Original Article

Smoking Raises the Risk of Total and Ischemic Strokes in Hypertensive Men

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To examine the relation between cigarette smoking and risk of stroke and coronary heart disease among Japanese, we conducted a 14-year prospective study of 3,626 men aged 40−69, initially free from history of stroke and coronary heart disease. We identified 257 strokes (75 hemorrhagic and 173 ischemic strokes) and 100 coronary heart disease events. When we adjusted for age and other cardiovascular risk factors, a significant excess risk among current smokers of >20 cigarettes/day *vs*. never-smokers was found for total stroke (relative risk (RR)=1.6 (95% confidence interval (CI), 1.1−2.4)). The excess risk of total stroke was particularly evident among hypertensives (RR=2.3 (1.2−4.4)). The multivariate RR of ischemic stroke was 1.6 (1.0−2.5) for total subjects, and 2.2 (1.0−5.0) among hypertensives. Significant excess risks among current smokers of >20 cigarettes/day *vs.* never-smokers were also found for coronary heart disease (RR=4.6 (1.6−12.9)) and total cardiovascular disease (1.9 (1.3−2.7)). The estimated proportion of the events attributable to current smoking was 30 (95% CI, 11−44)% for total stroke and 34 (5−54)% for coronary heart disease. In conclusion, current smoking of >20 cigarettes per day increased the risk of both total stroke and ischemic stroke among Japanese middle-aged men, and particularly among middle-aged hypertensive men. (*Hypertens Res* 2003; 26: 209−217)

***Key Words*: smoking, stroke, coronary heart disease, follow-up studies, risk factors**

Introduction

Japan has a high prevalence of smoking for men and a low prevalence for women: the respective prevalences were 54.0% and 14.5% in 1999, although the prevalence of smoking for men has decreased since 1965 (*1*). There is limited evidence that smoking increases the risk of stroke in Japanese populations, whereas the relation between smoking and risk of coronary heart disease has been consistently reported (*2*–*6*). Previous Japanese cohort studies of approximately 1,000 to 8,000 individuals did not find any significant relationship between cigarette smoking and risks of total or ischemic stroke (*7*–*9*). On the other hand, a significant association between smoking and risk of total stroke was reported in a 7.7-years follow-up study of 6,359 Japanese white-collar workers aged 35–59 years, but the number of incidents of stroke was only 33 (*10*). A 13-year follow-up study of over 120,000 men showed a 30% higher age-adjusted mortality from total stroke and a 70% higher mortality from subarachnoid hemorrhage associated with smoking, but no excess mortality from ischemic stroke (*5*). Another 14-year follow-up study of 40,861 Japanese men showed a significant association between smoking and age-adjusted mortality from total stroke (*11*). These two studies, however, did not present multivariate relative risks adjusting for potential confounding factors. Moreover, mortality data on stroke are of limited value in identifying the etiologic role of smoking, because

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one-third of fatal strokes do not appear as the underlying cause of death (*12*).

We postulated that the lack or weakness of association between smoking and risks of stroke in most previous Japanese studies, in contrast to Caucasian studies, is due in part to the different proportions of ischemic stroke subtypes (lacunar infarction and large-artery occlusive infarction) between Japanese and Caucasians, a low statistical power to detect significant associations, and a lower concern for hypertension, a strong cardiovascular risk factor (*13*). We hypothesized that smoking raises the risk of total stroke, ischemic stroke, and coronary heart disease among middle-aged Japanese men, and that these trends are more evident among hypertensive men. Then, we used data from a long-term follow-up study of 3,626 men in three Japanese populations to investigate the relationship between smoking and risk of stroke and its subtypes as well as coronary heart disease.

Methods

Populations

The population surveyed included 3,754 men aged 40–69 years examined between 1975 and 1980 in Ikawa, a north-eastern rural community, between 1981 and 1986 in Kyowa, a mid-eastern rural community, and between 1975 and 1984 in the district of Yao City, a mid-western community. The overall participation rate was 63%. Persons who did not provide information on their smoking status ($n=7$) or persons with a history of stroke and/or coronary heart disease ($n=121$) were not entered into our study. Thus, data from a total of 3,626 men were used for the analyses. We excluded women from this analysis because women rarely smoke in Japan; the prevalence of current smokers in our cohort was only 8% in women compared with 69% in men. Subjects were followed-up to determine cardiovascular disease endpoints occurring by the end of 1997. The number of persons who moved out of the communities during the follow-up was 177 (5%) and that of persons who died was 709 (20%). They were censored at the date of moving out or the date of death. The average follow-up period was 14.3 years.

Surveillance of Incident Cardiovascular Disease

Participant follow-up included annual cardiovascular risk surveys to obtain histories of incident stroke and coronary heart disease and neurological examinations by the study physicians. For those patients who did not participate in the follow-up examinations, strokes were ascertained by mailed questionnaires, national insurance claims, ambulance records, reports by local physicians, and reports by public health nurses and health volunteers (*14*). From death certificates, cases with stroke as an underlying cause of death (International Statistical Classification of Diseases and Related Health Problems (ICD) 9 classification: stroke, 430–438; coronary heart disease, 410–414, 428 and 429) were selected and histories were obtained from their families. To confirm the diagnosis, all living patients were visited or called and their medical histories were taken by study physicians or public health nurses. Then, we reviewed the medical records, including ECG and CT and/or MRI films, for both non-fatal and fatal cases.

Stroke was defined as a rapid-onset focal neurological disorder persisting for ≥24 h, or until death. Transient ischemic attack was not included. The stroke subtype, *i.e.*, intraparenchymal hemorrhage, subarachnoid hemorrhage, or ischemic stroke, was determined primarily by CT or MRI using standardized criteria (*15*). Stroke cases that were diagnosed clinically but showed no lesion on CT or MRI were classified as ischemic stroke. The CT or MRI films were available for 75% of the stroke cases. Stroke cases without CT or MRI films were classified according to the clinical criteria (*16*) based on the criteria of Millikan (*17*). Previous studies have confirmed the validity of stroke subtype classification by clinical criteria (*18*).

The criteria for coronary heart disease were modified from those of a WHO Expert Committee (*19*). Painless types of coronary heart disease were not investigated because of the difficulty of making a definite diagnosis. Definite myocardial infarction was indicated by typical chest pain (lasting for ≥30 min) with the appearance of abnormal and persistent Q or QS waves and/or elevations of cardiac enzymes. Possible myocardial infarction was indicated by typical chest pain without positive changes in the ECG or enzyme elevation. Effort-associated angina pectoris was defined as repeated episodes of chest pain during effort, especially when walking, usually disappearing rapidly after the cessation of effort or by use of sublingual nitroglycerin. Sudden cardiac death was defined as death within 1 h from the abrupt onset of symptoms, unassociated with a previous diagnosis of coronary heart disease, stroke, or other identified causes of death. Definite and possible myocardial infarction, effort-associated angina pectoris, and sudden cardiac death were combined and presented as total coronary heart disease. Using these standardized criteria, final diagnoses were made by a panel of two or three study physician-epidemiologists who were blinded to baseline risk factor data.

Population Surveys of Cardiovascular Risk Factors

Risk factors for cardiovascular disease were measured at a baseline examination. An interviewer assessed the smoking history and the number of cigarettes smoked per day. Ex-smokers were defined as individuals who had quit smoking at least 3 months previously. To assess the reliability of smoking rate, a subsample (67%) of the baseline participants ($n=2,435$) were asked again about their smoking status at 3 to 7 years (5.1 years in average) after the baseline examination; the proportion of men who retained their same smoking status was 82% for never-smokers, 87% for ex-smokers,

59% for current smokers of ≤20 cigarettes per day, and 76% for current smokers of >20 cigarettes per day.

We measured several potential confounders: body mass index, arterial blood pressure, serum total cholesterol, proteinuria, ethanol intake, diabetes mellitus, hypertensive ophthalmoscopic changes, and ECG evidence of atrial fibrillation and ischemic myocardial change. Height in stocking feet and weight in light clothing were measured. Body mass index was calculated as weight (kg) divided by the square of height (m^2). Arterial blood pressures were measured by trained observers using standard mercury sphygmomanometers on the right arm of seated participants after a 5-min rest (*20*). Hypertension was defined as systolic blood pressure of ≥160 mmHg and/or use of antihypertensive medication. Serum total cholesterol was measured by the Liebermann-Burchard direct method using an Autoanalyzer II (Technicon, Terrytown, USA) (*21*). The laboratory was standardized by the Lipid Standardization Program of the Centers for Disease Control and Prevention in Atlanta, USA and successfully met the criteria of precision and accuracy of cholesterol measurements (*22*). Urine was analyzed for proteinuria (positive: ≥+) with Uristix (Ames Co., Elkhart, USA). An interview was conducted to determine the usual weekly intake of ethanol in *go* units (a Japanese traditional unit of volume corresponding to 23 g ethanol), which was converted to g of ethanol per day. Ex-drinkers were defined as men who had quit drinking at least 3 months previously. Diabetes mellitus was defined as fasting glucose of ≥7.0 mmol/l, or a non-fasting glucose of ≥11.1 mmol/l, and/or use of medication for diabetes.

To estimate athero-arteriosclerotic end-organ damages, a color photograph of the right ocular fundus was taken and coded according to Scheie's classification (*23*). Grades II or higher hypertensive or arteriosclerotic changes in the retinal arterioles were regarded as significant changes. Reliable photographs for grading were obtained in 90% of the participants; most of the remaining cases had cataract and were regarded as missing data. A resting ECG was obtained in the supine position and coded according to the Minnesota Code, second version (*19*). We regarded Minnesota Codes atrial fibrillation (8-3-1) and atrial flutter (8-3-2) as atrial fibrillation, and ST-T changes (4-1 to 4-3 or 5-1 to 5-3) as ischemic myocardial changes.

Statistical Analysis

Incidence rates per 1,000 person years were calculated according to the four smoking-status categories: never-smokers, ex-smokers, current smokers of ≤20 cigarettes per day, and current smokers of >20 cigarettes per day. Differences in age-adjusted mean values and the prevalence of potential confounding factors among the four smoking-status categories were tested by an analysis of covariance and χ^2 test, respectively. When the overall difference was significant ($p<0.05$), comparison of confounding factors between never-smokers and the other smoking categories was made using a Student's *t*-test or χ^2 test. The relative risk (RR) and 95% confidence interval (CI) relative to never-smokers were calculated after adjusting for age and other potential confounding factors using the Cox proportional hazards model. The proportionality was tested and accepted for each model. Potential confounding factors were age (years), systolic blood pressure levels (mmHg), antihypertensive medication use (yes *vs.* no), serum total cholesterol category (<4.14, 4.14–4.65, 4.65–5.17, 5.17–5.69 and ≥5.69 mmol/l), quartiles of sex-specific body mass index (kg/m^2), proteinuria (positive *vs.* negative), diabetes mellitus (yes *vs.* no), hypertensive and/or arteriosclerotic ophthalmoscopic changes (yes *vs.* no), atrial fibrillation (yes *vs.* no), ischemic myocardial changes (yes *vs.* no), ethanol intake category (non-current drinkers, current drinkers of <23, 23–46, 46–69, ≥69 g/day), and community. We used dummy variables for the covariates in the multivariate analyses, with the exception of age and systolic blood pressure levels, which were continuous variable. The relation between smoking and risk of total stroke was examined further after stratification by the two hypertension subgroups (systolic blood pressure <160 mmHg free from antihypertensive medication, and ≥160 mmHg or using antihypertensive medication). The stratified analysis was not conducted for coronary heart disease because of the small number of cases among never-smokers. Because the relation between smoking and cardiovascular disease was similar among the three surveyed populations, we presented the results of the combined cohorts adjusted for community. The population-attributable fraction was calculated by $P\times(1-1/RR)$, where P represents the prevalence of smokers among cases. The formula of Greenland was used for calculation of the 95% CI (*24*).

Results

During the 14.3-year follow-up, there were 257 incident strokes and 100 coronary heart disease events. The total number of cases of cardiovascular disease was 345, since 12 cases suffered from both stroke and coronary heart disease. There were 50 intraparenchymal hemorrhages, 25 subarachnoid hemorrhages, 173 ischemic strokes and 9 unclassified strokes. Among the coronary heart disease events, there were 64 myocardial infarctions, 24 effort-associated angina pectoris and 12 sudden cardiac deaths.

To examine confounders for smoking-disease associations, mean age and age-adjusted values of selected risk factors at baseline were compared among smoking categories (Table 1). Ex-smokers and smokers of ≤20 cigarettes per day were 1 to 2 years older than never-smokers. Mean systolic blood pressure and the prevalence of hypertension were higher in smokers of >20 cigarettes per day than in never-smokers, but such a difference was not found for mean diastolic blood pressure or the prevalence of antihypertensive medication use. Mean serum total cholesterol levels were

Table 1. Age-Adjusted Mean Values of Prevalence (%) or Risk Factors at Baseline According to Smoking Status in 3,626 Men Aged 40−69 Years

	Never-smokers	Ex-smokers	Current smokers	
			1–20/day	>20/day
Number	531	599	951	1,545
Age (years)	52	54***	53**	52
Systolic blood pressure (mmHg)	136	135	137	139**
Diastolic blood pressure (mmHg)	83	82	82	83
Use of antihypertensive medication (%)	14	13	13	13
Hypertension† (%)	21	19	22	25*
Serum total cholesterol (mmol/l)	4.79	4.91*	4.73	4.69*
Body mass index (kg/m^2)	23.6	23.4	22.5***	22.8***
Proteinuria (%)	4	3	5	6
Diabetes mellitus (%)	3	2	3	3
Atrial fibrillation on ECG (%)	1	2*	1	1
ST-T change on ECG (%)	3	6*	6*	4
Hypertensive and/or arteriosclerotic fundal changes (%)	23	13***	16**	19
Alcohol intake (g/day)	23	21	28**	33***
Ex-drinkers (%)	24	30*	21	18**

† Hypertension was defined as systolic blood pressure of ≧160 mmHg and/or use of antihypertensive medication. * $p<0.05$, ** $p<0.01$, *** $p<0.001$, compared with never smokers.

higher in ex-smokers, and lower in smokers of >20 cigarettes per day than in never-smokers. Mean body mass index was lower in current smokers than in never-smokers. The prevalence of proteinuria and diabetes mellitus did not vary among smoking categories. The prevalence of atrial fibrillation and ST-T changes on ECG was higher in ex-smokers than in never-smokers. The prevalence of hypertensive and/or arteriosclerotic ophthalmoscopic changes was lower in ex-smokers and smokers of ≤20 cigarettes per day than in never-smokers. Mean ethanol intake was higher in current smokers than in never-smokers, while the prevalence of ex-drinkers was higher in ex-smokers and was lower in current smokers of >20 cigarettes per day than in never-smokers.

The age and community-adjusted RR of total strokes was 1.9 (95% CI, 1.3–2.7) for smokers of >20 cigarettes per day compared with never smokers, and the trend remained statistically significant after adjustment for cardiovascular risk factors (Table 2). The respective age and community-adjusted RR of hemorrhagic stroke was 2.2 (1.1–4.4), but the association was no longer statistically significant after further adjustment for cardiovascular risk factors. The respective age and community-adjusted RR of ischemic stroke was 1.7 (1.1–2.8) and remained of borderline significance ($p=0.07$) after further adjustment for cardiovascular risk factors. The age and community-adjusted RR for smokers of >20 cigarettes per day was 1.9 (0.8–4.2) for intraparenchymal hemorrhage, 3.2 (0.7–14.1) for subarachnoid hemorrhage, 1.6 (0.8–3.3) for lacunar stroke and 1.9 (0.5–6.8) for large-artery occlusive stroke; none of these values reached the level of statistical significance, probably due to the small number of cases.

The age and community-adjusted RRs of coronary heart disease relative to never-smokers were 4.2 (1.4–12.6) for ex-smokers, 4.2 (1.5–12.1) for smokers of ≤20 cigarettes per day, and 4.5 (1.6–12.6) for smokers of >20 cigarettes per day. These relations did not change substantially after further adjustment for cardiovascular risk factors. The age and community-adjusted and multivariate RRs of total cardiovascular disease for smokers of >20 cigarettes per day were 2.1 (1.5–3.0) and 1.9 (1.3–2.7), respectively. Ex-smokers had no excess risk of total cardiovascular disease.

Table 3 provides multivariate RRs of total and ischemic strokes according to two subgroups of hypertension status. The data for coronary heart disease are not presented because the number of cases was not large enough for the stratification analysis. The excess risk of total stroke associated with current smoking of >20 cigarettes per day was observed primarily among hypertensive men. We also observed an excess risk of ischemic stroke among hypertensive men who smoked >20 cigarettes per day (RR=2.2 (1.0–5.0), $p=0.045$).

Because some of the previous studies used combined data on never and ex-smokers, we also combined these groups in our analysis in order to facilitate a more direct comparison among studies. The multivariate RRs of smokers of >20 cigarettes per day were 1.8 (1.3–2.5) for total stroke, 1.6 (0.8–3.4) for intraparenchymal hemorrhage, 3.1 (0.9–11.0) for subarachnoid hemorrhage, 1.7 (1.2–2.5) for ischemic stroke, 2.0 (1.1–3.6) for lacunar infarction, and 1.9 (0.7–5.0) for large-artery occlusive infarction, and 1.8 (1.1–3.1) for coronary heart disease (not shown in the table).

To estimate the impact of any current cigarette smoking

Table 2. Age, Community-Adjusted and Multivariate RRs of Stroke and Coronary Heart Disease According to Smoking Status in 3,626 Men Aged 40−69 Years

Cardiovascular disease	Never-smokers	Ex-smokers	Current smokers	
			1–20/day	>20/day
Person years for stroke	8,361	8,241	13,366	22,472
Total stroke (n=257)				
Number of cases	32	26	57	142
Age and community-adjusted RR	1.0	0.9 (0.5–1.5)	1.2 (0.8–1.8)	1.9 (1.3–2.7)
Multivariate RR†	1.0	0.8 (0.5–1.3)	1.1 (0.7–1.7)	1.6 (1.1–2.4)
Hemorrhagic stroke (n=75)				
Number of cases	9	4	13	49
Age and community-adjusted RR	1.0	0.5 (0.1–2.2)	0.9 (0.4–2.2)	2.2 (1.1–4.4)
Multivariate RR†	1.0	0.5 (0.2–1.8)	0.7 (0.3–1.8)	1.5 (0.7–3.2)
Intraparenchymal hemorrhage (n=50)				
Number of cases	7	3	8	32
Age and community-adjusted RR	1.0	0.5 (0.1–1.9)	0.8 (0.3–2.1)	1.9 (0.8–4.2)
Multivariate RR†	1.0	0.5 (0.1–2.2)	0.6 (0.2–1.7)	1.3 (0.5–3.1)
Subarachnoid hemorrhage (n=25)				
Number of cases	2	1	5	17
Age and community-adjusted RR	1.0	—	1.6 (0.3–8.2)	3.2 (0.7–14.1)
Multivariate RR†	1.0	—	1.2 (0.2–6.3)	2.4 (0.5–10.7)
Ischemic stroke (n=173)				
Number of cases	22	21	42	88
Age and community-adjusted RR	1.0	1.1 (0.6–2.0)	1.3 (0.8–2.2)	1.7 (1.1–2.8)
Multivariate RR†	1.0	0.8 (0.4–1.6)	1.2 (0.7–2.1)	1.6 (1.0–2.5)
Lacunar infarction (n=70)				
Number of cases	10	6	13	41
Age and community-adjusted RR	1.0	0.6 (0.2–1.7)	0.8 (0.4–1.9)	1.6 (0.8–3.3)
Multivariate RR†	1.0	0.5 (0.2–1.5)	0.7 (0.3–1.7)	1.5 (0.7–3.0)
Large-artery occlusive infarction (n=23)				
Number of cases	3	4	2	14
Age and community-adjusted RR	1.0	1.3 (0.3–6.2)	0.4 (0.1–2.6)	1.9 (0.5–6.8)
Multivariate RR†	1.0	1.3 (0.3–6.3)	0.5 (0.1–3.0)	2.2 (0.6–8.0)
Person years for coronary heart disease	8,554	8,276	13,518	23,003
Coronary heart disease (n=100)				
Number of cases	4	19	29	48
Age and community-adjusted RR	1.0	4.2 (1.4–12.6)	4.2 (1.5–12.1)	4.5 (1.6–12.6)
Multivariate RR†	1.0	3.7 (1.2–11.2)	4.1 (1.4–11.8)	4.6 (1.6–12.9)
Person years for total cardiovascular disease	8,336	8,164	13,367	22,270
Total cardiovascular disease (n=345)				
Number of cases	36	41	83	185
Age and community-adjusted RR	1.0	1.2 (0.7–1.9)	1.5 (1.0–2.2)	2.1 (1.5–3.0)
Multivariate RR†	1.0	1.0 (0.6–1.6)	1.4 (0.9–2.0)	1.9 (1.3–2.7)

† Adjusted for age, systolic blood pressure levels, antihypertensive medication use, serum total cholesterol category, body mass index, proteinuria, diabetes mellitus, atrial fibrillation, ST-T changes, fundus changes, ethanol intake and community. RR, relative risk.

on cardiovascular disease, we calculated the population-attributable fraction by combining the data on never and ex-smokers. The population attributable fraction associated with current smoking was 28 (95% CI, 9–43) % for total stroke, 33 (3–54) % for coronary heart disease and 31 (15–44) % for total cardiovascular diseases (data not shown).

Discussion

The present study confirmed that, in Japanese men, smoking

Table 3. Multivariate RRs of Total and Ischemic Strokes According to Smoking Stratified by Hypertension Status in 3,626 Men Aged 40−69 Years

	Never-smokers	Ex-smokers	Current smokers	
			1–20/day	>20/day
Total stroke				
Non-hypertensives				
Person years	6,631	6,571	10,683	17,513
Number at risk	422	474	739	1,168
Number of cases	20	13	26	67
Multivariate RR†	1.0	0.5 (0.3–1.1)	0.7 (0.4–1.3)	1.2 (0.7–2.0)
Hypertensives				
Person years	1,730	1,670	2,684	4,959
Number at risk	109	125	212	377
Number of cases	12	13	31	75
Multivariate RR†	1.0	1.2 (0.5–2.8)	1.6 (0.8–3.2)	2.3 (1.2–4.4)
Ischemic stroke				
Non-hypertensives				
Person years	6,631	6,571	10,683	17,513
Number at risk	422	474	739	1,168
Number of cases	14	8	18	44
Multivariate RR†	1.0	0.5 (0.2–1.2)	0.7 (0.4–1.5)	1.3 (0.7–2.4)
Hypertensives				
Person years	1,730	1,670	2,684	4,959
Number at risk	109	125	212	377
Number of cases	8	13	24	44
Multivariate RR†	1.0	1.4 (0.5–3.7)	1.9 (0.8–4.3)	2.2 (1.0–5.0)

Non-hypertensives were defined as having systolic blood pressure <160 mmHg and free of antihypertensive medication; hypertensives were defined as having systolic blood pressure ≥160 mmHg and/or use of antihypertensive medication. † Adjusted for age, systolic blood pressure levels, antihypertensive medication use, serum total cholesterol category, body mass index, proteinuria, diabetes mellitus, atrial fibrillation, ST-T changes, fundus changes, ethanol intake and community. RR, relative risk.

>20 cigarettes per day is a significant risk factor for both total stroke and coronary heart disease in comparison with nonsmoking. An excess risk for ischemic stroke was of borderline statistical significance after adjustment for known cardiovascular risk factors. We found the excess risk of total and ischemic strokes associated with current smoking of >20 cigarettes per day primarily among hypertensive men. Hypertension may have a synergetic effect with smoking on risk of total stroke among Japanese men. This finding was supported by the Hisayama study, which found that current smoking tended to raise the risk of non-embolic cerebral infarction among hypertensive men, but not non-hypertensive men (*4*). However, the Framingham study (*25*) and the Nurses' Health study (*26*) showed that the smoking-stroke association was similar between hypertensives and non-hypertensives.

A positive association between smoking and risks of total and ischemic strokes has been consistently reported in Western countries. According to a meta-analysis of 32 observational studies mostly among Caucasians, the pooled RRs were 1.5 (95% CI, 1.3–1.6) for total stroke and 1.9 (1.7–2.2) for ischemic stroke (*27*). However, in Japanese, the relation between smoking and risk of ischemic stroke has been weak and inconsistent (*7–10, 28–30*). The Shibata study, a 15.5-year follow-up study of Japanese men (n=961), showed a positive relationship between smoking and risk of ischemic stroke (multivariate RR for smoking of ≥20 cigarettes *vs.* <20 cigarettes per day=2.8 (95% CI, 1.3–6.2)) (*31*), but a 20.0-year follow-up of the same cohort showed no significant association (*32*). The Hisayama study, a 32-year follow-up study of 707 Japanese men, reported no significant association between smoking and total, hemorrhagic or ischemic strokes, but did report a two-fold higher risk of lacunar infarction among male current smokers than among non-current smokers (*33*). That study, however, did not discriminate between ex-smokers and never-smokers, but rather combined these two categories as a referent group. In the present study, when we similarly grouped ex- and never-smokers as non-current smokers, there was a comparable excess risk of lacunar infarction; the multivariate RR was 2.0 (1.1–3.6) for smokers of >20 cigarettes per day.

The reasons for the inconsistent association between smoking and risk of ischemic stroke in Japanese populations are not clear. One possible explanation is that there is a high-

er proportion of lacunar infarctions among ischemic strokes in Japanese (30–40%) than in Caucasians (15%) (*34*), since previous studies have shown that smoking was less strongly associated with risk of lacunar infarction than large-artery occlusive infarction (*15*, *35*). The Nurses' Health study (*15*) showed the multivariate RR of large-artery occlusive infarction of current smoking compared with never smoking was 3.4 (2.2–5.0), whereas that of lacunar infarction was 2.8 (2.0–3.9). A retrospective study in Taiwan (*35*) showed that the prevalence of smoking was significantly higher among patients with large-artery occlusive infarction (42%) than among those with lacunar infarction (29%). In the present study, the RRs (95% CI) for large-artery occlusive infarction and lacunar infarction were 1.9 (0.5–6.8) and 1.6 (0.8–3.3), respectively, and probably failed to reach the level of statistical significance due to the small number of cases. Smoking causes atherosclerosis of the large cerebral arteries (*36*) and carotid arteries (*37*) probably due to direct injury of endothelial cells (*38*), atheroma formation through low high-density lipoprotein (HDL)-cholesterol levels (*39*), and acceleration of thrombus formation through increased plasma fibrinogen (*40*), increased platelet aggregability (*41*) and decreased fibrinolytic activity (*42*). Another possibility is that nonsmokers may be heavily exposed to environmental tobacco smoke, and this exposure may weaken the associations between active smoking and risk of ischemic stroke. Our previous study showed that environmental tobacco smoke was associated with increased plasma fibrinogen levels (*43*), one of the risk factors for ischemic stroke (*44*). However, the information on the relation between environmental tobacco smoke and risk of ischemic stroke is limited (*45*).

In the present study, the excess risk of subarachnoid hemorrhage associated with smoking did not reach statistical significance probably due to the small number of cases. We previously reported that current smokers had a significantly higher risk of subarachnoid hemorrhage compared with never-smokers among Japanese women, but not among Japanese men (*46*). A positive relation between smoking and subarachnoid hemorrhage has been consistently reported in previous studies of Caucasians and Japanese Americans (*27*). The mechanism is not clear, but there are some lines of evidence which suggest that smoking increases hemodynamic stress on the Circle of Willis (*47*) through enhanced atherosclerosis in the carotid and basal cerebral arteries, as well as through increased release of proteinases from activated pulmonary macrophages, which enhance the fragility of cerebral aneurysms (*48*).

Our results showed that the risk of coronary heart disease was four times higher in current smokers than in never-smokers, which was consistent with previous reports on Caucasian populations (*49*) and Japanese populations (*2–6*). The impact of cigarette smoking on the development of coronary heart disease may be similar to that of large-artery occlusive infarction (*36–42*), but there are other mechanisms, including coronary artery spasm (*50*) and cardiac arrhythmia (*51*), which are enhanced by smoking.

The estimate of population-attributable fraction suggests that approximately one-fourth of total strokes were attributable to smoking. Previous studies have reported that 12% to 49% of strokes might be attributable to smoking among Caucasians (*52*, *53*), and that 27% of strokes might be attributable to smoking among Japanese men aged 40–64 (*32*), in agreement with the results of the present study. Therefore, smoking cessation may still be effective in preventing stroke among Japanese men.

As for the limitations of the present study, a single measurement for smoking status may weaken the associations due to regression dilution bias, since the prevalence of smoking declined from 66% to 60% during the 5 years after baseline measurement. We estimated that the regression dilution rate (*54*) was 0.79, and thus RRs after adjustment for the regression dilution effect should be 30% higher than those reported in the present study.

In conclusion, current smoking of $>$20 cigarettes per day increased the risk of total and ischemic strokes and coronary heart disease among Japanese middle-aged men. The excess risk of total and ischemic strokes associated with smoking was evident primarily among hypertensive men. Our study also suggests that smoking cessation may contribute to a reduced risk of total stroke.

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