Passive Smoking Is Not Associated with Risk of Intracranial Aneurysm Rupture in Nonsmoking Women

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■ BACKGROUND: **Active smoking is a major risk factor for intracranial aneurysm rupture (IAR); however, little is known about the effects of passive smoking on IAR. In China, female passive smoking is widespread and severe. This study aimed to assess whether passive smoking is associated with increased risk of IAR among nonsmoking women.**

■ METHODS: **We enrolled and retrospectively analyzed 385 consecutive female patients with intracranial aneurysms (IAs; 87 ruptured, 298 unruptured) who were admitted to our center between June 2015 and January 2017. Data on female active smoking, passive smoking, and other factors potentially influencing IAR were precisely compared between ruptured and unruptured IAs.**

■ RESULTS: **For all aneurysms, when adjusting for potential confounders, current smoking was significantly associated with IAR (odds ratio [OR], 3.31; 95% confidence interval [CI], 1.08–10.20; $P = 0.037$). Furthermore, bifurcation location (OR, 5.73; 95% CI, 3.27–10.03; $P < 0.001$) and educational level (OR, 1.90; 95% CI, 1.10–3.28; $P = 0.022$) significantly increased the risk of IAR. However, for nonsmoking female patients, approximately one fifth of those with IAs were affected by passive smoking; however, passive smoking was not significantly associated with IAR. The results also showed that bifurcation location (OR, 6.21; 95% CI, 3.46–11.15; $P < 0.001$) and the location of posterior circulation (OR, 3.23; 95% CI, 1.31–7.93; $P = 0.011$) significantly increased the risk of IAR.**

■ CONCLUSIONS: **Although active current smoking was strongly associated with aneurysm rupture in female patients, passive smoking was not an independent risk factor for aneurysm rupture in nonsmoking women.**

INTRODUCTION

Intracranial aneurysm (IA) rupture (IAR) accounts for 85% of cases of spontaneous subarachnoid hemorrhage (SAH), which is associated with high morbidity and mortality.[1] SAH occurs with an incidence of 10 per 100,000 person-years and 50%–70% more frequently in women than in men.[2] The female preponderance of SAH is because of the relatively higher incidence of IAs in women. However, several epidemiologic studies have also suggested that the female preponderance of IAR can be attributed to the effect of hormonal factors.[3] Moreover, some studies have proved that hormone replacement therapy (HRT) is associated with reduced risk of IAR.[4-6]

In addition, smoking is a major factor for IAR in both women and men. Thousands of studies have evaluated the impact of active smoking on IAR, and the toxic impact of active smoking is generally recognized.[7,8] In comparison, the effects of passive smoking on IAR are not fully understood. China is home to more than 300 million smokers, and female passive smoking is widespread and severe because of the high proportion of men who smoke. Moreover, the rates of exposure to secondhand smoke in Chinese women are among the highest in the world.[7,9] Inadequate evaluations of exposure may result in an underestimation of the

Key words
- Female
- Intracranial aneurysm
- Passive smoking
- Risk factors
- Rupture

Abbreviations and Acronyms
CI: Confidence interval
HRT: Hormone replacement therapy
IA: Intracranial aneurysm
IAR: Intracranial aneurysm rupture
OR: Odds ratio
SAH: Subarachnoid hemorrhage

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risks, if they do exist.[10] Therefore, in this 2-part study, we assessed the relationship between active smoking and the risk of IAR among women and then studied the relationship between passive smoking and the risk of IAR among female nonsmokers.

METHODS

Study Design and Ethics

The study population consisted of female patients with IAs evaluated and/or treated at the Beijing Tiantan Hospital between June 2015 and January 2017. The exclusion criteria were 1) fusiform, traumatic, multiple, or mycotic aneurysms; 2) intracranial hemorrhage for unknown reasons; and 3) aneurysms associated with arteriovenous malformations, arteriovenous fistulas, and moyamoya disease.

This study was approved by the Beijing Tiantan Hospital review committee. All participants provided informed consent.

Data Collection and Definitions

All female patients with IAs between the study dates were included. The clinical and radiologic data of female patients with IAs were precisely collected. Sociodemographic characteristics including age, sex, and educational level, and clinical characteristics including body mass index, medical comorbidities, alcohol use (current or previous intake >5 drinks per day), family history of IA, postmenopausal status, and history of postmenopausal hormone treatment were collected. The higher education level consisted of those who graduate from high school (higher secondary education), those with a university degree, or those with >12 years spent in formal education (beginning from first grade). Those who graduate from middle school (lower secondary education) or those with <12 years of formal education were classified into the lower education level.[11] Postmenopausal status was defined as at least 1 year of amenorrhea. Postmenopausal HRT was defined as previous or active hormone use (estrogen only or estrogen and progesterone).

We obtained information through a telephone survey and by using a structured questionnaire in a face-to-face interview conducted by trained interviewers. Information on smoking and passive smoking was obtained from the medical history recorded by the treating physicians during interviews of patients or family members. If the patient's information was incomplete, we obtained information using a telephone survey. We collected the female patients with ruptured aneurysms from interviews of patients or family members or telephone survey. Women were classified as nonsmokers if they reported never smoking or smoking <100 cigarettes during their lifetime.[12] Women environmentally exposed to cigarette smoke were defined as nonsmokers who declared staying at least 1 hour/day in rooms where cigarettes were smoked, or staying at least 30 minutes/day in the immediate vicinity of cigarette-smoking people, or sharing a flat with 1 or more persons smoking cigarettes at home.[13] We also collected data about sources of smoke exposure. First, we asked whether their husband or other family members ever smoked in the house. Second, the woman was asked whether someone ever smoked within 3 m around her in the workplace.[9]

The size and location of the aneurysm were also recorded. Bifurcation IAs were defined as aneurysms at artery bifurcations in the circle of Willis, originating from more than 1 parent vessel (internal carotid artery terminus, anterior communicating artery, internal carotid–posterior communicating artery, middle cerebral artery bifurcation, and apex of the basilar artery).[14] If the aneurysm originated from only 1 parent vessel, the aneurysm was defined as sidewall aneurysm.[15] Irregular aneurysm shape was defined as the presence of blebs, aneurysm wall protrusions, or multiple lobes.[16]

Statistical Analysis

All data were analyzed with SPSS version 22.0 (IBM Corp., Armonk, New York, USA). Differences in characteristics were assessed by using either χ^2 tests for categorical variables or t tests for continuous variables. Continuous data were expressed as means ± standard deviations, and categorical variables were calculated as frequencies (percentages). As predetermined, variables with a P value of < 0.20 in the univariate logistic regression analysis were evaluated in the multivariate analysis. To identify the independent risk factors that had significant correlations with aneurysm rupture in female patients, multivariate logistic regression analyses were separately performed for all the female patients with IAs and for nonsmoking female patients. We estimated the odds ratios (ORs) and 95% confidence intervals (CIs) for the association between factors and IAR, with $P < 0.05$ indicating statistical significance.

RESULTS

Factors Related to IAR in All Female Patients

A total of 385 women with IAs (87 ruptured and 298 unruptured) were enrolled (age range, 24–75 years). The mean patient age was 55.1 ± 9.3 years in the unruptured group and 55.9 ± 9.3 years in the ruptured group. The patient inclusion flowchart is shown in Figure 1. The demographics and main aneurysm characteristics in both groups are summarized in Table 1. The following covariates met our previously determined level of significance and were entered into the stepwise forward selection for the unconditional logistic model: age ($P = 0.055$), smoking status ($P = 0.025$), alcohol use ($P = 0.127$), education level ($P < 0.001$), hypertension ($P = 0.081$), cerebral ischemic comorbidities ($P = 0.098$), postmenopausal HRT ($P = 0.146$), aneurysm size ($P = 0.009$), bifurcation location ($P < 0.001$), and location of the anterior circulation artery ($P = 0.096$). However, postmenopausal status was far from being significantly associated with IAR in the female patients.

When adjusting for age, alcohol use, education level, hypertension, cerebral ischemic comorbidities, postmenopausal HRT, aneurysm size, and aneurysm location, the multivariate analysis indicated that current smoking was significantly associated with IAR (OR, 3.31; 95% CI, 1.08–10.20; $P = 0.037$). Furthermore, bifurcation location (OR, 5.73; 95% CI, 3.27–10.03; $P < 0.001$) and educational level (OR, 1.90; 95% CI, 1.10–3.28; $P = 0.022$) significantly increased the risk of IAR (Table 1).

Factors Related to IAR in All Nonsmoking Female Patients

After excluding smokers ($n = 28$), 357 female patients who had never smoked were enrolled, including 282 with unruptured IAs and 75 with ruptured IAs. Of the 282 patients with unruptured IAs, 67 (23.8%) were exposed to passive smoke, including 48 with home exposure, 13 with workplace exposure, and 6 with both