been elucidated. Thus, several studies have focused on the association between smoking and inflammatory response [6–8].

C-reactive protein (CRP) is one of the most widely used inflammatory markers because of its high level of accuracy and its availability. High-sensitivity assays for CRP that provide information on low-grade inflammation [9] have recently become available. Epidemiological studies have revealed that increased serum CRP level is positively associated with risk of development of cardiovascular diseases [6,7,10–16].

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However, it has not been determined whether a dose–response relationship between the number of cigarettes smoked and CRP level exits [6–8]. It has also not been determined whether there is a relationship between the length of smoking cessation period and serum CRP level [8,17].

In this study, we examined the association between number of cigarettes smoked per day and serum CRP levels and the association between length of the smoking cessation period and serum CRP levels in apparently healthy Japanese men.

Subjects and methods

Study subjects

This study is a part of the ongoing Iwate-KENCO Study (Iwate KENpoku COhort Study), which has been carried out since 2002 in Iwate Prefecture, Japan. The study area consists of four municipalities (Ninohe City, Ichinohe Town, Karumai Town and Kunohe Village) with a total population in 2002 of 62,605, including 13,046 men aged 40 to 69 years. Invitations to multiphasic health screening were issued by government offices in each community. In 2002, 2337 (17.9%) of the 13,046 men aged 40 to 69 years participated in annual health checkups. Of those participants, 1950 men gave written informed consent for participation in this study (acceptance rate: 86.9%).

Nineteen subjects with CRP levels greater than 10 mg/L were excluded to avoid analysis of data from subjects who had developed acute inflammatory disease [18]. Five subjects were excluded because of lack of anthropometrical data. The remaining 1926 men were enrolled in this study.

This study was approved by the Medical Ethics Committee of Iwate Medical University and conducted in accordance with the guidelines of the Declaration of Helsinki.

Measurements

Measurements of blood pressure were performed by well-trained staff. Participants were asked to avoid eating or exercise 30 min before measurements. Weight was measured with an automated scale (TANITA digital scale Model BWB-200). Height was measured using a digital handle scale (YAGAMI model 48525YG-200D). Blood pressure was measured twice in the sitting position using an automatic device (BP-103i IIModel 513000, Nippon Colin, Komaki, Japan) after urination and a 5-min rest. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were each calculated as the mean of two measurements. Body mass index (BMI) was calculated as weight (kg) divided by the square of body height (m).

Self-administered questionnaires on demographic characteristics, history of cardiovascular disease and apoplexy, drug use, alcohol consumption, smoking and dietary information were used to collect individual information. In this questionnaire, current smokers were asked about the number of cigarettes smoked per day and duration of smoking. Past smokers were asked about the number of cigarettes smoked per day and age at which they had stopped smoking.

Laboratory methods

Casual blood samples were drawn from antecubital veins of seated participants with minimal tourniquet use into vacuum tubes containing EDTA (glucose, HbA1c) or a serum separator gel (CRP, lipids). The samples were transported to a laboratory (Iwate Health Service Association) and analyzed.

Serum levels of CRP were determined by the latex-enhanced immunonephelemetric method (Dade Behring Diagnostic, Germany) with a threshold of 0.1 mg/L. In this estimation, CRP values under the minimum detectable level were regarded as being 0.1 mg/L. Total cholesterol (TC) levels were determined by an enzymatic assay, triglyceride (TG) levels were determined by an enzyme-colorimetric assay, high-density lipoprotein cholesterol (HDLC) levels and low-density lipoprotein cholesterol (LDLC) levels were determined by a direct quantitative assay, and plasma glucose levels were determined by the hexokinase ultraviolet method. All of the above biochemical data were analyzed using an automated analyzer (HITACHI 7700). Glycosylated hemoglobin (HbA1c) levels were determined by high-performance liquid chromatography using an automated analyzer (TOSOH HLC-723G7 Japan). Determinations of TC levels and HDLC levels were performed under the quality control program of the Center for Disease Control in the United States through the Osaka Medical Center for Health Science and Promotion, Japan.

Data handling and classification

To examine the relationships between CRP level and cardiovascular risk factors, participants were divided into quartile groups according to CRP level. To examine the relationship between the pack-years of smoking and CRP level, current smokers were subdivided into three groups according to pack-years of smoking. To examine the relationship between number of cigarettes smoked per day and CRP level, current smokers were also subdivided into three groups according to number of cigarettes smoked per day: a light smoker group (1–19 cigarettes/day), moderate smoker group (20–29 cigarettes/day) and heavy smoker group (≥30 cigarettes/day). To examine the relationship between length of smoking cessation period and CRP level, past smokers were subdivided into two groups according to length of smoking cessation period: a short cessation period group (no smoking for less than 5 years) and a long cessation period group (no smoking for 5 years or more).

Several studies have shown that alcohol intake [19,20] and exercise [21,22] are associated with serum CRP level. Regular drinking was defined as drinking 5 days or more per week and exercise habit was defined as doing exercise at least 60 min per month.

Statistical analysis

One-way analysis of variance (ANOVA) was used to test differences among three groups or more. Multiple comparisons were performed using Bonferroni's method. Comparisons of skewed data were performed using the Mann Whitney *U* test. Multiple linear regression analysis was performed using natural logarithm-transformed CRP (ln CRP) as a dependent variable and smoking status patterns (light smoker, moderate smoker, heavy smoker and past smoker), age, BMI, systolic blood pressure and levels of HbA1c, HDLC and LDLC, which were significantly related to CRP level in univariate analysis, as independent variables.

After adjusting for several confounding factors (those significantly related to ln CRP levels in a multiple regression analysis), geometric mean levels of CRP were compared using analysis of covariance (ANCOVA). Linear trends between number of cigarettes smoked per day and geometric mean levels of CRP and between pack-years of smoking and geometric mean levels of CRP were examined after adjusting for major confounders. A P value less than 0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS software (version 11.0, Chicago, IL).

Results

Characteristics according to smoking status are shown in Table 1. Age, BMI, HDLC levels and prevalence of exercise habit in current smokers were lower than those in non-smokers. The percentage of current smokers who were regular drinkers was higher than the percentage of non-smokers who were regular drinkers. Mean levels of crude CRP were 0.80 mg/L in non-smokers, 0.87 mg/L in past smokers and 0.98 mg/L in current smokers. Multiple comparisons using the Mann Whitney *U* test showed that serum CRP levels in current smokers were significantly higher than those in non-smokers ($P < 0.01$). The mean CRP levels in past smokers were intermediate between those in non-smokers and those in current smokers.

Characteristics according to quartile groups of CRP levels are shown in Table 2. Age, BMI, SBP, DBP, prevalence of smokers and levels of TC, TG, LDLC, plasma glucose and HbA1c were increased significantly with increase in CRP level. HDLC levels were inversely associated with CRP levels ($P < 0.01$).

Table 3 shows the results of multiple linear regression analysis using ln CRP as a dependent variable and using smoking status patterns (past smoker, light smoker, moderate smoker and heavy smoker) as independent variables. The three patterns of current smoking status were significantly related to ln CRP levels, while the standardized coefficients were similar. Past smoking status was also significantly related to ln CRP level. The levels of HDLC, LDLC and HbA1c were also related to ln CRP level. The high levels of

Table 1
Descriptive characteristics of 1926 men aged 40–69 years with CRP levels less than 10 mg/L according to smoking status

	Non-Smoker	Past smoker	Current smoker	*P* value
Number	661	503	768	
AGE (years)	60.2 (7.4)	59.4 (8.4)	56.1 (8.6)	< 0.001
BMI (kg/m^2)	24.0 (2.8)	24.2 (2.9)	23.5 (3.1)	< 0.001
SBP (mm Hg)	128.9 (19.1)	129.3 (19.4)	126.0 (19.6)	0.003
Regular drinker	41.3%	50.1%	58.8%	< 0.001*
Exercise habit	32.3%	37.9%	26.6%	< 0.001*
TC (mg/dL)	197.4 (33.8)	201.6 (32.8)	195.9 (34.6)	0.012
TG (mg/dL)	133.8 (91.5)	151.0 (119.2)	152.0 (95.5)	0.601
HDLC (mg/dL)	57.8 (14.8)	58.0 (15.7)	55.8 (14.9)	0.010
LDLC (mg/dL)	117.9 (31.2)	120.0 (29.6)	117.3 (32.7)	0.305
Plasma glucose (mg/dL)	114.8 (38.7)	112.9 (34.0)	115.1 (43.3)	0.604
HbA1c (%)	5.07 (0.78)	5.11 (0.76)	5.12 (0.87)	0.528
CRP (mg/L)	0.79 (1.20)	0.87 (1.24)	0.98 (1.30)	0.022

Data are expressed as means (standard deviation) or percentages. *P* values for comparison among three groups by ANOVA.
Abbreviations: TC, total cholesterol level; TG, triglyceride level; HDLC, high density lipoprotein cholesterol level; LDLC, low-density lipoprotein cholesterol level; HbA1c, percentage of glycosylated hemoglobin; SBP, systolic blood pressure.
* *P* values for χ^2 test among three groups.

correlation among the explanatory variables seem to exist. We also performed a multiple regression model using the products of pairs of explanatory variables as independent variables for adjusting for interactions among explanatory variables. The results were not changed even after adjusting for interactions among explanatory variables. And analysis of residuals showed the robustness of the multiple regression model.

Non-adjusted and adjusted geometric mean levels of CRP are shown in Table 4. Adjusted mean CRP levels were significantly different among three groups (Non-smoker vs. Current smoker, $P = 0.01$; Non-smoker vs. Past smoker, $P = 0.04$; Past smoker vs. Current smoker, $P < 0.01$). Adjusted mean CRP levels were different in the short cessation group and long cessation group (0.45 vs. 0.58, $P = 0.05$). Adjusted mean CRP level in the long cessation group was similar to that in the non-smoker group (0.45 vs. 0.41, NS).

A significant linear trend was not observed either in the relationship of adjusted CRP levels among subgroups according to the number of cigarettes smoked per day or in the relationship of CRP levels among subgroups according to the pack-years of smoking.

Discussion

The main findings of this study were (1) CRP levels were elevated in current smokers regardless of the number of cigarettes smoked per day both before and after adjusting for major confounders and (2) there were significant differences between adjusted CRP levels in the short cessation group and long cessation group.

Inconsistent results have been reported for the relationship between number of cigarettes smoked per day and CRP

Table 2
Descriptive characteristics of 1926 men aged 40–69 years with CRP levels less than 10 mg/L according to quartile groups of CRP levels

CRP levels (mg/L)	0.1–0.2	0.3–0.4	0.5–0.9	1.0–9.4	*P* value
Number	506	471	492	457	
Age (years)	57.4 (8.5)	58.2 (8.2)	58.3 (8.4)	59.6 (8.2)	< 0.001
BMI (kg/m^2)	22.8 (2.7)	23.8 (2.6)	24.4 (3.0)	24.5 (3.2)	< 0.001
SBP (mm Hg)	123.9 (18.7)	128.5 (19.0)	129.2 (19.6)	130.1 (19.8)	< 0.001
Regular drinker	50.0%	49.8%	50.0%	50.1%	0.532
Exercise habit	25.8%	33.2%	34.7%	32.8%	0.022
Current smoker	35.0%	38.0%	42.1%	48.2%	< 0.001
TC (mg/dL)	190.9 (30.9)	198.6 (32.1)	202.0 (35.1)	208.5 (36.5)	< 0.001
TG (mg/dL)	118.8 (72.6)	141.5 (93.4)	160.7 (112.1)	162.7 (116.6)	< 0.001
HDLC (mg/dL)	61.9 (15.0)	58.7 (14.9)	54.3 (13.9)	53.3 (14.9)	< 0.001
LDLC (mg/dL)	110.3 (28.3)	117.6 (30.6)	122.8 (31.6)	122.7 (33.5)	< 0.001
Plasma glucose (mg/dL)	110.6 (32.6)	124.7 (41.9)	113.5 (36.9)	119.4 (45.6)	0.002
HbA1c (%)	4.95 (0.56)	5.04 (0.75)	5.14 (0.91)	5.27 (0.95)	< 0.001

Data are expressed as means (standard deviation) or percentages. *P* values for linear trend tests among quartile groups.
Abbreviations: NS, not significant; TC, total cholesterol level; TG, triglyceride level; HDLC, high-density lipoprotein cholesterol level; LDLC, low-density lipoprotein cholesterol level; HbA1c, percentage of glycosylated hemoglobin; SBP, systolic blood pressure.

level and between pack-years of smoking and CRP level [6–8,23]. Tracy et al. did not find a dose–response relationship between pack-years of smoking and CRP level [23]. Koenig et al. analyzed the associations between number of cigarettes smoked per day and CRP level and between pack-years of smoking and CRP level, but they did not report a dose–response relationship between number of cigarettes smoked per day and CRP levels or between pack-years of smoking and CRP level [6,7]. Fröhlich et al. reported that the number of cigarettes smoked per day, pack-years of smoking and duration of smoking are positively associated with CRP levels in men, although CRP levels in moderate to heavy smokers (13 cigarettes or more per day) were similar in their study [8].

It has been reported that there is a strong and consistent dose–response relationship of smoking with coronary artery disease (CAD) and that there is a positive relationship between the risk of development of CAD and CRP level [4,7,24]. However, our data did not show a positive association between number of cigarettes smoked per day and CRP level in current smokers. This is in contrast to the dose–response relationship between number of cigarettes smoked per day and HDLC level found in our study (crude mean levels of HDLC: 56.3 mg/dL in mild smokers, 56.1 mg/dL in moderate smokers, 54.4 mg/dL in heavy smokers, linear trend test: $P < 0.05$) and in a previous study [25]. Variation of susceptibility to smoking may explain the lack of a dose–response relationship between CRP level and number of cigarettes smoked. Smokers with high CRP levels possibly have a high risk of development of CVD.

Table 3
Standardized regression coefficient by multiple regression analysis predicting logarithm-transformed CRP among 1926 men aged 40–69 years with CRP levels less than 10 mg/L

	Standardized coefficient	*P* value
Current smoking		
Number of cigarettes		
1–19/day	0.082	0.001
20–29/day	0.096	< 0.001
30/day	0.106	< 0.001
Ex-smoking	0.059	0.020
Age (years)	0.132	< 0.001
BMI (kg/m^2)	0.131	< 0.001
SBP (mm Hg)	0.069	0.006
HDLC (mg/dL)	0.182	< 0.001
LDLC (mg/dL)	0.113	< 0.001
HbA1c (%)	0.110	< 0.001

Abbreviations: BMI, body mass index; HDLC, high-density lipoprotein cholesterol level; LDLC, low-density lipoprotein cholesterol level; HbA1c, percentage of glycosylated hemoglobin; SBP, systolic blood pressure.

In past smokers, our data showed that CRP levels were intermediate between those in non-smokers and those in current smokers. Similar results regarding CRP levels in past smokers were reported [6,8]; on the other hand, some studies reported that mean CRP levels in past smokers were similar to those in nonsmokers [7].

As for the relationship between smoking cessation period and CRP levels, Fröhlich et al. reported that duration of smoking cessation is inversely associated with CRP levels in men. However, CRP levels in past smokers who had not smoked for more than 20 years were still higher than those in subjects who had never smoked [8]. In the present study, it was found that the longer the smoking cessation period was, the lower the CRP levels in past smokers were. Adjusted CRP levels in past smokers who had not smoked for 5 years or more were similar to those in subjects who had never smoked. Our results suggested that the risk reduction of CAD by smoking cessation could be explained by decline of CRP level.

There are several limitations of our study. First, smokers who are in good physical condition can continue to smoke the same number of cigarettes per day, whereas smokers who are not in good condition tend to cease smoking or reduce the number of cigarettes smoked per day. This may possibly explain the lack of a dose–response relationship between CRP level and number of cigarettes smoked per day. Second, some subjects in this study may have quit

Table 4
Non-adjusted and adjusted geometric means of CRP level for various categories of smoking status among 1926 men aged 40–69 years with CRP levels less than 10 mg/l

	Number	CRP (mg/L) geometric mean	Estimated CRP (mg/L) geometric mean	95% CI	
Smoking status					
Non-smoker	663	0.43	0.41	(0.39–0.45)[*]	[*]
Current smoker	762	0.54	0.57	(0.53–0.61)	
Past smoker	503	0.49	0.48	(0.44–0.52)	
Current smoker groups					
Number of cigarettes/day[**]					
1–19 /day	217	0.52	0.55	(0.48–0.62)	Linear trend NS
20–29 /day	371	0.54	0.56	(0.51–0.62)	
30 /day	172	0.58	0.63	(0.53–0.71)	
Pack-years of smoking[**]					
0.3–25.0 years	257	0.49	0.53	(0.46–0.59)	Linear trend NS
25.2–39.0 years	229	0.61	0.57	(0.50–0.64)	
40.0–105.0 years	273	0.48	0.61	(0.54–0.68)	
Past smoker groups[***]					
Length of cessation period					
<5 years	219	0.63	0.58	(0.49–0.70)	[*]
≥5 years	354	0.47	0.45	(0.41–0.50)	

Estimated CRP level's for persons aged 58.4 years with BMI of 23.9 (kg/m^2), SBP of 127.8 (mm Hg), HDLC of 57.0 (mg/dL), LDLC of 118.2 (mg/dL), and HbA1c of 5.10 (%). 95% CI (confidence interval) is based on standard errors from analysis of covariance.
[*] $P < 0.05$ by multiple comparisons (Bonferroni's method)
[**] $P < 0.01$ by multiple comparisons (Bonferroni's method)
[**] Numbers of cigarettes smoked per day were unknown in two current smokers.
[**] Smoking duration was unknown in one current smoker.
[***] Cessation periods were unknown in 30 past smokers.

smoking because of poor physical condition. Third, since past smokers who had not smoked for more than 5 years had a rather short smoking history and short smoking exposure period, the likelihood of smoking-related inflammation seems to low in those subjects. These factors may have accentuated the difference between CRP levels in the short cessation group and long cessation group. Finally, it is necessary to test in a longitudinal prospective investigation whether current smokers with high CRP levels have a high risk of developing CVD and whether CRP levels recover to former levels after smoking cessation.

In conclusion, CRP levels in current smokers are elevated but unrelated to the number of cigarettes smoked per day. The longer the smoking cessation period is, the lower are CRP levels in past smokers. The reduction in risk of development of CVD can be partially explained by decline of CRP level due to smoking cessation.

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Surveillance and measuring trends of stroke in Japan: The Takashima Stroke Registry (1988 – present)

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Stroke surveillance

Disease surveillance provides essential information that can be used for designing effective prevention strategies, appropriate allocation of health resources, assessment of effectiveness of the health programs, etc. Disease registries for chronic diseases, including stroke, are essential in determining the incidence and trends in a particular population.

Takashima Stroke Registry

The Takashima Stroke Registry is an integrated part of the ongoing Takashima Cardio-cerebrovascular Disease Registry, a disease registration system for stroke and acute myocardial infarction established in Japan in 1988. The registration study is a population-based prospective, observational study whose objective is to measure trends in the incidence and case fatality of stroke and to compare them with other populations within and outside Japan.

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Geographical setting

Figure 1 shows Takashima County, Shiga prefecture in the map of Japan. Takashima County is located in the predominantly rural area of Shiga prefecture in a central area of Japan. It is primarily composed of mountainous rural areas. The largest freshwater lake in Japan, Biwako Lake, is located to the east of Takashima County. Weather in the Shiga follows four very distinct seasons: winter, spring, summer, and autumn, with significant seasonal fluctuations.

Population characteristics

Table 1 shows the characteristics of the residents of Takashima County. It is a farming community with inhabitants mainly classified culturally into the same subgroup and has similar standards of living. The population has remained fairly stable during the 16-year study period, with a population of 55 451 (49·2% male and 50·7% female) in the year 2000 (1), with 22·3% of the population aged 65 years or more.

Case finding and registration process

Takashima County contains two community hospitals: Takashima General Hospital, a public facility with 261 beds located in the south of the county, and Makino Hospital, a private facility with 72 beds located in the north. Additionally, there is also a geriatric hospital, Imazu Hospital, which is the only dedicated facility for elderly people in the county. It has been estimated that approximately 98% of all hospital admissions are seen at these community hospitals (2). The remaining patients are seen at three tertiary care hospitals: Shiga University of Medical Science Hospital and Otsu Red Cross hospital in Otsu City, and Shiga Medical Center for Adults in Moriyama City, which have more sophisticated facilities for advanced treatment. These are located outside the county but within the Shiga prefecture.

Registered patients included all residents of the county who were hospitalized with stroke in the two community hospitals and the geriatric hospital. Also, the patients who are residents of Takashima County but were hospitalized with a stroke at any of the three tertiary hospitals outside the county were also included. Internist and specialist investigative personnel trained by neurologists and epidemiologists carried out both the case finding and registration of patients who met the criteria. Before final decisions on inclusion in the registry, physicians and epidemiologists checked the records for absolute verification for eligibility. Registration procedures were investigated once every 3 months at the six facilities. We registered all cases that met the inclusion criteria (2, 3) on the basis of the medical records from all the relevant hospitals inside and outside the county and the county ambulance records. We used the registration form of the Monitoring System for Cardiovascular Disease commissioned by the Ministry of Health and Welfare, Japan (3). Registered stroke pa-

