

# Cigarette Smoking and Risk of Stroke and its Subtypes Among Middle-Aged Japanese Men and Women The JPHC Study Cohort I

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**Background and Purpose**—We examined sex-specific relationships of smoking with risk of total stroke and stroke subtypes in Asian populations because of the limited data available.

**Methods**—A total of 19 782 men and 21 500 women aged 40 to 59 years who were free of prior diagnosis of stroke, coronary heart disease, or cancer and reported their smoking status were followed in the Japan Public Health Center–based Prospective Study on Cancer and Cardiovascular Disease (JPHC Study) from 1990 to 1992 to the end of 2001.

**Results**—During a 461 761 person-year follow-up, 702 total strokes were documented among men, of which 619 were confirmed by imaging studies, including 219 intraparenchymal hemorrhages, 73 subarachnoid hemorrhages, and 327 ischemic strokes. The respective numbers of cases among women were 447, 411, 129, 106, and 176. Multivariate relative risks (95% CIs) for current smokers compared with never-smokers after adjustment for cardiovascular risk factors and public health center were 1.27 (1.05 to 1.54) for total stroke, 0.72 (0.49 to 1.07) for intraparenchymal hemorrhage, 3.60 (1.62 to 8.01) for subarachnoid hemorrhage, and 1.66 (1.25 to 2.20) for ischemic stroke. The respective multivariate relative risks among women were 1.98 (1.42 to 2.77), 1.53 (0.86 to 4.25), 2.70 (1.45 to 5.02), and 1.57 (0.86 to 2.87). There was a dose-response relation between the number of cigarettes smoked and risks of ischemic stroke for men. A similar positive association was observed between smoking and risks of lacunar infarction and large-artery occlusive infarction, but not embolic infarction.

**Conclusions**—Smoking raises risks of total stroke and subarachnoid hemorrhage for both men and women and risk of ischemic stroke, either lacunar or large-artery occlusive infarction, for men. (*Stroke*. 2004;35:1248-1253.)

**Key Words:** cigarette smoking ■ stroke ■ risk factors ■ follow-up studies

A previous meta-analysis on smoking and risk of stroke in 1989 showed that current smoking raised the risk of total stroke (relative risk[RR]=1.5), subarachnoid hemorrhage (RR=2.9), and ischemic stroke (RR=1.9) but did not raise the risk of intraparenchymal hemorrhage (RR=0.7).<sup>1</sup> However, in that meta-analysis the data from Asian countries were limited to 2 Japanese cohort studies that showed no significant association between smoking and stroke risk.<sup>2,3</sup> Other cohort studies in Japan<sup>4-11</sup> and Korea<sup>12</sup> reported inconsistent results, and no study examined sex-specific relation-

ships of smoking with risk of total stroke and stroke subtypes comprehensively.

Compared with Western countries, Japanese men had a high proportion of current smokers (53%), while Japanese women had a low proportion (13%) in 1998.<sup>13</sup> However, the proportion of current smokers among Japanese women aged 20 to 49 years has increased since 1990.<sup>14</sup> Mortality from stroke was 2- to 3-fold higher in Japan than in Western countries.<sup>15</sup> Because of the high proportion of current smokers among men and the increasing proportion

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among women with a high stroke mortality, the investigation of smoking and stroke should be of value to formulate public health recommendations for the prevention of stroke. For this purpose, we used the data of the Japan Public Health Center-based prospective study on cancer and cardiovascular diseases (JPHC Study) Cohort I to determine sex-specific relationships of smoking with risk of total stroke and stroke subtypes.

## Subjects and Methods

### Study Cohort

We studied a population-based cohort of 27 063 men and 27 435 women who were born between 1930 and 1949 (aged 40 to 59 years) and were registered in 14 administrative districts supervised by 4 public health center (PHC) areas in January 1, 1990: the JPHC Study Cohort I.<sup>16</sup> The population included 6022 men and 6269 women from Ninohe city and Karumai town in the Ninohe PHC area of Iwate prefecture, 7559 men and 8223 women from Yokote city and Omonogawa town in the Yokote PHC area of Akita, 6173 men and 6046 women from 8 districts of Minami-Saku county in the Saku PHC area of Nagano, and 7309 men and 6897 women from Gushikawa city and Onna village in the Ishikawa PHC area of Okinawa. The geographic profiles of the 4 areas were reported previously.<sup>16</sup> The study protocol was approved by the human ethics review committees of the National Cancer Center.

### Baseline Survey

A self-administered questionnaire was distributed to all registered noninstitutional residents in 1990, asking them to report on their demographic characteristics, medical history, smoking and drinking habits, and diet. Of these, 20 665 men (76%) and 22 484 women (82%) completed and returned the questionnaires between January 1990 and May 1992, mostly between February 1990 and October 1990. We excluded subjects who reported stroke, myocardial infarction, angina pectoris, and cancer at baseline (667 men and 883 women), those who did not report their smoking habits (196 men and 85 women), and those who were lost from the follow-up (14 men and 14 women). A total of 19 782 men and 21 500 women were entered in the present analysis.

Smoking habit was represented in the questionnaire by the present state of smoking and categorized into 3 classes for both sexes: never-smokers, ex-smokers, and current smokers. Persons who reported current smoking were asked for further details on the usual number of cigarettes smoked. Smoking habit for men was further classified into 5 categories: never-smoker, ex-smoker, current smoker, and number of cigarettes 1 to 19/d, 20 to 39/d, and  $\geq 40$ /d.

The frequency of weekly intake of 27 food items was reported under 4 categories: rarely, 1 to 2 d/wk, 3 to 4 d/wk, and almost every day. The weekly frequency for each food item including fruit; green, yellow, and other vegetables; and fresh and dried fish was calculated according to a score assigned to each frequency category (0, 1.5, 3.5, and 7, respectively).

Histories of hypertension and diabetes were ascertained by the following question: "Have you been diagnosed with the following conditions by physicians?" A list including hypertension, diabetes, and other chronic diseases followed this question.

### Confirmation of Stroke and Classification of Stroke Subtypes

We registered a total of 29 hospitals facilitated by CT or MRI in the 4 PHC areas. The items were as follows: 14 hospitals for the Ninohe PHC area, 2 hospitals for the Yokote PHC area, 3 hospitals for the Saku PHC area, and 10 hospitals for the Ishikawa PHC area. These were all major hospitals to which acute stroke cases would be admitted. In each hospital, medical records were reviewed by registered hospital workers or PHC physicians who

were blinded to the lifestyle data. Stroke events were registered if they occurred after the date of return of the baseline questionnaire and before January 1, 2002.

To complete the surveillance for fatal stroke, we also conducted a systematic search for death certificates. All death certificates were forwarded to the PHC in the area of residency, and mortality data were sent centrally to the Ministry of Health, Welfare, and Labor and coded for the National Vital Statistics. For all fatal strokes (*International Classification of Diseases, Ninth Revision*, codes 430 to 438) listed on the death certificate but not registered, medical records in registered hospitals were reviewed by hospital workers, PHC physicians, or research physicians/epidemiologists. When no medical records were available (death certificate information only), we regarded these fatal strokes as probable strokes (24% of fatal strokes).

For nonfatal strokes, we inquired by letter or telephone regarding the onset of stroke and asked for permission to review the medical records of 274 persons who reported history of nonfatal stroke on the 10-year follow-up questionnaire (88% followed) and who had not been registered as stroke cases. Of these 274 persons, 233 (85%) were reached, of which 169 reported confirmatory information of stroke. Of these 169 persons, 151 (89%) provided written informed consent to review their medical records. All of these medical records were reviewed by hospital physicians, PHC physicians, or research physicians, and 104 cases were found to be cases of definite stroke on the basis of imaging studies or autopsy. Nonfatal strokes for which confirmatory information was obtained by letter or telephone, but for which no medical records were available, were regarded as probable (2% of nonfatal strokes). For the analyses of total stroke, both confirmed and probable strokes were used.

Stroke was confirmed by medical records according to the criteria of the National Survey of Stroke,<sup>17</sup> which requires a constellation of neurological deficits of sudden or rapid onset lasting at least 24 hours or until death; events were classified as subarachnoid hemorrhages, ischemic strokes (thrombotic or embolic), or stroke of undetermined type. Subarachnoid hemorrhage was defined as hemorrhage in the subarachnoid space, usually caused by rupture of a saccular aneurysm of the cerebral arteries and less commonly by arteriovenous malformations or other causes. Ischemic stroke included cerebral infarction caused by thrombi (thrombotic stroke) or by emboli from extracranial sources (embolic stroke). For each subtype of stroke, a definite diagnosis was established on the basis of examination of CT scan or MRI. If such radiological workup was not performed, a probable diagnosis was made. All confirmed thrombotic strokes were further classified as large-artery occlusive infarction, lacunar infarction, or unclassified thrombotic infarction on the basis of results of CT scan or MRI according to the criteria applied for the Nurse's Health Study.<sup>18</sup>

### Statistical Analysis

Statistical analyses were based on incidence rates of stroke during 11.0 years of follow-up from 1990 to 2001. For each man, person-months of follow-up were calculated from the date of return of the baseline questionnaire to the first end point, death, or January 1, 2002, whichever was first. The RR of stroke was defined as the incidence of stroke among men and women in categories of smoking habits (never-smokers, ex-smokers, current smokers of 1 to 19, 20 to 39, and  $\geq 40$ /d for men, and never-smokers, ex-smokers, and current smokers for women) divided by the corresponding rate among men and women of never-smokers.

The RRs and 95% CIs were calculated after adjustment for age and other potential confounding factors with the use of the Cox proportional hazards model. Test for trend across the smoking categories among current male smokers was conducted by assigning median values for each category. Potential confounding factors for the adjustment were baseline values of age; alcohol intake (nondrinkers [ $< 1$  d/mo]; occasional drinkers [1 to 3 d/mo]; weekly alcohol intake of 1 to 149, 150 to 299, 300 to 449, and  $\geq 450$  g/wk); histories of hypertension and diabetes; sports during leisure time; dietary intake categories of fruits, total vegetables,

**TABLE 1. Age-Adjusted Mean Values or Prevalence of Risk Characteristics at Baseline According to Cigarette Smoking**

	Men						Women		
	Never-Smoker	Ex-Smoker	Current Smoker	Cigarettes Smoked per Day			Never-Smoker	Ex-Smoker	Current Smoker
				1–19	20–39	≥40			
No. of participants	4818	4445	10 519	3035	6250	1234	19 924	367	1209
Age, y	49.6	50.2	49.0	49.5	48.9	47.7	49.6	49.0	48.6
Alcohol intake, g/wk	252.7	305.6	333.2	301.1	335.8	402.6	106.8	165.7	238.3
Mean body mass index, kg/m <sup>2</sup>	23.9	23.9	23.2	23.0	23.1	23.9	23.6	24.1	23.4
History of hypertension, %	16.4	19.6	15.0	15.4	14.8	14.6	15.2	21.4	14.6
History of diabetes, %	4.9	5.2	5.6	5.5	5.3	7.8	2.4	4.1	3.3
College or higher education, %	15.3	16.3	13.2	14.0	12.4	14.8	12.0	18.7	10.9
Sports at leisure ≥1 d/wk, %	19.3	21.4	15.1	18.1	13.8	14.1	14.5	17.1	13.5
Diet, frequency									
Fruit, d/wk	3.4	3.2	2.8	3.0	2.8	2.7	4.1	3.7	3.3
Green vegetables, d/wk	3.7	3.6	3.5	3.6	3.4	3.3	4.0	3.7	3.7
Yellow vegetables, d/wk	2.9	2.8	2.5	2.7	2.5	2.3	3.4	3.1	3.0
Other vegetables, d/wk	3.8	3.8	3.7	3.9	3.7	3.6	4.3	4.0	3.9
Fresh fish, d/wk	2.8	2.7	2.8	2.8	2.8	2.8	3.0	2.7	2.7
Dried fish, d/wk	1.8	1.8	2.0	2.0	2.0	2.0	2.1	1.7	1.9

and fish; education; and PHC area. These confounding variables were treated as dummy variables in the models. Subjects were censored from the follow-up analysis at the date of death or movement from a PHC area. The significance of the interaction of sex with smoking status was tested with an interaction term of sex by categorical variables of smoking status in multivariate models.

To examine the effect of smoking cessation on risk of total stroke, we used never-smokers as the reference category for the analysis of RR among current smokers, and we used current smokers as the reference category for the analysis of RR among ex-smokers according to years since quitting (0 to 1, 2 to 4, 5 to 9, 10 to 14, and ≥15 years). In that analysis, we adjusted for age at which a person started smoking (<20, 20 to 24, 25 to 29, and ≥30 years) as well as the aforementioned confounding variables.

The population-attributable risk percentage was calculated by  $P(RR-1)/RR$ , where P represents the prevalence of smokers among cases and RR represents multivariate RR for current smokers compared with those who were not current smokers. The formula of Greenland<sup>19</sup> was used for calculation of the 95% CI.

## Results

During an average follow-up period of 11.0 years, 702 total strokes were documented among men, of which 619 were confirmed by imaging studies, including 219 intraparenchymal hemorrhages, 73 subarachnoid hemorrhages, 327 ischemic strokes (144 lacunar infarctions, 56 large-artery occlusive infarctions, 86 embolic infarctions, and 41 other ischemic strokes). The respective number of cases among women was 447 for total stroke, 411 for confirmed total stroke, 129 for intraparenchymal hemorrhage, 106 for subarachnoid hemorrhage, and 176 for ischemic stroke (90 for lacunar infarction, 33 for large-artery occlusive infarction, 31 for embolic infarction, and 22 for other ischemic stroke).

The baseline characteristics according to various categories of smoking status are shown in Table 1. Compared with never-smokers, current smokers were 0.6 to 1.0 year younger, and ex-smokers were 0.6 year older for men and 0.4 year younger for women. Mean alcohol intake was higher in

ex-smokers and current smokers with increased number of cigarettes smoked compared with never-smokers. Mean body mass index was lower in current smokers than in never-smokers. Hypertension was more prevalent in ex-smokers than in never-smokers and current smokers. Diabetes was more prevalent in ex-smokers and current smokers than in never-smokers. The percentage of higher education and sports during leisure time and the frequency of fruit and green, yellow, and other vegetable intakes were lower among current smokers than among never-smokers and past smokers. The frequency of fish intake did not vary among smoking categories.

Table 2 shows sex-specific age-adjusted and multivariate RRs of stroke and stroke subtypes according to smoking status compared with never-smokers. The interaction of sex with current smoking was of borderline statistical significance for total stroke ( $P=0.05$ ) but was not significant for any stroke subtypes. Current smoking was positively associated with age-adjusted risk of total stroke and subarachnoid hemorrhage for both sexes and with age-adjusted risk of ischemic stroke for men. These associations remained statistically significant after adjustment for known cardiovascular risk factors, the frequency of selected food intake, and PHC area. The multivariate RRs (95% CI) for current smokers compared with never-smokers were 1.27 (1.05 to 1.54) for total stroke, 3.60 (1.62 to 8.01) for subarachnoid hemorrhage, and 1.56 (1.17 to 2.10) for ischemic stroke. The respective multivariate RRs among women were 1.98 (1.42 to 2.77), 2.70 (1.45 to 5.02), and 1.57 (0.86 to 2.87). There was a dose-response relation between the number of cigarettes smoked and risks of ischemic stroke for men. A similar and significant positive association was observed between smoking and risks of lacunar infarction and large-artery occlusive infarction, but not embolic infarction.

**TABLE 2. Relative Risk and 95% CI of Total Stroke and Stroke Subtypes According to Cigarette Smoking**

	Men						<i>P</i> for Trend	Women		
	Never-Smoker	Ex-Smoker	Current Smoker	Cigarettes Smoked per Day				Never-Smoker	Ex-Smoker	Current Smoker
				1–19	20–39	≥40				
Person-years	53 420	49 204	114 527	32 922	68 115	13 490		227 558	4030	13 022
<b>Total stroke</b>										
No. of cases	153	129	420	111	258	51		395	11	41
Age-adjusted RR	1.0	0.87 (0.69–1.10)	1.34 (1.11–1.61)	1.19 (0.93–1.52)	1.39 (1.13–1.69)	1.53 (1.11–2.10)	<0.001	1.0	1.62 (0.89–2.94)	1.97 (1.42–2.72)
Multivariate RR	1.0	0.82 (0.65–1.04)	1.27 (1.05–1.54)	1.14 (0.88–1.46)	1.32 (1.07–1.62)	1.34 (0.98–1.88)	0.005	1.0	1.47 (0.80–2.70)	1.98 (1.42–2.77)
<b>Intraparenchymal hemorrhage</b>										
No. of cases	59	45	115	29	76	10		114	4	11
Age-adjusted RR	1.0	0.80 (0.55–1.19)	0.95 (0.69–1.30)	0.81 (0.52–1.26)	1.06 (0.75–1.49)	0.76 (0.39–1.48)	0.55	1.0	2.04 (0.75–5.52)	1.79 (0.97–3.33)
Multivariate RR	1.0	0.72 (0.49–1.07)	0.90 (0.65–1.25)	0.77 (0.49–1.21)	1.01 (0.71–1.44)	0.68 (0.34–1.35)	0.74	1.0	1.54 (0.56–4.25)	1.53 (0.86–4.25)
<b>Subarachnoid hemorrhage</b>										
No. of cases	7	8	58	15	36	7		92	1	13
Age-adjusted RR	1.0	1.25 (0.45–3.45)	4.03 (1.84–8.84)	3.59 (1.46–8.81)	4.21 (1.87–9.48)	4.20 (1.47–12.0)	<0.001	1.0	n/a	2.67 (1.49–4.78)
Multivariate RR	1.0	1.12 (0.40–3.10)	3.60 (1.62–8.01)	3.19 (1.29–7.93)	3.78 (1.66–8.64)	3.74 (1.28–10.9)	<0.001	1.0	n/a	2.70 (1.45–5.02)
<b>Ischemic stroke</b>										
No. of cases	62	55	210	57	126	27		161	3	12
Age-adjusted RR	1.0	0.90 (0.62–1.29)	1.66 (1.25–2.20)	1.49 (1.04–2.14)	1.67 (1.23–2.27)	2.08 (1.33–3.28)	0.02	1.0	1.07 (0.34–3.35)	1.44 (0.80–2.59)
Multivariate RR	1.0	0.87 (0.60–1.25)	1.56 (1.17–2.10)	1.41 (0.98–2.04)	1.60 (1.17–2.19)	1.81 (1.14–2.88)	0.04	1.0	1.10 (0.35–3.49)	1.57 (0.86–2.87)
<b>Lacunar infarction</b>										
No. of cases	29	20	95	32	48	15		82	0	8
Age-adjusted RR	1.0	0.71 (0.40–1.26)	1.61 (1.06–2.45)	1.81 (1.09–2.99)	1.37 (0.86–2.17)	2.43 (1.30–4.55)	0.05	1.0	n/a	1.89 (0.91–3.91)
Multivariate RR	1.0	0.70 (0.40–1.25)	1.54 (1.00–2.38)	1.69 (1.01–2.83)	1.34 (0.83–2.15)	2.19 (1.16–4.17)	0.07	1.0	n/a	2.15 (1.01–3.62)
<b>Large-artery occlusive infarction</b>										
No. of cases	9	10	37	7	26	4		30	2	1
Age-adjusted RR	1.0	1.14 (0.46–2.80)	2.03 (0.98–4.21)	1.27 (0.47–3.42)	2.40 (1.12–5.12)	2.11 (0.65–6.86)	0.04	1.0	3.70 (0.88–15.5)	n/a
Multivariate RR	1.0	1.23 (0.49–3.04)	2.16 (1.02–4.56)	1.35 (0.50–3.68)	2.61 (1.20–5.69)	2.08 (0.63–6.92)	0.04	1.0	4.03 (0.91–17.8)	n/a
<b>Embolic infarction</b>										
No. of cases	18	18	50	10	35	5		29	0	2
Age-adjusted RR	1.0	0.99 (0.52–1.91)	1.35 (0.79–2.31)	0.89 (0.41–1.92)	1.58 (0.90–2.80)	1.34 (0.50–3.63)	0.71	1.0	0	1.37 (0.32–5.76)
Multivariate RR	1.0	0.87 (0.45–1.68)	1.13 (0.64–1.97)	0.77 (0.35–1.69)	1.34 (0.74–2.42)	0.97 (0.35–2.69)	0.52	1.0	0	1.33 (0.31–5.75)

Values in parentheses are 95% CIs. RR indicates relative risk. Data are adjusted for age (5-year categories); alcohol intake (6 categories); body mass index (quintiles); history of diabetes (yes); education level (3 categories); sports at leisure (3 categories); frequency of fruit, vegetable, and fish servings (4 categories); and public health centers.

We examined the relationship of years since cessation of smoking with risk of mortality from total stroke among men. We did not use the data of women since the number of ex-smokers was small. The multivariate RR (95% CI) of total stroke was 0.82 (0.49 to 1.38) within 2 years since cessation of smoking, 0.62 (0.40 to 0.96) at 2 to 4 years, 0.61 (0.42 to 0.87) at 5 to 9 years, 0.61 (0.40 to 0.93) at 10 to 14 years, and 0.65 (0.46 to 0.93) at ≥15 years after cessation of smoking, while the RR for never-smokers was 0.42 (0.20 to 0.88).

The multivariate RR (95% CI) of total stroke among current smokers versus non-smokers was 1.40 (1.19 to 1.64) for men and 1.96 (1.40 to 2.73) for women. On the basis of these estimates and proportions of current smokers among strokes (60% for men and 9% for women), the population-attributable risk percentage for total stroke was 17% (9% to 25%) for men and 5% (2% to 7%) for women.

### Discussion

The present large prospective study confirmed a positive relationship between smoking and risk of total stroke and

subarachnoid hemorrhage for both men and women after adjustment for known cardiovascular risk factors and selected lifestyles. The association of smoking and risk of subarachnoid hemorrhage was particularly strong: men had a 3.6-fold and women had a 2.7-fold excess risk. Furthermore, men had a 1.6-fold excess risk of ischemic stroke among current smokers than among never-smokers, while women had a similar but nonsignificant excess risk. Furthermore, the present study first showed that the smoking-associated excess risk was found for both lacunar and large-artery occlusive infarctions but not for embolic infarctions. There was no significant relation of smoking and risks of intraparenchymal hemorrhage or embolic infarction.

A previous huge Japanese cohort study of 122 261 men and 142 857 women showed that age-adjusted RR of mortality from total stroke for current daily smokers compared with non-smokers was 1.13 (95% CI, 1.07 to 1.20) in men and 1.21 (95% CI, 1.10 to 1.34) in women.<sup>4</sup> However, in that study no incident data or multivariate adjustment was available. Most

of the other cohort studies reported that RRs of incident total or ischemic strokes were approximately  $\leq 1.5$ , with no statistical significance.<sup>2,3,5,8</sup> A recent report from the Hisayama Study showed a significant association between smoking and risk of lacunar infarction, with a multivariate RR of 2.2 (95% CI, 1.3 to 3.9), but no association with the risk of total ischemic stroke, atherothrombotic infarction (mostly large-artery occlusive infarction), or cardioembolic infarction.<sup>9</sup> A recent report from the follow-up study of NIPPON DATA 80, a cohort of national representative samples aged  $\geq 30$  years, showed that male heavy smokers of  $>40$  cigarettes per day had a significant multivariate RR of ischemic heart disease compared with nonsmokers (RR=2.2), but male light-to-moderate smokers had no significant excess risk.<sup>6</sup> Another recent Japanese study showed that the multivariate RR of ischemic stroke for current smokers compared with never-smokers was 1.6 (95% CI, 1.0 to 2.5) among total men and 2.2 (95% CI, 1.0 to 5.0) among hypertensive men.<sup>10</sup>

There are several plausible mechanisms for the relation of smoking with risk of ischemic stroke. First, smoking is associated with increased fibrinogen concentrations,<sup>20</sup> increased platelet aggregability,<sup>21</sup> increased hematocrit,<sup>22</sup> reduced fibrinolytic activity,<sup>23</sup> and reduced blood flow in brain due to vasoconstriction,<sup>24</sup> which may contribute to accelerated thrombus formation. Second, smoking reduces HDL cholesterol<sup>25</sup> and directly injures endothelial cells,<sup>26</sup> which contribute to atheroma formation. Considered together, the smoking-related biological effects may contribute to the increased risk of ischemic stroke. The mechanism for smoking and risk of subarachnoid hemorrhage is uncertain. There is, however, some evidence that smoking increases the release of proteinases from activated pulmonary macrophages, which enhances the fragility of cerebral aneurysms,<sup>27</sup> and that smoking increases hemodynamic stress on the circle of Willis<sup>28</sup> through the enhanced atherosclerosis in basal cerebral and carotid arteries.

Japan has a high incidence of subarachnoid hemorrhage, which is comparable to that in Finland, where the incidence of subarachnoid hemorrhage appears to be higher than that in other parts of the world.<sup>29</sup> The high proportion of smokers among both Japanese and Finnish men may explain this fact since smoking is a strong risk factor for subarachnoid hemorrhage,<sup>30–32</sup> as shown in the present study. Because the risk of subarachnoid hemorrhage is in part genetically determined,<sup>33</sup> it is possible that the high prevalence in Japan and Finland of genes linked to aneurysm formation may also play a role in the high incidence of subarachnoid hemorrhage in these countries.

No significant excess risk of total stroke or stroke subtypes for ex-smokers compared with never-smokers may correspond to the previous epidemiological findings that smoking cessation led to a fall of stroke risk within 5 years.<sup>34–36</sup> In the present study we found that the excess risk of total stroke fell by 18% within the first 2 years after cessation of smoking, and the maximum effect of cessation of smoking, a 38% risk decline, occurred at 2 to 4 years.

We also estimated that 17% of total strokes for men and 5% of total strokes for women were attributable to current

smoking. In 1999, the estimated number of stroke patients according to the National Patient Survey was 719 000 for men and 756 000 for women, and the number of annual stroke deaths was 66 452 for men and 72 537 for women.<sup>37</sup> Therefore, approximately 160 000 stroke events (122 000 in men and 38 000 in women) and 15 000 stroke deaths (11 000 in men and 4000 in women) could be preventable by smoking prevention and cessation in Japan.

A potential limitation of our study is that we used self-reported histories of hypertension and diabetes. However, the prevalence of undetected hypertension and diabetes may be small because of nationwide health screenings in Japan.<sup>37</sup> Second, the generalizability of our findings to women and older men is uncertain.

In conclusion, the present large cohort study showed that smoking raises the risk of total stroke, with a strong effect of smoking on risk of subarachnoid hemorrhage for both men and women and a moderate effect on risk of ischemic stroke for men. Smoking cessation led to an 18% reduction of total stroke within 2 years after quitting, and another 20% reduction was observed at 2 to 4 years after quitting. Strokes may be preventable through smoking prevention or cessation by 17% for men and 5% for women. Because of the large number of stroke patients and deaths, smoking prevention and cessation have a large impact on stroke prevention in Japan.

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