Early Menarche and Ischemic Stroke Risk Among Postmenopausal Women

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SUMMARY

Background: Results from previous studies regarding relationships between age at menarche and cardiovascular disease remain controversial. This study investigated the association between endogenous estrogen exposure and ischemic stroke risk.

Methods: A total of 189 ischemic stroke patients and 192 age-matched healthy postmenopausal women were recruited. Age at menarche and menopause and risk factors of ischemic stroke were recorded through structured questionnaires by well-trained research assistants. Lifetime estrogen exposure was calculated as the number of years between age of menarche and menopause.

Results: Study subjects with a history of hypertension and diabetes mellitus have a 2.8- and 6.2-fold increased risk for ischemic stroke, respectively. In addition, study subjects with waist circumferences ≥ 80 cm also have a 2.6-fold increased risk of ischemic stroke. Conversely, subjects who experienced menarche at an early age may have a significantly decreased risk of 0.3-fold for ischemic stroke. Moreover, there was a significant and joint protective effect for study subjects without any risk factors of ischemic stroke, including a history of hypertension and diabetes mellitus, late age at menarche, and shorter lifetime estrogen exposure; these subjects were found to have the lowest risk (0.03-fold) for the development of ischemic stroke.

Conclusion: Our study provides strong evidence that a significant joint protective effect was observed for patients who undergo early menarche, have longer estrogen exposure and no history of hypertension or diabetes mellitus on the risk of ischemic stroke. [International Journal of Gerontology 2010; 4(1): 16–22]

Key Words: ischemic stroke, menarche, menopause

Introduction

Previous studies have demonstrated that the incidence rate of cardiovascular disease in premenopausal women is lower than that in either postmenopausal women or men[1,2]. This has been related to a protective effect exerted by ovarian hormones against cardiovascular disease. However, recent large, well-designed, randomized placebo-controlled clinical trials have reported that postmenopausal hormone replacement therapy (HRT) increases[3,4] or has no significant effect on stroke risk[5]. These conflicting results have led to the recommendation that there are important differences on the effect on stroke risk between physiologic endogenous estrogens and exogenous hormones administered after menopause. In addition, several prospective studies

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have indicated that women who experience natural menopause at an early age have a higher risk of coronary heart disease[6–9]. However, the relationship with earlier age at menarche and cardiovascular disease is not clear[10–13]. Therefore, we hypothesized that if endogenous estrogens were protective, indicators of high estrogen exposure leading to early menarche, late menopause and a longer estrogen exposure would be associated with a lower risk of ischemic stroke. Hence, we conducted a case-control study to examine the above estrogen exposure indicators in relation to the risk of ischemic stroke.

Subjects and Methods

Female acute ischemic stroke patients who had suffered at least one episode of symptomatic ischemic stroke or transient ischemic attack were recruited from Chi Mei Medical Center, Lotung Poh-Ai Hospital, Wan-Fang Hospital, and Taipei Medical University Hospital. Ischemic stroke was defined as a recent infarct in the clinically relevant area of the brain on a computed tomography or magnetic resonance imaging brain scan performed within 10 days of the event. Controls were age-matched women who had not suffered a stroke. Most were recruited from a community-based prospective study in Taipei, which was described in a previous study[14]. Some were selected from subjects who attended the annual health examinations of the health center at Taipei Medical University Hospital. All study subjects were postmenopausal women. Informed consent for participants in the study was obtained from all cases as well as controls. The study was approved by the ethics committees of the participating hospitals and Taipei Medical University on the understanding that all data would be coded and patient anonymity would be guaranteed. There were 189 ischemic stroke patients and 192 age-matched healthy controls consecutively recruited in this study.

Data collection and risk factor definition

Information concerning menstrual history, including menstrual status and regularity, age at menarche and menopause, was collected through a structured questionnaire by well-trained research assistants. The definition of menopause was the age at the definitive cessation of menstruation, whether natural or resulting from oophorectomy. The duration of estrogenic lifetime was calculated as the number of years between age of menarche and menopause. The history of oral contraceptive or HRT use was recorded. Each participant was asked how often she had consumed soybean-containing food, such as tofu, miso soup and beans, on average per week. Isoflavone intake was determined in the same manner. Body mass index was defined as the individual's body weight divided by square of their height (kilogram per squared meter). The definition of hypertension and diabetes mellitus were based on disease history from the questionnaires among patients. For controls, hypertension and diabetes mellitus were classified according to their blood pressure and fasting glucose level in the serum. Hypertensive subjects were diagnosed if their systolic blood pressure was ≥ 140 mmHg or diastolic blood pressure was ≥ 90 mmHg or if they were taking an antihypertensive drug. Diabetes mellitus was defined as fasting serum glucose level of ≥ 126 mg/dL or a history of oral hypoglycemic agent use or insulin injection.

Statistical analysis

Quantitative data were compared between cases and controls by the unpaired Student *t* test and expressed as mean $\pm$ standard deviation. Categorical variables were assessed using the χ^2 test and were expressed as frequency and percentage. A logistic regression model was performed to estimate the odd ratio (OR) and 95% confidence interval (CI). Stepwise logistic regression analysis was employed to determined potential risk factors for ischemic stroke. We further evaluated the combined effect of late menarche age (>15 years), shorter lifetime estrogen exposure (≤ 36 years) and history of hypertension or diabetes mellitus on the ischemic stroke risk and, therefore, classified the study subjects into eight groups. Statistical differences were considered significant at $p<0.05$. SAS version 9.1 statistical software (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis.

Results

The mean age of participants was 66.4 ± 9.5 years for cases and 64.9 ± 8.9 years for controls ($p>0.05$). Table 1 shows the frequency distribution and the ORs with the 95% CIs for the traditional risk factors in the 189 patients and 192 controls. An education level greater than 12 years was more frequent in controls than in cases. Diabetes mellitus and hypertension history were major

Table 1. *Traditional risk factors and risk of ischemic stroke*

Characteristics	Healthy controls ($n=192$)	Stroke patients ($n=189$)	OR (95% CI)	OR* (95% CI)
Education level, *n* (%), yr				
≤12	62/164 (37.8)	140/160 (87.5)	1.0	1.0
≥13	102/164 (62.2)	20/160 (12.5)	0.1 (0.05–0.2)†	0.1 (0.1–0.2)†
Hyperlipidemia, *n* (%)				
No	96/185 (51.9)	79/155 (51.0)	1.0	1.0
Yes	89/185 (48.1)	76/155 (49.0)	1.0 (0.7–1.6)	1.1 (0.6–1.9)
Diabetes mellitus, *n* (%)				
No	168/189 (88.9)	81/158 (51.3)	1.0	1.0
Yes	21/189 (11.1)	77/158 (48.7)	8.0 (4.6–14.0)†	6.2 (3.2–11.9)†
Hypertension, *n* (%)				
No	99 (51.6)	43/179 (24.0)	1.0	1.0
Yes	93 (48.4)	136/179 (76.0)	3.4 (2.2–5.3)†	2.8 (1.6–4.9)†
Cigarette smoking, *n* (%)				
No	181 (94.3)	144/158 (91.1)	1.0	1.0
Yes	11 (5.7)	14/158 (8.9)	1.6 (0.7–3.6)	1.4 (0.5–3.7)
BMI, *n* (%)				
≤27	127/159 (79.9)	107/162 (66.0)	1.0	1.0
>27	32/159 (20.1)	55/162 (34.0)	2.0 (1.2–3.4)‡	1.8 (1.0–3.2)
Waist circumference, *n* (%)				
<80	125 (65.1)	73 (38.6)	1.0	1.0
≥80	67 (34.9)	116 (61.4)	3.0 (2.0–4.5)†	2.6 (1.6–4.5)†

**Adjustment for age and education level; †$p<0.001$; ‡$p<0.01$. OR = odds ratio; CI = confidence interval; BMI = body mass index.*

risk factors with the strongest effects on risk of ischemic stroke in this study, showing significant differences in the age- and education-adjusted risks of 6.2- and 2.8-fold, respectively. Obesity indicators, including body mass index and waist circumference, also indicated differences between cases and controls. A significant difference on the risk of ischemic stroke was observed for waist circumference (OR, 2.6; 95% CI, 1.6–4.5). However, the effect of body mass index on ischemic stroke risk was nonsignificant after adjusting for age and education level. Hyperlipidemia and cigarette smoking revealed no evidence of an association with ischemic stroke in these study subjects.

The relationship between the history of oral contraceptive use, HRT use, dietary intake of soybeans or isoflavones and ischemic stroke are listed in Table 2. After adjusting for age and education level, subjects with an HRT history had significant decreased risk of ischemic stroke. Compared with participants who have an average dietary intake of soybeans < three times per week, those who consumed soybeans ≥ three times per week have a significantly decreased risk of ischemic stroke (OR, 0.5; 95% CI, 0.2–0.8). A 0.5-fold decreased risk of ischemic stroke was observed for those who have intake of isoflavone ≥ three times per week, but the OR did not reach statistical significance.

Table 3 summarizes the effects of estrogen exposure indicators including age at menarche, age at menopause, and the duration of lifetime estrogenic exposure on the risk of ischemic stroke. Compared with those study subjects whose menarche age was ≥16 years as a reference group, menarche between the ages of 14 and 15 seemed to be related to a lower risk of ischemic stroke and a significantly decreased risk was observed in those whose menarche age was <14 (OR, 0.3; 95% CI, 0.1–0.7). A significant trend test indicates that the earlier menarche commenced, the lower the risk of ischemic stroke. Although late menopause age seemed to be related to a lower risk of ischemic stroke, the ORs of ischemic stroke risk among study subjects whose menopause age ranged 49–50 years or >50 years were not significant. However, a borderline significant trend

Table 2. *Relationship between history of oral contraceptive use, hormone replacement therapy (HRT) use, dietary intake of soybeans or isoflavone and ischemic stroke*

	Healthy controls ($n=192$)	Stroke patients ($n=189$)	OR (95% CI)	OR* (95% CI)
History of oral contraceptive, *n* (%)				
No	147/191 (77.0)	146/177 (82.5)	1.0	1.0
Yes	44/191 (23.0)	31/177 (17.5)	0.7 (0.4–1.2)	0.8 (0.4–1.6)
History of HRT, *n* (%)				
No	131/189 (69.3)	153/176 (86.9)	1.0	1.0
Yes	58/189 (30.7)	23/176 (13.1)	0.3 (0.2–0.6)†	0.4 (0.2–0.7)‡
Intake of soybeans (per week), *n* (%)				
< three times	123/191 (64.4)	139/174 (79.9)	1.0	1.0
≥ three times	68/191 (35.6)	35/174 (20.1)	0.5 (0.3–0.7)‡	0.5 (0.2–0.8)§
Intake of isoflavone (per week), *n* (%)				
< three times	177/191 (92.7)	169/174 (97.1)	1.0	1.0
≥ three times	14/191 (7.3)	5/174 (2.9)	0.4 (0.1–1.1)‖	0.5 (0.2–1.8)

**Adjustment for age and education level; †$p<0.001$; ‡$p<0.01$; §$p<0.05$; ‖$0.05<p<0.1$. OR = odds ratio; CI = confidence interval.*

Table 3. *Effects of age at menarche, age at menopause, and lifetime estrogen exposure on risk of ischemic stroke*

	Healthy controls ($n=192$)	Stroke patients ($n=189$)	OR (95% CI)	OR* (95% CI)
Age at menarche, *n* (%), yr				
≥ 16	47/179 (26.3)	68/125 (54.4)	1.0†	1.0†
14–15	59/179 (33.0)	44/125 (35.2)	0.5 (0.3–0.9)‡	0.6 (0.3–1.1)
< 14	73/179 (40.8)	13/125 (10.4)	0.1 (0.1–0.2)§	0.3 (0.1–0.7)‖
Age at menopause, *n* (%), yr				
≤ 48	50/170 (29.4)	46/139 (33.1)	1.0	1.0¶
49–50	42/170 (24.7)	43/139 (30.9)	1.1 (0.6–2.0)	0.8 (0.4–1.8)
≥ 51	78/170 (45.9)	50/139 (36.0)	0.7 (0.4–1.2)	0.6 (0.3–1.1)
Lifetime estrogen exposure, *n* (%), yr				
≤ 32	41/166 (24.7)	39/109 (35.8)	1.0†	1.0
33–36	50/166 (30.1)	38/109 (34.9)	0.8 (0.4–1.5)	0.6 (0.3–1.4)
≥ 37	75/166 (45.2)	32/109 (29.4)	0.4 (0.2–0.8)‖	0.5 (0.2–1.1)

**Adjustment for age and education level; †p value for trend test <0.05; ‡$p<0.05$; §$p<0.001$; ‖$p<0.01$; ¶p value for trend test: $0.05<p<0.1$. OR = odds ratio; CI = confidence interval.*

Table 4. *Stepwise logistic regression: odds ratios of risk factors associated with ischemic stroke after adjustment for covariates*

	Odds ratio	95% CI
Education level > 13 yr	0.1	0.03–0.3*
Diabetes mellitus	3.4	1.3–8.8†
Waist circumference ≥ 80 cm	1.1	1.0–1.1*
Age at menarche < 14 yr	0.2	0.05–0.6‡
Intake of soybeans < three times per week	3.2	1.1–9.2†

**$p<0.001$; †$p<0.05$; ‡$p<0.01$. CI = confidence interval.*

test was observed ($p=0.09$). A longer estrogenic exposure was associated with a lower risk of stroke, i.e., the lowest OR of risk of ischemic was obtained through study subjects with the longest duration of estrogen exposure. However, the association was not significant after adjusting for age and education level.

Factors significantly associated with an increased risk of ischemic stroke provided by the stepwise logistic regression model after adjustment for potential covariates are presented in Table 4. Consequently, both an age at menarche < 14 years and an education level > 13 years were independent factors for a decreased risk of

	Hypertension or DM	Age at menarche > 15 yr	Lifetime estrogen exposure ≤ 36 yr	OR* (95% CI)	Group OR* (95% CI)
Reference	Yes	Yes	Yes	1.0	1.0†
I	Yes	Yes	No	1.1 (0.2–4.8)	
I	Yes	No	Yes	0.4 (0.2–0.9)‡	
I	No	Yes	Yes	0.2 (0.1–0.5)§	0.4 (0.2–0.7)§
II	Yes	No	No	0.2 (0.1–0.4)‖	
II	No	Yes	No	0.4 (0.1–2.9)	
II	No	No	Yes	0.1 (0.02–0.3)‖	0.1 (0.1–0.3)‖
III	No	No	No	0.03 (0.003–0.2)‖	0.03 (0.003–0.2)‖

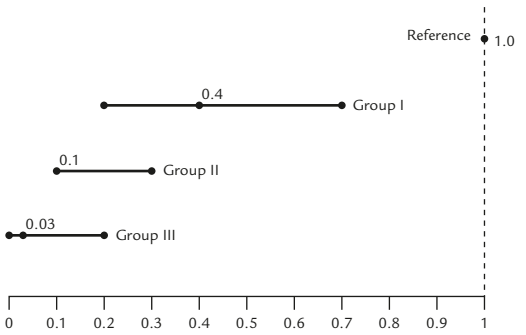

Figure. Joint effect on risk of ischemic stroke between history of hypertension or diabetes mellitus, age at menarche, and lifetime estrogen exposure. *Adjustment for age and education level; †p value for trend test <0.05; ‡$p<0.05$; §$p<0.01$; ‖$p<0.001$. DM = diabetes mellitus; OR = odds ratio; CI = confidence interval.

ischemic stroke. Diabetes mellitus, waist circumference ≥ 80 cm, and dietary intake of soybeans < three times per week were independently associated with increased risk of ischemic stroke. A 58.76% of –2 log likelihood implied that the model shown in Table 4 accounted for more than half of the variance of ischemic stroke risk.

A joint effect on the risk of ischemic stroke between three risk factors including history of hypertension or diabetes mellitus, age at menarche > 15 years and lifetime estrogen exposure ≤ 36 years are listed in the Figure. Compared with a reference group that included subjects with all three risk factors mentioned above, those without any risk factors would have the significantly lowest risk of ischemic stroke (OR, 0.03; 95% CI, 0.003–0.2). A significantly decreased risk of 0.1- and 0.4-fold for ischemic stroke was observed among study subjects with one and two risk factors, respectively. A significant trend test indicated that study subjects with a fewer number of risk factors would have the lower risk for suffering from an ischemic stroke (p for trend, 0.0002).

Discussion

In this case-control study, early menarche was independently associated with a lower risk of ischemic stroke, after adjusting for risk factors of cardiovascular disease. In addition, late menopause and a longer lifetime estrogen exposure also tended to be related with a decreased risk of ischemic stroke. These findings support the hypothesis proposed by previous observational studies that exposure to endogenous estrogens protects against ischemic stroke.

Since women who reach menarche at an early age are exposed to endogenous estrogen for a longer period than those who reach menarche at a later age, one might expect the groups of menarche at an early age to have a lower risk of cardiovascular disease. Many studies in Western countries indicated an inverse relationship between early menarche and cardiovascular disease[15,16]. However, the Japan Collaborative Cohort study in Japan found that a late age at menarche was prone to be associated with an increased risk of mortality from stroke among total subjects aged 40–79 years. Nonetheless, the OR did not reach a significant level[10]. This inconsistent result might be due to ethnic differences. Many studies have gone on to show that early menarche is associated with increased cardiovascular disease because of increased body fatness in childhood, and there are more obese adolescent girls in Western countries than in Asian countries including Taiwan. Our study also found that increased age at menopause and a longer lifetime estrogen exposure had protective effects on a decreased risk of ischemic stroke. This finding is consistent with those showing that early menopause and a shorter estrogenic lifetime exposure were correlated with a higher risk of mortality from cardiovascular disease among American and European women[7,17,18]. The reasons for the depletion of estrogen itself may have a deleterious effect on the development of atherosclerosis because of elevated serum total or LDL-cholesterol levels[19], endothelial dysfunction[20] and increased platelet aggregation[21].

Hypertension, diabetes mellitus, obesity, and exposure to cigarette smoke are well-documented and modifiable risk factors for ischemic stroke[22]. Our study also showed that hypertension, diabetes mellitus, and obesity were associated with ischemic stroke; however, cigarette smoking was not. This could be explained by the very low prevalence of smoking among the women in our study.

To assess the joint effect of ischemic stroke for late menarche age (>15 years), shorter lifetime estrogen exposure (≤36 years) and history of hypertension or diabetes mellitus, we calculated the combined risk of ischemic stroke for study subjects with different combinations of the three factors. Our study provided strong evidence that the fewer risk factors the study subjects have, the lower their risk of ischemic stroke, resulting in a significant joint effect in the absence of these risk factors by decreasing risk 85% (from 0.2- to 0.03-fold) for ischemic stroke. As is the case in many studies, the observed correlation here could be a chance finding. Determining whether there is causal relationship between these risk factors and their effect on stroke should be further confirmed by data derived from different and larger populations.

Previous observational studies have reported that the use of HRT is associated with a reduced risk of coronary heart disease[23]. A similar result was also found in the present study. Although randomized clinical trials demonstrated no advantage of HRT on the risk of coronary heart disease[3–5], a potential benefit of estrogen therapy was found for young postmenopausal women aged 50–59 years[24]. In our study, we found that 82.2% of control subjects and 64.7% of cases used HRT before 60 years of age. This might be the reason why the use of HRT was related with a lower risk of ischemic stroke in our study.

Evidence is mounting that consumption of soy protein could lower blood cholesterol levels and may also reduce the risk of cardiovascular disease[25]. Dietary soybeans with their high polyunsaturated fat, fiber, vitamin, and mineral content combined with its low saturated fat content may be beneficial to cardiovascular health[26]. Soy-derived isoflavones have been associated with a reduced risk of cerebral and myocardial infarctions[27]. Our study found that a lower frequency of dietary intake of soybeans was significantly associated with increased ischemic stroke, but the effect of isoflavone intake was not significant. This might have resulted from few subjects who consumed isoflavones ≥ three times per week.

There were some potential limitations of this study. First, it cannot be ruled out that misclassifications regarding the age at menarche and age at menopause may have occurred as a result of study subjects' recall bias. However, we did try and prevent this by asking subjects questions like what school grade they were in when menarche occurred. In addition, we tried to preempt such bias by excluding women who could not be sure of their age at menarche. Furthermore, reproducibility and validity studies have indicated that most women are able to report the age at menopause and even the age at menarche with a high degree of accuracy[28–30]. Those studies also pointed out that data regarding reliability depend mainly on the subject's age and education. Although the education level was significantly higher in controls, the association between menstrual factors and ischemic stroke remained consistent when using stratification analysis by education level. However, the controls recruited in our study were aged-matched with cases, and education level was adjusted in our study. The consequence of a non-differential misclassification of recall bias might not influence the results in our study.

Second, a larger sample size is needed to validate the association between menstrual factors and ischemic stroke risk.

In conclusion, our study found that early menarche was associated with a reduced risk of ischemic stroke, which can be explained by a protective effect of endogenous estrogen on the development of atherosclerosis. A significant joint protective effect on the risk of ischemic stroke was also observed among study subjects without risk factors such as hypertension and diabetes mellitus, late age at menarche, and a shorter lifetime exposure to estrogen.

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