American Heart Association.

Impact of Smoking Status on Stroke Recurrence

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Background—Smoking is a well-established risk factor of stroke and smoking cessation has been recommended for stroke prevention; however, the impact of smoking status on stroke recurrence has not been well studied to date.

Methods and Results—Patients with first-ever stroke were enrolled and followed in the NSRP (Nanjing Stroke Registry Program). Smoking status was assessed at baseline and reassessed at the first follow-up. The primary end point was defined as fatal or nonfatal recurrent stroke after 3 months of the index stroke. The association between smoking and the risk of stroke recurrence was analyzed with multivariate Cox regression model. At baseline, among 3069 patients included, 1331 (43.4%) were nonsmokers, 263 (8.6%) were former smokers, and 1475 (48.0%) were current smokers. At the first follow-up, 908 (61.6%) patients quit smoking. After a mean follow-up of 2.4±1.2 years, 293 (9.5%) patients had stroke recurrence. With nonsmokers as the reference, the adjusted hazard ratios for stroke recurrence were 1.16 (95% CI, 0.75–1.79) in former smokers, 1.31 (95% CI, 0.99–1.75) in quitters, and 1.93 (95% CI, 1.43–2.61) in persistent smokers. Among persistent smokers, hazard ratios for stroke recurrence ranged from 1.68 (95% CI, 1.14–2.48) in those who smoked 1 to 20 cigarettes daily to 2.72 (95% CI, 1.36–5.43) in those who smoked more than 40 cigarettes daily (*P* for trend <0.001).

Conclusions—After an initial stroke, persistent smoking increases the risk of stroke recurrence. There exists a dose–response relationship between smoking quantity and the risk of stroke recurrence. (***J Am Heart Assoc.*** 2019;8:e011696. DOI: 10.1161/ JAHA.118.011696.)

Key Words: recurrence • smoking • smoking cessation • stroke

C igarette smoking is a well-established and modifiable risk factor of stroke.[1] Smoking cessation could reduce the risk of stroke.[1–3] For this reason, smoking cessation was recommended in the current guidelines.[4] However, the impact

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of smoking and smoking cessation on stroke recurrence has not been well established, largely because of the inconsistencies in classifying smoking status. Theoretically, former smokers have an intermediate risk of stroke,[3] but they were usually assigned as either smokers[5,6] or nonsmokers.[7] A large proportion of smokers may quit smoking after stroke, but they were usually defined as persistent smokers according to baseline assessments.[8,9] In this circumstance, the effects of smoking cessation after stroke, therefore, were neglected. Because of the complexity of smoking status, a presumptive dose–response relationship between smoking and risk of stroke recurrence has not been determined to date.

Stroke survivors bear a higher risk of subsequent stroke, and recurrent stroke is more fatal and disabling than first-ever stroke.[10,11] The 1-year recurrence rate after the first-ever stroke has been reported to be as high as 17.7% in Chinese patients.[12] The prevalence of smoking has been reported to be as high as 52.9% in Chinese men.[13] The high stroke recurrence and smoking prevalence in the Chinese population provided us with conditions to estimate the impact of smoking status on risk of stroke recurrence, and to determine whether a dose–response relationship exists.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Population

Patients with first-ever ischemic stroke were consecutively enrolled in the NSRP (Nanjing Stroke Registry Program) from January 1, 2013 to December 31, 2016. NSRP is a prospective, hospital-based stroke registry. Detailed information about NSRP has been published previously.[14] The study was approved by the Ethics Review Board of Jinling Hospital. Written informed consent was obtained from each participant or proxy respondent.

Patients were eligible for this study if they (1) had first-ever ischemic stroke diagnosed within 14 days of onset; (2) were aged 18 years or older; and (3) had a head computed tomography or magnetic resonance imaging scan during hospitalization. Patients who died, were lost to follow-up, or experienced a recurrent nonfatal stroke within the first 3 months were excluded from data analysis (Figure S1).

Smoking Status and Quantity

Smoking status and quantity of cigarettes smoked were investigated with a face-to-face questionnaire. The main items of the survey included smoking history, smoking intensity (average cigarettes consumed per day), smoking duration (years of smoking), smoking cessation, and cessation time. The cumulative amount of smoking was measured in pack-years, which was calculated by the average number of packs per day and years of smoking. If the patient could not answer the questionnaire, an appropriate proxy was invited. Patients were classified as smokers and nonsmokers according to

baseline assessments. Smokers were defined as those who had smoked >400 cigarettes in their lifetime.[15–17] Smokers were further classified as former and current smokers according to their status at the time of the index stroke. Former smokers were defined as those who had quit smoking for at least 30 days immediately before the index stroke. Smokers who did not meet the criterion of former smokers were classified as current smokers. Current smokers were further classified as quitters and persistent smokers. Quitters were defined as those who had quit for at least 1 month, and maintained cessation at the first follow-up. Persistent smokers were defined as those who continued smoking at the first follow-up. Those who quit for a time and resumed smoking and those who quit for <1 month were categorized as persistent smokers.

Baseline Assessments

The severity of the index stroke was evaluated by the National Institutes of the Health Stroke Scale on admission.[18] Ischemic stroke was further classified with reference to TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria.[19] Socioeconomic details, including occupation, education years, annual family income, and residence, were investigated with a standardized questionnaire.

End Point and Follow-Up Assessments

The primary end point was defined as fatal or nonfatal recurrent stroke after 3 months of the index stroke. Recurrent stroke was defined as a new neurological deficit or a sudden deterioration of a previous deficit that fits the definition of ischemic stroke or hemorrhagic stroke,[20] in the absence of apparent causes other than that of vascular origin. Recurrent stroke was confirmed by a cranial computed tomography scan, magnetic resonance imaging, or autopsy. Any interim symptoms were recalled and evaluated for a possible stroke recurrence at each follow-up. A computed tomography or magnetic resonance imaging scan was arranged whenever a recurrent stroke was indicated. Clinical manifestations, neuroimaging results, medical records, death certificates, and other available data were used to determine stroke recurrence.

Patients were followed via telephone interviews or clinical visits at 3, 6, and 12 months after the index stroke and annually thereafter. The follow-up started at 3 months after the index stroke, and it extended to the date of the first recurrent fatal or nonfatal stroke, or censoring. Patients were censored at the date of death from other causes other than stroke, the date of the emigration from this study, or the end of the assigned follow-up period (December 31, 2017).

Statistical Analysis

Continuous variables were presented as mean± SD and categorical variables as number and percentage. The distribution pattern of continuous variables was checked by Kolmogorov–Smirnov test. Categorical variables were compared with χ^2 test and continuous variables with Mann–Whitney *U* test or Student *t* test as appropriate. Cox proportional hazards regression was used to assess the association between smoking status and the risk of stroke recurrence by calculating hazard ratio (HR) and 95% CI. The Cox model was adjusted for age, sex, other stroke risk factors (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, coronary heart disease), and other potential confounders (body mass index, baseline National Institutes of the Health Stroke Scale score, stroke subtypes, and socioeconomic status). A subgroup analysis was performed to assess the dose–response relationship between smoking and the risk of stroke recurrence among persistent smokers. The proportional hazards assumption was tested by scaled Schoenfeld residuals and no appreciable violations were observed. Multiple imputation with chain equations was performed to account for missing values. Five imputation data sets were created, with all model variables included in the imputation process. In addition, sensitivity analysis was performed using subgroups consisting of complete cases only. A forward stepwise method was used in the multivariate analyses, with entry or removal based on a *P*<0.10.

An interaction was examined between smoking status, and relevant risk factors (age, sex, body mass index, hypertension, diabetes mellitus, atrial fibrillation, dyslipidemia, coronary heart diseases) or socioeconomic status.

Statistical significance was accepted at *P*<0.05 in 2 sides. All analyses were performed with SPSS version 22.0 (IBM, New York, NY) and R statistical software (R, version 3.5.1; R Project).

Results

A total of 3318 patients with first-ever ischemic stroke were identified from the NSRP. Among these, we excluded 128 patients who were lost to follow-up, 39 patients who died, and 27 patients who experienced a nonfatal stroke within the first 3 months. We also excluded 55 patients whose smoking status could not be determined. Therefore, a total of 3069 (92.5%) patients who survived the first 3 months without recurrence were analyzed in this study. The mean age was 59.6±11.7 years (range, 18–93 years), and 887 (28.9%) patients were women. During an average follow-up of 2.4±1.2 years (range, 0.25–5.01 years), 293 (9.5%) patients had recurrence, including 260 ischemic stroke events and 33 hemorrhagic stroke events. Patients with recurrence were older (62.8±11.3 versus 59.3±11.6, *P*<0.001), had a higher prevalence of atrial fibrillation (13.0% versus 6.8%, *P*<0.001), were less likely to have a high family income (annual family income >$17 391, 7.2% versus 13.5%, *P*<0.001), and were more likely to be manual workers (57.3% versus 48.1%, *P*=0.002). The proportions of smokers (63.1% versus 55.9%, *P*=0.015) and persistent smokers (24.8% versus 17.8%, *P*=0.015) were higher in patients with recurrence than in those without (Table 1).

Of the 3069 enrolled patients, 1331 (43.4%) were nonsmokers, 263 (8.6%) were former smokers, and 1475 (48.0%) were current smokers. Among current smokers, 908 (61.6%) quit smoking (Figure S2). Current smokers were younger (57.7±11.1 versus 60.6±12.1, *P*<0.001), had a lower prevalence of hypertension (69.2% versus 74.5%, *P*=0.002), atrial fibrillation (5.2% versus 9.7%, *P*<0.001), and coronary heart diseases (5.2% versus 7.7%, *P*=0.008) than nonsmokers. They had a higher proportion of alcohol drinking (36.6% versus 6.6%, *P*<0.001, Table S1). Persistent smokers were younger (56.5±11.2 versus 58.5±10.9, *P*<0.001), were less likely to have a high National Institutes of the Health Stroke Scale score on admission (eg, National Institutes of the Health Stroke Scale >14, 0.8% versus 10.5%, *P*<0.001), and had a lower proportion of atrial fibrillation than quitters (3.7% versus 6.1%, *P*=0.047, Table S2).

In univariate Cox analysis, when compared with nonsmokers, the unadjusted HRs for stroke recurrence were 1.26 (95% CI, 0.82–1.93) in former smokers, 1.20 (95% CI, 0.90–1.60) in quitters, and the HR increased significantly among persistent smokers (HR, 1.52; 95% CI, 1.13–2.05). After adjusting for major covariates, persistent smokers still had a higher likelihood of stroke recurrence when compared with nonsmokers (HR, 1.93; 95% CI, 1.43–2.61). Similar results were found in the association between smoking status and the risk of recurrent ischemic stroke (Table 2). After adjustment for the previously described variables, smoking cessation was independently associated with a reduction in risk of stroke recurrence (HR, 0.71; 95% CI, 0.51–0.97) and in risk of ischemic stroke recurrence (HR, 0.64; 95% CI, 0.46–0.90, Table 3).

Persistent smokers were stratified according to smoking intensity at baseline into 3 levels, and according to smoking pack-years into 4 levels (quartiles). Those who smoked 1 to 20, 20 to 40, and >40 cigarettes per day had an adjusted HR of 1.68 (95% CI, 1.14–2.48), 2.21 (95% CI, 1.45–3.37), and 2.72 (95% CI, 1.36–5.43) for recurrence compared with nonsmokers, respectively (*P* for trend <0.001). Those with 0.05 to 24.50, 24.50 to 39.00, 39.00 to 58.75, and 58.75 or more pack-years had corresponding HRs of 1.35 (95% CI, 0.72–2.56), 1.78 (95% CI, 1.02–3.10), 1.93 (95% CI, 1.18–3.18), and 2.60 (95% CI, 1.70–3.98, *P* for trend <0.001, Tables 4 and 5).

Table 1. Baseline Characteristics of Patients With First-ever Stroke by Stroke Recurrence

Variables	Recurrence		P Value
	With (n=293)	Without (n=2776)	
Age, y, mean±SD	62.8±11.3	59.3±11.6	<0.001
Male, n (%)	215 (73.4)	1967 (70.9)	0.365
Han ethnic, n (%)	291 (99.3)	2751 (99.1)	0.704
BMI, kg/m^2, mean±SD	24.9±2.9	24.8±3.1	0.415
Alcohol drinking, n (%)	75 (25.6)	632 (22.8)	0.274
NIHSS score, n (%)			
0–4	165 (56.9)	1712 (62.1)	0.116
4–14	99 (34.1)	867 (31.5)	
>14	26 (9.0)	177 (6.4)	
Stroke subtypes, n (%)			
Large-artery atherosclerosis	139 (47.4)	1240 (44.7)	0.044
Cardioembolism	32 (10.9)	205 (7.4)	
Small-artery occlusion	34 (11.6)	437 (15.7)	
Others	88 (30.1)	894 (32.2)	
Education years, n (%)			
0–6	104 (37.0)	791 (30.0)	0.069
6–9	122 (43.4)	1228 (46.5)	
9–12	34 (12.1)	345 (13.1)	
>12	21 (7.5)	277 (10.4)	
Occupation*, n (%)			
Category I	81 (30.9)	801 (31.5)	0.002
Category II	31 (11.8)	519 (20.4)	
Category III	150 (57.3)	1224 (48.1)	
Annual family income, $, n (%)			
1–1739	38 (16.0)	230 (9.6)	<0.001
1739–5455	53 (22.4)	435 (18.2)	
5455–8696	69 (29.1)	658 (27.5)	
8696–17 391	60 (25.3)	747 (31.2)	
>17 391	17 (7.2)	322 (13.5)	
Rural residence, n (%)	107 (36.5)	860 (31.0)	0.052
Hypertension, n (%)	212 (72.4)	2009 (72.4)	0.996
Diabetes mellitus, n (%)	98 (33.4)	820 (29.5)	0.195
Dyslipidemia, n (%)	22 (7.5)	247 (8.9)	0.424
History of TIA, n (%)	9 (3.1)	62 (2.2)	0.364
Atrial fibrillation, n (%)	38 (13.0)	189 (6.8)	<0.001
CHD, n (%)	26 (8.9)	185 (6.7)	0.155
Smoking status			
Nonsmokers	108 (36.9)	1223 (44.1)	0.015
Former smokers	26 (8.9)	237 (8.5)	
Quitters	86 (29.4)	822 (29.6)	
Persistent smokers	73 (24.8)	494 (17.8)	

BMI indicates body mass index; CHD, coronary heart diseases; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

*Occupation: category I includes professionals, administrators, and technicians; category II, clerical and service workers; category III, manufacturing workers, peasants, and the jobless.

Missing data (recurrence, no recurrence): Annual family income (56, 384), BMI (1, 27), Education years (12, 135), NIHSS score (3, 20), Occupation (31, 232).

Table 2. HRs (95% CIs) for the Association Between Smoking Status and Stroke Recurrence

	Nonsmokers (n=1331)	Former Smokers (n=263)	Quitters (n=908)	Persistent Smokers (n=567)
Total stroke				
Case number	108	26	86	73
Unadjusted	1 (reference)	1.26 (0.82–1.93)	1.20 (0.90–1.60)	1.52 (1.13–2.05)
Adjusted*	1 (reference)	1.16 (0.75–1.79)	1.31 (0.99–1.75)	1.93 (1.43–2.61)
Sensitivity analysis†	1 (reference)	1.05 (0.63–1.75)	1.32 (0.95–1.83)	1.75 (1.23–2.47)
Ischemic stroke				
Case number	93	22	76	69
Unadjusted	1 (reference)	1.23 (0.77–1.96)	1.23 (0.91–1.66)	1.67 (1.22–2.28)
Adjusted*	1 (reference)	1.14 (0.71–1.82)	1.36 (1.00–1.85)	2.15 (1.56–2.96)
Sensitivity analysis†	1 (reference)	0.97 (0.56–1.70)	1.34 (0.95–1.88)	1.84 (1.28–2.64)

BMI indicates body mass index; CHD, coronary heart disease; HR, hazard ratio; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment.
*Adjusted for age, sex, BMI, NIHSS score, TOAST, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, CHD, and socioeconomic status, including occupation, education years, annual family income, and rural residence.
†Adjusted for these variables in those cases without missing values.

Restricting the analysis to patients with complete information yielded the same trends (Tables 2, 4, and 5). When compared with nonsmokers, only persistent smokers had a significantly higher HR for total stroke recurrence (HR, 1.75; 95% CI, 1.23–2.47) and ischemic stroke recurrence (HR, 1.84; 95% CI, 1.28–2.64). The similar dose–response relationships remained in the sensitivity analysis. However, smoking cessation was no longer associated with a reduction both in risk of total stroke recurrence (HR, 0.78; 95% CI, 0.54–1.12)

Table 3. HRs (95% CIs) for the Association Between Smoking Cessation and Stroke Recurrence

	Persistent Smokers (n=567)	Quitters (n=908)
Total stroke		
Case number	73	86
Unadjusted	1 (reference)	0.79 (0.58–1.08)
Adjusted*	1 (reference)	0.71 (0.51–0.97)
Sensitivity analysis†	1 (reference)	0.78 (0.54–1.12)
Ischemic stroke		
Case number	69	76
Unadjusted	1 (reference)	0.74 (0.53–1.02)
Adjusted*	1 (reference)	0.64 (0.46–0.90)
Sensitivity analysis†	1 (reference)	0.76 (0.52–1.10)

BMI indicates body mass index; CHD, coronary heart disease; HR, hazard ratio; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment.
*Adjusted for age, sex, BMI, NIHSS score, TOAST, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, CHD, and socioeconomic status, including occupation, education years, annual family income, and rural residence.
†Adjusted for these variables in those cases without missing values.

and in risk of ischemic stroke recurrence (HR, 0.76; 0.52–1.10, Table 3).

No significant interaction was found between smoking status and age, sex, body mass index, hypertension, diabetes mellitus, atrial fibrillation, dyslipidemia, coronary heart diseases, or socioeconomic status (all P for interaction >0.1).

Discussion

This study observed that patients who continued smoking after the index stroke had a nearly 2-fold risk of stroke recurrence than nonsmokers. There was a dose–response relationship between smoking quantity and the risk of stroke recurrence.

The effect of smoking cessation on stroke has been studied in previous studies.[1–3] The risk of stroke decreases after 2 to 4 years of smoking cessation and returns to the level of nonsmokers by 5 years of smoking cessation.[1,2] Smoking increases the risk of stroke in the short term by promoting thrombosis[21] and reducing cerebral blood flow via arterial vasoconstriction.[22] The thrombotic process can be reversible,[23] and cerebral blood flow can have a significant improvement soon after quitting.[22] Previous studies have reported that the smoking cessation rate was 40% to 94% at 1 year[24,25] and 37% at 5 years[26] after the first stroke. However, most studies just assessed smoking status at baseline, and only 2 studies detected the effect of smoking cessation after stroke. Alvarez et al[27] did not observe a reduction in recurrent risk, possibly because of the small sample size and short follow-up time. Another landmark study observed a 33% decrease within 5 years among quitters when

Table 4. HRs (95% CIs) for the Association Between Smoking Intensity and Stroke Recurrence Among Persistent Smokers

| | Nonsmokers (n=1331) | Smoking Intensity, Cigarettes Smoked Per Day | | | |
		1 to 20 (n=325)	20 to 40 (n=190)	>40 (n=51)	P for Trend
Total stroke					
Case number	108	35	29	9	...
Unadjusted	1 (reference)	1.28 (0.87–1.87)	1.79 (1.19–2.69)	2.07 (1.05–4.09)	<0.001
Adjusted*	1 (reference)	1.68 (1.14–2.48)	2.21 (1.45–3.37)	2.72 (1.36–5.43)	<0.001
Sensitivity analysis[†]	1 (reference)	1.40 (0.89–2.21)	2.31 (1.45–3.68)	2.96 (1.35–6.49)	<0.001
Ischemic stroke					
Case number	93	33	27	9	...
Unadjusted	1 (reference)	1.34 (0.94–2.08)	1.93 (1.26–2.97)	2.41 (1.21–4.77)	<0.001
Adjusted*	1 (reference)	1.83 (1.22–2.75)	2.53 (1.63–3.93)	3.28 (1.64–6.55)	<0.001
Sensitivity analysis[†]	1 (reference)	1.53 (0.96–2.46)	2.42 (1.49–3.94)	3.39 (1.54–7.46)	<0.001

BMI indicates body mass index; CHD, coronary heart disease; HR, hazard ratio; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment.
*Adjusted for age, sex, BMI, NIHSS score, TOAST, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, CHD, and socioeconomic status, including occupation, education years, annual family income and rural residence.
[†]Adjusted for these variables in those cases without missing values. Information about smoking intensity of 1 patient was missing, and he was excluded in this analysis.

compared with persistent smokers.[28] No clinical trials have studied the effect of smoking after stroke. In this study, we observed a nonsignificant 22% decrease in recurrent risk among quitters, probably because of the relatively short follow-up time.

Several studies have elucidated a dose–response relationship between cigarette smoking and risk of stroke.[29–31] However, whether there is a similar relationship between cigarette smoking and the risk of stroke recurrence has not been confirmed. In this study, because of changes of smoking behavior (eg, smoking cessation and resumption or smoking reduction) after the first stroke, we just detected the association according to their baseline smoking status among persistent smokers. Smoking promotes atherosclerosis by producing oxidative stress, endothelial dysfunction, inflammation, and lipid modification in the long term, which could lead to the incidence of ischemic stroke.[21] In addition, smoking damages the arterial wall[32] and elevates blood

Table 5. HRs (95% CIs) for the Association Between Pack-Years and Stroke Recurrence Among Persistent Smokers

| | Nonsmokers (n=1331) | Quartiles of Pack-Years of Smoking | | | | |
		Q1(0.05–24.50) (n=140)	Q2 (24.50–39.00) (n=141)	Q3 (39.00–58.75) (n=141)	Q4 (≥58.75) (n=141)	P for Trend
Total stroke						
Case number	108	11	15	19	28	
Unadjusted	1 (reference)	0.91 (0.49–1.69)	1.26 (0.73–2.16)	1.67 (1.02–2.71)	2.28 (1.51–3.46)	<0.001
Adjusted*	1 (reference)	1.35 (0.72–2.56)	1.78 (1.02–3.10)	1.93 (1.18–3.18)	2.60 (1.70–3.98)	<0.001
Sensitivity analysis[†]	1 (reference)	1.01 (0.46–2.22)	1.44 (0.76–2.75)	2.19 (1.29–3.71)	2.49 (1.52–4.05)	<0.001
Ischemic stroke						
Case number	93	11	13	17	28	
Unadjusted	1 (reference)	1.06 (0.57–1.97)	1.27 (0.71–2.27)	1.73 (1.03–2.89)	2.65 (1.74–4.05)	<0.001
Adjusted*	1 (reference)	1.56 (0.82–2.95)	1.80 (0.99–3.11)	2.11 (1.25–3.57)	3.07 (2.00–4.71)	<0.001
Sensitivity analysis[†]	1 (reference)	1.17 (0.53–2.59)	1.50 (0.76–2.95)	2.17 (1.24–3.82)	2.82 (1.72–4.64)	<0.001

BMI indicates body mass index; CHD, coronary heart disease; HR, hazard ratio; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment.
*Adjusted for age, sex, BMI, NIHSS score, TOAST, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, CHD, and socioeconomic status, including occupation, education years, annual family income, and rural residence.
[†]Adjusted for these variables in those cases without missing values. Information about pack-years of 4 patients was missing, and they were excluded in this analysis.

pressure,[33] which cause the rupture of small intraparenchymal arteries and aneurysm[34] and lead to the subsequent hemorrhagic events.[35] We found a positive and graded relationship between smoking and risk of stroke recurrence, which was similar in studies on the risk of stroke.[29]

Several limitations should be addressed when interpreting the results of the current study. First, this is an observational study, which may generate biases. The effect of quitting may be partly attributable to lifestyle changes (eg, more exercise, healthier diet, and better compliance with medical advice among quitters).[28,36] Randomized control trials are likely to reduce such bias, and thus seem to be necessary. However, considering the ethics and compliance involved in the random assignment of patients to continue or quit smoking, it seems infeasible to conduct such a randomized trial. Second, this is a single-center study, which may limit the generalization of the results to other populations. Third, smoking status was assessed by self-report, and smoking status may be misclassified because of memory biases.

In China, since 2011, smoking has been strictly prohibited in public places (eg, schools, hospitals, restaurants, railway stations, airports, gymnasiums, parks) and in workplaces by law. Printing the health hazards of smoking on the cigarette packages has become mandatory. Cigarette advertisement of any form has been forbidden. Tobacco taxes and prices have been substantially raised. These policies may have contributed to the decreasing smoking prevalence in China in recent years.[37] However, China still has the largest number of smokers in the world. Considering the significant impact of smoking on risk of stroke and many other chronic diseases, more active policies, such as subsidization for nicotine replacement therapy, should be implemented.

Conclusions

After an initial stroke, persistent smoking increases the risk of stroke recurrence. There exists a strong dose–response relationship between smoking quantity and the risk of stroke recurrence. These results highlight the importance of smoking cessation for secondary stroke prevention.

Source of Funding

Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Baseline Characteristics of Patients with First-ever Stroke by Smoking Status.

Variables	Nonsmokers (n=1331)	Former smokers (n=263)	Current smokers (n=1475)	*P* Value§	*P* Value‖
Age, y, mean±SD	60.6±12.1	65.2±10.2	57.7±11.1	<0.001	<0.001
Male, n (%)	473 (35.5)	263 (100.0)	1446 (98.0)	<0.001	0.042
Han ethnic, n (%)	1315 (98.8)	261 (99.2)	1466 (99.4)	0.096	0.777
BMI, kg/m^2, mean±SD	24.8±3.2	24.9±2.8	24.8±3.0	0.813	0.741
Alcohol drinking, n (%)	88 (6.6)	77 (29.3)	540 (36.6)	<0.001	0.020
NIHSS score, n (%)				0.362	0.555
0-4	789 (59.9)	170 (65.9)	918 (62.4)		
4-14	439 (33.3)	73 (28.3)	454 (30.9)		
>14	89 (6.8)	15 (5.8)	99 (6.7)		
Stroke subtypes, n (%)				<0.001	0.204
Large-artery atherosclerosis	506 (38.0)	132 (50.2)	741 (50.2)		
Cardioembolism	144 (10.8)	21 (8.0)	72 (4.9)		
Small-artery occlusion	222 (16.7)	37 (14.1)	212 (14.4)		
Others	459 (34.5)	73 (27.7)	450 (30.5)		
Education years, n (%)				<0.001	<0.001
0-6	481 (37.6)	85 (34.8)	329 (23.5)		
6-9	523 (40.9)	93 (38.1)	734(52.5)		
9-12	151 (11.8)	37 (15.2)	191 (13.7)		
>12	124 (9.7)	29 (11.9)	145 (10.3)		
Occupation*, n (%)				<0.001	0.021
Category Ⅰ	334 (27.6)	100 (41.8)	448 (33.0)		
Category Ⅱ	216 (17.9)	40 (16.7)	294 (21.6)		
Category Ⅲ	659 (54.5)	99 (41.5)	616 (45.4)		
Annual family income, $, n (%)				<0.001	0.214
0-1739	122 (10.9)	29 (12.8)	117 (9.1)		
1739-5455	241 (21.5)	43 (19.0)	204 (15.9)		
5455-8686	310 (27.7)	62 (27.4)	355 (27.7)		

	Nonsmokers	Former smokers	Current smokers	§P	‖P
8696-17391	324 (28.9)	65 (28.8)	418 (32.6)		
>17391	123 (11.0)	27 (12.0)	189 (14.7)		
Rural residence, n (%)	486 (36.5)	82 (31.2)	399 (27.1)	<0.001	0.168
Hypertension, n (%)	991 (74.5)	210 (79.8)	1020 (69.2)	0.002	<0.001
Diabetes mellitus, n (%)	420 (31.6)	81 (30.8)	417 (28.3)	0.058	0.404
Dyslipidemia, n (%)	116 (8.7)	29 (11.0)	124 (8.4)	0.770	0.167
History of TIA, n (%)	28 (2.1)	7 (2.7)	36 (2.4)	0.550	0.832
Atrial fibrillation, n (%)	129 (9.7)	22 (8.4)	76 (5.2)	<0.001	0.037
CHD, n (%)	102 (7.7)	32 (12.2)	77 (5.2)	0.008	<0.001
Smoking intensity, mean±SD	-	20.8±11.6	23.9±13.7	-	0.001
Smoking duration, y, mean±SD	-	29.0±11.2	33.7±11.1	-	<0.001

CHD indicates coronary heart diseases; BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack. *Occupation: category Ⅰ includes professionals, administrators and technicians; category Ⅱ includes clerical and service workers; category Ⅲ includes manufacturing workers, peasants and the jobless. §Nonsmokers vs. current smokers; ‖Former smokers vs. current smokers; Missing data (nonsmokers, former smokers, current smokers): Annual family income (211,37, 192), BMI (13,0,15), Education years (52,19,76), NIHSS score (14,5,4), Occupation (122,24,117), Smoking intensity (-,19, 28), Smoking duration (-,24,38).

Table S2. Baseline Characteristics of Quitters and Persistent smokers.

Variables	Persistent smokers (n=567)	Quitters (n=908)	P Value
Age, y, mean±SD	56.5±11.2	58.5±10.9	<0.001
Male, n (%)	554 (97.7)	892 (98.2)	0.475
Han ethnic, n (%)	561 (98.9)	905 (99.7)	0.161
BMI, kg/m^2, mean±SD	24.9±2.9	24.7±3.0	0.283
Alcohol drinking, n (%)	217 (38.3)	323 (35.8)	0.337
NIHSS score, n (%)			<0.001
0-4	431 (76.1)	487 (53.8)	
4-14	131 (23.1)	323 (35.7)	
>14	4 (0.8)	95 (10.5)	
Stroke subtypes, n (%)			<0.001
Large-artery atherosclerosis	250 (44.1)	491 (54.1)	
Cardioembolism	13 (2.3)	59 (6.5)	
Small-artery occlusion	105 (18.5)	107 (11.8)	
Others	199 (35.1)	251 (27.6)	
Education years, n (%)			0.013
0-6	105 (19.6)	224 (26.0)	
6-9	288 (53.7)	446 (51.7)	
9-12	88 (16.4)	103 (11.9)	
>12	55 (10.3)	90 (10.4)	
Occupation*, n (%)			0.049
Category Ⅰ	173 (32.0)	275 (33.6)	
Category Ⅱ	135 (25.0)	159 (19.4)	
Category Ⅲ	232 (43.0)	384 (47.0)	
Annual family income, $, n (%)			0.001
0-1739	30 (5.8)	87 (11.4)	
1739-5455	74 (14.2)	130 (17.0)	
5455-8686	142 (27.3)	213 (27.9)	
8696-17391	185 (35.6)	233 (30.5)	
>17391	89 (17.1)	100 (13.2)	
Rural residence, n (%)	128 (22.6)	271 (29.8)	0.002
Hypertension, n (%)	384 (67.7)	636 (70.0)	0.348
Diabetes mellitus, n (%)	155 (27.3)	262 (28.9)	0.529
Dyslipidemia, n (%)	57 (10.1)	67 (7.4)	0.072
History of TIA, n (%)	17 (3.0)	19 (2.1)	0.273
Atrial fibrillation, n (%)	21 (3.7)	55 (6.1)	0.047
CHD, n (%)	28 (4.9)	49 (5.4)	0.700
Smoking intensity, mean±SD	25.9±13.5	22.5±13.7	<0.001
Smoking duration, y, mean±SD	33.5±11.1	33.8±11.1	0.239

CHD indicates coronary heart diseases; BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack. *Occupation: category Ⅰ includes professionals, administrators and technicians; category Ⅱ includes clerical and service

workers; category Ⅲ includes manufacturing workers, peasants and the jobless. Missing data (quitters, persistent smokers): Annual family income (145, 47), BMI (12, 3), Education years (45, 31), NIHSS score (3, 1), Occupation (90, 27), Smoking intensity (27, 1), Smoking duration (34, 4).
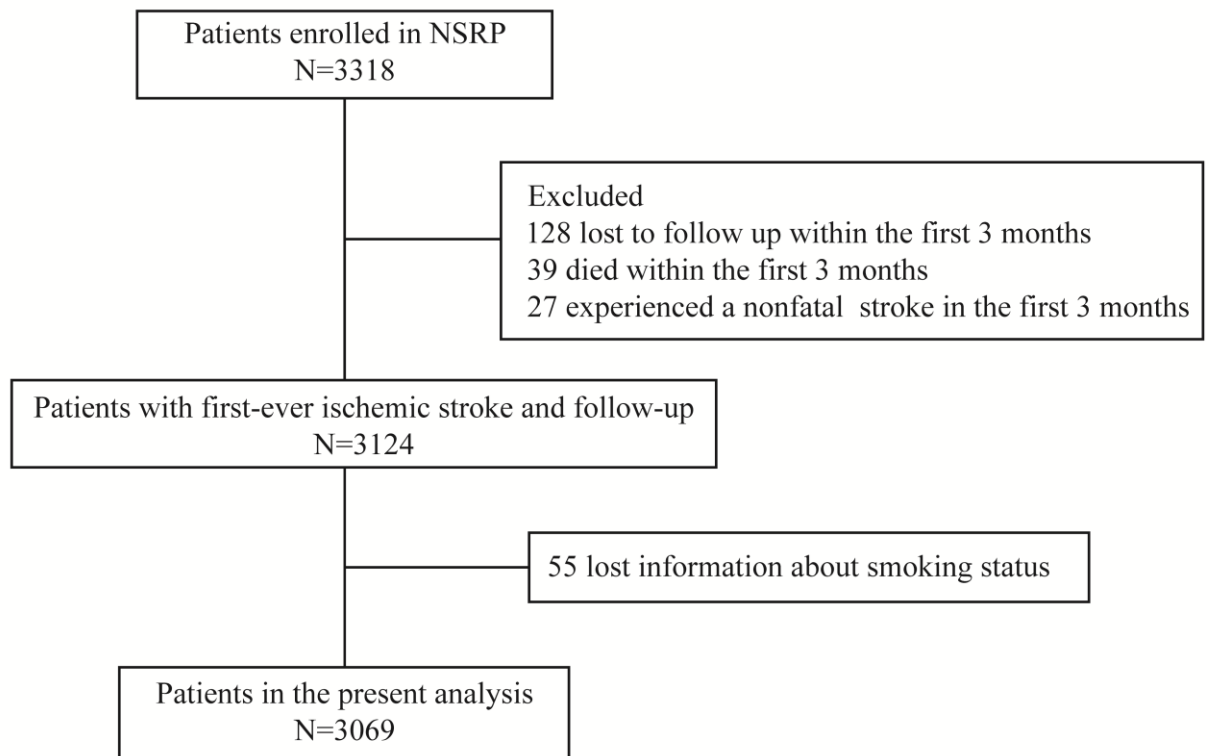
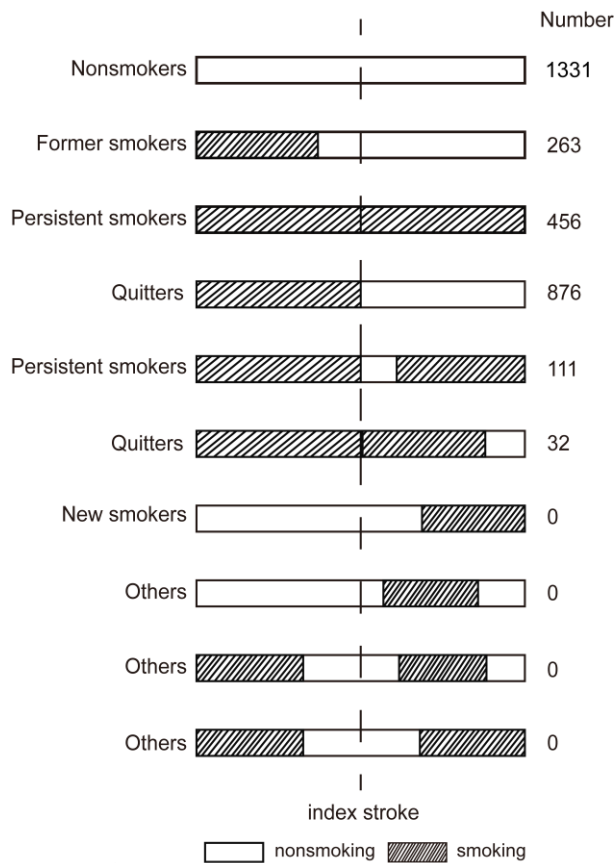**Figure S1**. **Study flowchart**.

Figure S2. The schematic diagram for different smoking status. New smokers were defined as those who were nonsmokers at the time of the index stroke and then became smokers. Other status included those who became new smokers and quit smoking, those who were former smokers at the time of the index stroke, resumed and maintained smoking after stroke, and those who were former smokers at the time of the index time, resumed and then quit smoking.