Smoking and Hemorrhagic Stroke Mortality in a Prospective Cohort Study of Older Chinese

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Background and Purpose—Hemorrhagic stroke is more common in non-Western settings and does not always share risk factors with other cardiovascular diseases. The association of smoking with hemorrhagic stroke subtypes has not been established. We examined the association of cigarette smoking with hemorrhagic stroke, by subtype (intracerebral hemorrhage and subarachnoid hemorrhage), in a large cohort of older Chinese from Hong Kong.

Methods—Multivariable Cox regression analysis was used to assess the adjusted associations of smoking at baseline with death from hemorrhagic stroke and its subtypes, using a population-based prospective cohort of 66,820 Chinese aged ≥65 years enrolled from July 1998 to December 2001 at all the 18 Elderly Health Centers of the Hong Kong Government Department of Health and followed until May 31, 2012.

Results—After follow-up for an average of 10.9 years (SD=3.1), 648 deaths from hemorrhagic stroke had occurred, of which 530 (82%) were intracerebral hemorrhage. Current smoking was associated with a higher risk of hemorrhagic stroke (hazard ratio, 2.19; 95% confidence interval, 1.49–3.22), intracerebral hemorrhage (1.94; 1.25–3.01), and subarachnoid hemorrhage (3.58; 1.62–7.94), adjusted for age, sex, education, public assistance, housing type, monthly expenditure, alcohol use, and exercise. Further adjustment for hypertension and body mass index slightly changed the estimates.

Conclusions—Smoking is strongly associated with hemorrhagic stroke mortality, particularly for subarachnoid hemorrhage. (Stroke. 2013;44:00-00.)

Key Words: hemorrhagic ■ stroke ■ mortality ■ smoking

In most Western settings, stroke mortality rates are declining, and most strokes are ischemic, with hemorrhagic stroke relatively rare.1 In contrast, stroke mortality rates tend to be higher in non-Western settings, with a greater predominance of hemorrhagic strokes, for reasons that have not been fully elucidated.1,2 In the United States, hemorrhagic stroke accounts for <30% of stroke deaths, whereas in China, hemorrhagic stroke accounts for ≥30% to 40% of all stroke deaths.3,4 The role of cigarette smoking in most types of stroke is well established. The 2004 US Surgeon General Report concluded that smoking is causally associated with ischemic stroke and subarachnoid hemorrhage (SAH).5 However, the association of smoking with intracerebral hemorrhage (ICH) and total hemorrhagic stroke is weak and unclear.6 A meta-analysis of 3313 strokes from 32 studies found that smoking was associated with a 50% higher risk of stroke, but the association differed by stroke subtype: the relative risk (RR) was 1.9 for ischemic stroke and 2.9 for SAH, whereas no association was found for ICH.7 However, the Asia Pacific Cohort Studies Collaboration found that cigarette smoking was associated with a slightly higher risk of hemorrhagic stroke (RR=1.19),8 with no difference between Asia and Australia/New Zealand. Lack of clarity on the association of smoking with hemorrhagic stroke might be partly because of insufficient number of cases in well-studied Western populations. Tobacco control is a major public health issue in many non-Western settings, where local evidence can be particularly effective, but it takes several decades for the full effects of smoking to become evident. The smoking epidemic is further advanced in Hong Kong than the rest of China and Asia; thus, Hong Kong may provide a sentinel for smoking in China and other similar locations. We took advantage of a large, prospective cohort study in Hong Kong, a setting with a high stroke incidence, to examine the association of smoking with hemorrhagic stroke mortality using the Elderly Health Service Cohort study.

Methods

In July 1998, 18 elderly health centers were established to deliver health examinations and some primary care services for older adults by the Department of Health of the Government of the Hong Kong Special Administrative Region. All residents in Hong Kong aged 65 years were encouraged to enroll. This study covered all 66,820 enrollees from July 1998 to December 2001. All Hong Kong residents
aged ≥65 years are eligible to enroll for a small annual fee of HK$ (US$1=HK$7.8; waived for those on public social security assistance). More women were enrolled than men (44 140 versus 22 680); otherwise, the participants were similar to the general elderly population in age, socioeconomic position, current smoking, and hospital use.8

Nurses and doctors conducted health assessments using standardized structured interviews and comprehensive clinical examinations. Information on demographic characteristics, socioeconomic position, lifestyle, and personal disease history was collected. Details of the methods have been reported elsewhere.9,10 Ethics approval was obtained from Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. The study complied with the Declaration of Helsinki.

Exposure
Participants were asked whether he/she smoked or had ever smoked ≥1 cigarette a day for 1 year in his/her whole life up to the time of interview. Never smokers were defined as participants who had never smoked as much as 1 cigarette a day or equivalent for a duration of 1 year. Former smokers were defined as participants who had smoked ≥1 cigarette a day for ≥1 year but had stopped smoking for ≥1 year. Current smokers were defined as participants who had smoked ≥1 cigarettes daily during the past year. To assess dose response, current smokers were further classified by amount per day using a definition suitable for the population as 1 to 9 and ≥10 cigarettes per day.

Outcome
Vital status was ascertained from death registration in Hong Kong by record linkage using the unique Hong Kong identity card number. The last date of follow-up or censor date for living participants was May 31, 2012. Most participants in the elderly health center cohort remain in Hong Kong, and any deaths that occur outside Hong Kong are also usually registered in Hong Kong by relatives. For those whose vital status could not be ascertained from death registration or record linkage to use of routine services, telephone interviews were conducted on an ongoing basis (ie, in 2004, 2006, and 2009) to obtain vital status and cause of death. Causes of death obtained were routinely coded according to the International Classification of Disease (ICD), Ninth Revision before 2001 and Tenth Revision in and after 2001 and checked by the Department of Health. Most Hong Kong residents died in the hospital, enabling accurate ascertainment of cause of death, which we had used in previous studies.10,11

The outcomes were death from total stroke (ICD-9 430–438 or ICD-10 I60–I69), ischemic stroke (ICD-9 433–435, 437 or ICD-10 I63, 165–167), hemorrhagic stroke (ICD-9 430–432 or ICD-10 I60–I62), and subtypes of hemorrhagic stroke: ICH (ICD-9 431–432 or ICD-10 I61–I62) and SAH (ICD-9 430 or ICD-10 I60).

Statistical Analysis
Chi-square tests or ANOVA was used to compare baseline characteristics of participants by smoking status. The Cox proportional hazards model was used to calculate adjusted hazard ratios (HRs) with 95% confidence intervals. The Cox proportional assumption was checked by visual inspection of plots of log (−log S) against time, where S is the estimated survival function. Model 1 adjusted for age and sex. Model 2 additionally adjusted for education, marital status, housing, monthly expenditure, public assistance, alcohol drinking, and exercise. Model 3 additionally adjusted for body mass index and hypertension history because people may give up smoking in response to a diagnosis of hypertension. All potential confounders were categorized as in Table 1. Participants were asked the number of days per week in which they drank, the type of drinking, and the amount of alcohol use for regular drinkers. Based on this information, alcohol use was classified as never, former, social (<1 day per week and social type of drinking), and regular drinkers. Participants who died other than from hemorrhagic stroke were regarded as censored at the date of death.12,13 We assessed whether the association of smoking with death from hemorrhagic stroke, ICH, and SAH varied by sex or age (grouped as < or ≥75 years) from the significance of interaction terms (P<0.05). As no evidence suggested different associations by sex or age (P for interaction 0.52 and 0.71, respectively), all analyses were conducted by pooling men and women together in all age groups.

Results
Among 66 820 participants (22 680 men and 44 140 women) enrolled at baseline, 65 510 (98%) reporting smoking status were included in the present data analysis. Sixty-two thousand eight hundred twenty-four participants had vital status ascertained from record linkage, including 19 452 deaths, 2539 had vital status obtained by telephone interview, including 393 deaths, and 1457 had vital status that could not be ascertained and were presumed to be alive. After follow-up for an average of 10.9 years (SD=3.1), 648 deaths from hemorrhagic stroke had occurred, accounting for ≈33.3% of total stroke deaths (n=19 453). Most of the hemorrhagic strokes, 530 (82%), were ICH, and 118 (18%) were SAH.

A minority of men (21%) and women (4%) were current smokers. Former smokers tended to be older than never or current smokers (both P<0.001). In both men and women, compared with never or former smokers, current smokers had lower socioeconomic position, indicated by lower education, more on public assistance and fewer living in privately owned housing, but had higher monthly expenditure and were more likely to be regular alcohol drinkers (all P<0.001). Furthermore, current smokers also tended to be less physically active, had lower body mass index, and had less self-reported hypertension (all P<0.001), probably because of a younger age and lower body mass index (Table 1).

Table 2 shows that current smoking was associated with a higher risk of total stroke (HR, 1.39; 95% confidence interval, 1.18–1.63), ischemic stroke (1.65; 1.03–2.67), hemorrhagic stroke (1.92; 1.48–2.48), ICH (1.80; 1.35–2.40), and SAH (2.63; 1.47–4.69) (model 3), after adjustment for age, sex, education, public assistance, housing type, monthly expenditure, alcohol use, exercise, body mass index, and self-reported hypertension. Relative to current smokers, the total, ischemic, and hemorrhagic stroke and ICH and SAH mortality rates were lower by 19%, 8%, 36%, 31%, and 60%, respectively, in those who had stopped smoking. The Figure shows that smoking was associated with both hemorrhagic stroke (P for trend was 0.001 for men and 0.002 for women) and ICH in men and women (P for trend was 0.01 for men and 0.005 for women) and with SAH in all participants (P for trend was 0.002) with a dose–response pattern.

Discussion
In this large prospective cohort of older Chinese people, current smoking was associated with a higher risk of death from total and ischemic stroke, consistent with several previous large prospective cohort studies in Western populations,14–16 in terms of RR, supporting the validity of our data.9 Furthermore, for the first time we showed that cigarette smoking was associated with a higher mortality risk of hemorrhagic stroke and both its major subtypes, ie, ICH and SAH, based on a large community-based sample and a sufficient follow-up period.
The risk for hemorrhagic stroke with smoking seemed to be greater than that from ischemic stroke. Previous reports have shown that the association between cigarette smoking and hemorrhagic stroke is weak and inconsistent. For example, a study in Japan with 9638 participants found that cigarette smoking was associated with a nonsignificant lower risk of hemorrhagic stroke (HR, 0.42 and 0.68 for those who smoked 1–20 cigarettes and ≥20 cigarettes, respectively). Another prospective cohort study of 2421 Japanese also did not find any association of smoking with hemorrhagic stroke. As the number of deaths from hemorrhagic stroke in Japan has decreased sharply since about 1965, less than one quarter of the stroke deaths were classified as cerebral hemorrhage. Small studies might not have sufficient events for reliable prospective analysis, especially in populations with a low incidence and mortality of hemorrhagic stroke.

Earlier studies from Western settings also showed inconclusive results, with positive association of smoking with hemorrhagic stroke incidence in some but not all studies. A nested case–control study in Sweden, including 147 ICH cases and 1029 controls, reported that smoking was not a risk factor for primary ICH incidence or deaths. Another study of ≈45 000 Swedish women also found no statistically significant association of smoking with ICH incidence or deaths, although the risk for ICH was higher in women who smoked 1 to 9 cigarettes per day (HR=1.5), the small number of ICH cases (n=15) did not provide sufficient statistical power for a more reliable conclusion. A recent pooled cohort of the Atherosclerosis Risk In Community study and Cardiovascular Health Study of 15 792 US adults did not find any consistent or independent relationship of smoking with ICH incidence or deaths. However, this and other such studies might also be underpowered because of low hemorrhagic stroke incidence, although most of these studies found indications of a harmful effect.

Several large prospective studies have shown a positive association of smoking with hemorrhagic stroke. In 2003, 2 prospective US studies reported higher incident risks of fatal and nonfatal total hemorrhagic stroke, ICH, and SAH in men and women smokers, respectively. The Multiple Risk Factor Intervention Trial and Asia Pacific Cohort Studies Collaboration also showed a significant association of smoking with deaths from SAH and ICH. However, as the smoking status was dichotomized as yes/no in these 2 studies,
pooing former smokers and current smokers into ever-smokers would result in conservative risk estimation. A recent prospective study followed 36,686 Finnish people for 13 years and found that smoking was associated with a higher incident risk of total hemorrhagic stroke.16 The risk estimation in the present study was comparable with those from the above studies by showing that current smoking was associated with a 2-fold risk of hemorrhagic stroke.

Prospective studies in Chinese adults on the association of cigarette smoking and hemorrhagic stroke are scarce, and the results are inconclusive.25,26 A study using the China National Hypertension Survey showed that current smoking was associated with all stroke incidence or mortality.25 However, the risk estimate (RR, 1.25 for stroke incidence and 1.14 for stroke mortality) of all strokes was lower than that in Western populations, where the RR ranged from 1.5 to 2.5.7 Furthermore, the risks for subtypes of stroke were not reported in this study.25 A more recent study on 26,607 middle-aged Chinese adults found that smoking was associated with incidence of total and ischemic stroke, but not hemorrhagic stroke,26 perhaps because of insufficient power. However, the smoking epidemic in China is at an earlier stage than that in Hong Kong, by ≈20 years, or the United States, by ≈40 years.27 Smokers in mainland China tend to have a shorter duration of smoking and to have smoked less daily, and the estimates from mainland China may not represent the full effects of smoking.

### Table 2. HR With 95% CI for Death From Stroke and Stroke Subtype by Smoking Status in 65,510 Participants in the Elderly Health Center Cohort From 1998 to 2001 Followed Up Until End of May 2012

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Total Stroke</th>
<th>Ischemic Stroke</th>
<th>Hemorrhagic Stroke</th>
<th>ICH</th>
<th>SAH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of deaths, n</td>
<td>Incidence rate, per 10,000 person-years</td>
<td>HR, 95% CI</td>
<td>No. of deaths, n</td>
<td>Incidence rate, per 10,000 person-years</td>
</tr>
<tr>
<td>Never Smokers</td>
<td>1246</td>
<td>24.1</td>
<td>1.00 (1.00–1.00)</td>
<td>419</td>
<td>6.8</td>
</tr>
<tr>
<td>Former Smokers</td>
<td>445</td>
<td>34.3</td>
<td>1.19 (1.06–1.34)</td>
<td>141</td>
<td>10.9</td>
</tr>
<tr>
<td>Current Smokers</td>
<td>217</td>
<td>34.0</td>
<td>1.40 (1.20–1.64)</td>
<td>73</td>
<td>11.5</td>
</tr>
<tr>
<td>P for Trend</td>
<td>...</td>
<td>...</td>
<td>&lt;0.001</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Model 1: adjusted for age and sex; model 2: adjusted for age, sex, education, public assistance, housing type, monthly expenditure, alcohol use, and exercise; model 3: additionally adjusted for body mass index and self-reported hypertension.

CI indicates confidence interval; HR, hazard ratio; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage.
on hemorrhagic stroke, whereas estimates from Hong Kong may forewarn what will happen in the rest of China and also in other developing Asian countries.

Possible mechanisms exist by which smoking may increase the risk of specifically hemorrhagic stroke. Tobacco smoke contains >7000 different chemicals and compounds, including hundreds of toxins that promote the development of free radicals, causing vascular endothelial dysfunction and inflammation. Structural damage to the arterial wall may also play a role in the development of hemorrhagic stroke. There is strong evidence showing an association of smoking with aneurysm formation, progression, and rupture, which increases risk of SAH. For ICH, elevating blood pressure and arterial wall damage in current smokers may cause the rupture of small intraparenchymal arteries and lead to the subsequent development of ICH.

There are several limitations of this study. First, the causal inference between smoking and hemorrhagic stroke cannot be confirmed based on an observational study. Residual confounding might account for part of the estimates. However, because smoking is a well-documented health hazard, randomized controlled trials can only examine the effects of smoking reduction. We found no randomized controlled trial of smoking cessation/reduction on the effect of stroke, probably because randomized controlled trials studying rare events require very large sample sizes. Second, information on smoking status was self-reported and did not include duration of smoking or cessation. Furthermore, updated information concerning changes in smoking during the 10 years of follow-up was not available for the current study. Quitting smoking reduces risk, and our estimates are conservative. Third, although this is a population-based study, it is not population representative, and it cannot rule out the possibility that smokers at particular risk of stroke were excluded, which would make our estimates conservative. Fourth, stroke subtypes are difficult to classify, and most strokes were not identified as ischemic or hemorrhagic. However, smoking was associated with higher risk of any stroke. Finally, we adjusted for self-reported hypertension in this current study because people may give up smoking in response to a diagnosis of hypertension, and the HR of hemorrhagic stroke for self-reported hypertension was 1.49 (95% confidence interval, 1.28–1.74; data not shown). Using information by self-reporting might lead to misclassification of hypertension status, and subjects with new diagnosis of hypertension could not be identified. However, as there is no evidence that newly diagnosed hypertension will cause smoking, it is unlikely to be a confounder between smoking and stroke. The strength of the current study is that, given the large number of stroke deaths, we had sufficient statistical power to assess prospectively the association of smoking with death from subtypes of hemorrhagic stroke. Furthermore, most Hong Kong residents die in the hospital, enabling accurate diagnosis, and misclassification of cause of death is unlikely.

In conclusion, this prospective study with >10 years of follow-up showed that smoking was associated with higher mortality risk of hemorrhagic stroke and its subtypes. Our results add to the cumulative health benefits that can be obtained by quitting smoking.

Disclosures

None.

References

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