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Dose-Response Relationship Between Cigarette Smoking and Risk of Ischemic Stroke in Young Women

Viveca M. Bhat, MD, John W. Cole, MD, MS, John D. Sorkin, MD, PhD, Marcella A. Wozniak, MD, PhD, Ann M. Malarcher, PhD, Wayne H. Giles, MD, MS, Barney J. Stern, MD, and Steven J. Kittner, MD, MPH

University of Maryland, School of Medicine, Departments of Neurology (V.M.B., J.W.C., M.A.W., B.J.S., S.J.K.) and Epidemiology and Preventive Medicine (J.W.C., S.J.K.), Baltimore, Md; the Geriatrics Research, Education, and Clinical Center (J.D.S., S.J.K.), Claude D. Pepper Older Americans Independence Center (J.D.S.), Medical Research Service (J.W.C., S.J.K.), Department of Veterans Affairs Medical Center, Baltimore, Md; and the Centers for Disease Control and Prevention (W.H.G., A.M.M.), Atlanta, Ga

Abstract

Background and Purpose—Although cigarette smoking is known to be a risk factor for ischemic stroke, there are few data on the dose-response relationship between smoking and stroke risk in a young ethnically diverse population.

Methods—We used data from the Stroke Prevention in Young Women Study, a population-based case-control study of risk factors for ischemic stroke in women aged 15 to 49 years to examine the relationship between cigarette smoking and ischemic stroke. Historical data, including smoking history, was obtained through standardized interviews. Odds ratios (OR) were estimated using logistic regression. Cases (n=466) were women with stroke in the greater Baltimore-Washington area, and controls (n=604) were women free of a stroke history identified by random digit dialing.

Results—After multivariable adjustment, the OR comparing current smokers to never smokers was 2.6 ($P<0.0001$); no difference in stroke risk was observed between former smokers and never smokers. Adjusted OR increased with increasing number of cigarettes smoked per day (OR=2.2 for 1 to 10 cigs/d; 2.5 for 11 to 20 cigs/d; 4.3 for 21 to 39 cigs/d; 9.1 for 40 or more cigs/d).

Conclusion—These results suggest a strong dose-response relationship between cigarette smoking and ischemic stroke risk in young women and reinforce the need for aggressive smoking cessation efforts in young adults.

Keywords

stroke; women; smoking

Current smoking is known to be an important risk factor for ischemic stroke.^{1–4} However, few studies have examined this relationship among young ethnically diverse populations.⁵ Furthermore, some studies that have included young adults have not addressed issues of dose response. In 2005, an estimated 20.7% of U.S. women ages 18 to 24 were current

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Correspondence to Dr John W. Cole, Bressler Building, Room 12-006, University of Maryland, Baltimore, 655 W. Baltimore St, Baltimore, MD 21201. jcole@som.umaryland.edu.

Disclosures

None.

cigarette smokers.⁶ Given that the prevalence of smoking in teenage girls and young women remains high and has not changed substantially in the past several years, it is important to further characterize the stroke risk associated with smoking in this population.³ We undertook this study to assess the dose-response between cigarette smoking and risk of ischemic stroke in young women.

Subjects and Methods

The Stroke Prevention in Young Women Study (SPYW) is a population-based case-control study initiated to examine risk factors for ischemic stroke in young women. Study recruitment and data collection occurred in 2 waves: SPYW-1 was conducted between 1992 and 1996 and SPYW-2 was conducted between 2001 and 2003. Cases were women, aged 15 to 49 years, hospitalized with a first cerebral infarction identified by discharge surveillance from one of 59 hospitals in the greater Baltimore-Washington area and direct referral from regional neurologists. The methods for discharge surveillance, chart abstraction, case adjudication, and assignment of probable and possible underlying causes have been described elsewhere.^{7,8} Controls were women free of a history of stroke identified by random-digit dialing and were frequency-matched to the cases by age and geographic region of residence. For SPYW-1, recruitment within 1 year of stroke was required for participation, whereas recruitment within 3 years of stroke was required for SPYW-2.

We conducted interviews with both case patients and controls to assess demographic (age, race, and educational level) and medical (history of hypertension, diabetes, elevated total cholesterol and coronary heart disease [angina and/or myocardial infarction]) characteristics. For cases that were deceased or who had cognitive or language impairment, proxies were interviewed. Women were considered to have hypertension, diabetes mellitus, elevated cholesterol, or coronary heart disease if they responded affirmatively to whether they had ever been told by a physician that they had the condition. Body mass index (BMI) was based on self-report and calculated as the weight in kilograms (kg) divided by the square of the height in meters (m). Oral contraceptive (OC) use was based on reported use of OC in the 30 days before stroke (cases) or interview (controls). Analyses were restricted to participants with complete information for analysis variables leaving an analysis sample of 466 cases, including 10 cases with proxy interviews, and 604 controls.

A detailed smoking history was obtained during the face-to-face interview. Women were classified according to their smoking status as never smokers, former smokers, and current smokers. Never smokers (n=500) were defined as those who had never smoked greater than 100 cigarettes or 5 packs of cigarettes in their lifetime. Current smokers (n=386) were defined as those who had smoked greater than 100 cigarettes in their lifetime and also had smoked in the 30 days preceding their stroke (for cases) or their interview (for controls). Former smokers (n=184) were defined as those who had smoked greater than 100 cigarettes in their lifetime, but had not smoked in the 30 days before their stroke/interview (cases/controls). Amount of current smoking (cigarettes/d) was stratified into 4 categories: 1 to 10 cigs/d, 11 to 20 cigs/d, 21 to 39 cigs/d, and 40+ cigs/d. Data on measurements of serum cotinine or other markers for objectively validating smoking status were not available.

Statistical analyses were conducted using SAS v9 (SAS Institute). χ^2 tests were used to compare proportions. Logistic regression was used to estimate the odds ratio (OR) for ischemic stroke comparing women in different smoking categories to the reference group of never smokers while controlling for potential confounders. In regression analyses, we performed age-adjusted and multivariate analyses (adjusted for study period, age, race, education category, hypertension, diabetes mellitus, coronary heart disease, elevated total cholesterol, OC use and BMI). We tested whether each of the variables used in adjustment

modified the dose-response relationship between amount of smoking and stroke by including interaction terms in the logistic regression. Model parameter estimates were computed using maximum-likelihood and 95% confidence intervals (CI) were based on the standard error of the model coefficients. All probability values were 2-sided and $P < 0.05$ was considered statistically significant.

Results

Table 1 demonstrates the demographics and other selected characteristics of the studied population. Also shown is the percentage of controls that are current smokers and former/never smokers and corresponding probability values within each category.

Table 2 demonstrates the odds ratios for stroke risk between cases and controls by smoking status and by cigarettes smoked daily. Former smokers did not have an increased stroke risk. Current smokers had a multivariate-adjusted OR of 2.6 ($P < 0.0001$). Multivariate-adjusted analysis showed increasing OR with increasing number of cigarettes smoked per day: 2.2 for 1 to 10 cigs/d; 2.5 for 11 to 20 cigs/d; 4.3 for 21 to 39 cigs/d; 9.1 for 40 or more cigs/d. The risk associated with smoking even 1 to 10 cigarettes per day was statistically significant and the test for trend using logistic regression was also highly significant ($P < 0.0001$). The dose-response relationship between smoking amount and stroke risk was not modified by any of the covariates, including race.

Stroke risk compared to never smokers also increased with increasing pack years of smoking. The multivariate-adjusted OR for 1 to 10 pack years was 2.1 ($P = 0.0004$), for 11 to 20 pack years was 2.7 ($P < 0.0001$), and for 21+ pack years it was 4.8 ($P < 0.0001$). When smoking amount and smoking duration were both included in a multivariate logistic model, smoking amount remained highly significant ($P < 0.002$) but smoking duration was not statistically significant ($P = 0.6$).

Discussion

There is prior evidence for a dose-response between amount of smoking in middle-aged to older adults and stroke risk⁴ but few data to document a dose-response in young adults.^{9,10} Our study extends this finding to young women in an ethnically-diverse population. In addition, we found a steeper dose response than has been reported in other populations with OR of 2.3 for 1 to 10 cigarettes/d and 9.4 for 40 or more cigarettes per day. The study by Love⁹ in young adults did report that in young adults 15 to 45 years of age, the number of cigarettes smoked daily was a significant risk factor ($P = 0.028$) for cerebral infarction with risk increasing by a factor of 1.014 for each additional cigarette smoked and an OR of 1.035 per each additional pack year of smoking (with a quadratic relationship). In the Nurses Health Study, among women ages 30 to 55 years of age, the multivariate-adjusted relative risk for ischemic stroke was 1.8 for 1 to 14 cigarettes/d and 4.0 for 35 or more cigarettes per day.^{11,12} Other studies have reported a dose response among middle-aged to older men^{13,14} and both men and women^{15,16}, but none have shown a dose-response as strong as our study suggests. Our study also found that there were a high number of blacks who were smokers in both our cases and controls (Table 1), which emphasizes that smoking is an under-recognized public health problem in this population.

Smoking is known to promote atherosclerosis and a procoagulant state.⁴ It has been established in older adults that the stroke risk associated with cigarette smoking falls to the lowest levels within 5 years of smoking cessation,^{15,17} suggesting that induction of a procoagulant state is the primary mechanism. Cigarette smoking causes vascular endothelial dysfunction^{18–20} with associated alteration in hemostatic and inflammatory markers.¹⁷

Smoking also increases fibrinogen concentration,²¹ reduces fibrinolytic activity,²² increases platelet aggregability,²³ and causes polycythemia.²⁴

Our study has several limitations. Recall bias remains possible, given the retrospective design. Objective markers of smoking exposure, such as serum cotinine levels, were not available. In addition, we did not control for factors such as alcohol consumption and physical activity in our model, which may have resulted in unmeasured or residual confounding of our risk estimates.

Our study also has several strengths. It is one of the largest studies of early-onset stroke in young women. The large sample size allowed relatively precise estimates of dose-response. The study population was ethnically diverse with roughly 50% blacks.

Almost 120 000 women and 105 000 men in America under the age of 45 have suffered a stroke.²⁵ Despite the evidence that smoking is a risk factor for many diseases, including stroke,¹ 20.9% (45.1 million) of the United States population defined themselves as current smokers in 2005,⁶ and every year, nearly 750 000 young people become regular smokers.²⁶ Smoking prevalence in the United States among young women age 18 to 24 years was 20.7% and was 21.4% among women age 25 to 44 years. According to the CDC, almost all smokers begin smoking as teenagers, and if current trends continue, more than 6 million young people who are regular smokers will eventually die from a tobacco-related disease.²⁶

Cigarette smoking remains prevalent, even among young stroke survivors. Arquizan et al assessed the control of risk factors in young patients with cryptogenic stroke and found that 54% to 58% still smoked during follow-up, demonstrating that management of vascular risk factors is not achieved after stroke in the young.²⁷

Stroke risk decreases significantly 3 years after cessation of cigarette smoking and is at the level of nonsmokers by 5 years.^{11,15,28} Although smoking cessation has major and immediate health benefits for men and women of all ages,²⁹ the benefit is greater the earlier in life one quits. Persons who quit before the age of 35 years have a life expectancy that is similar to nonsmokers.³⁰ There is strong evidence that sustained mass media campaigns and increased price of tobacco products are effective in reducing initiation and promoting cessation of cigarette smoking among adolescents and young adults.^{31,32}

Summary

Our study supports the need to target smoking as a preventable and modifiable risk factor for cerebrovascular disease in young women. The dose-response relationship between number of current cigarettes smoked and ischemic stroke risk in a young ethnically-diverse population of women makes large-scale public health campaigns promoting smoking abstinence, cessation, and reduction imperative.

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Appendix

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Table 1

Demographics and Other Selected Characteristics of Studied Population, Including Percentage of Control Subjects Who Were Current Smokers or Former and Never Smokers (Total Cases, n=466; Total Controls, n=604)

Factor	Category	Cases n (%)	Controls n (%)	P*	Current Smokers [†] n (%)	Former and Never Smokers [†] n (%)	P*
Age	<18	7 (1)	18 (3)	0.0374	5 (3)	13 (3)	0.3497
	18–24	26 (6)	44 (7)		7 (8)	37 (8)	
	25–35	106 (23)	166 (28)		47 (28)	119 (27)	
	>35	327 (70)	376 (62)		108 (65)	268 (61)	
Race	White	211 (45)	331 (55)	0.0082	75 (45)	256 (59)	0.0061
	Blacks	216 (46)	229 (38)		80 (48)	149 (34)	
	Other	39 (8)	44 (7)		12 (7)	32 (7)	
Education, years	<12	62 (13)	64 (11)	0.1729	33 (20)	31 (7)	<0.0001
	12	404 (87)	540 (89)		134 (80)	406 (93)	
Hypertension	Yes	160 (34)	83 (14)	<0.0001	29 (17)	54 (12)	0.1098
	No	306 (66)	521 (86)		138 (83)	383 (88)	
Diabetes Mellitus	Yes	66 (14)	22 (4)	<0.0001	8 (5)	14 (3)	0.3518
	No	400 (86)	382 (96)		159 (95)	423 (97)	
Coronary artery disease	Yes	58 (13)	19 (3)	<0.0001	7 (4)	12 (3)	0.3626
	No	408 (87)	585 (97)		160 (96)	425 (97)	
Hypertlipidemia	Yes	89 (19)	105 (17)	0.4704	31 (19)	74 (17)	0.6350
	No	377 (81)	499 (83)		136 (81)	363 (83)	
Body Mass Index	30	173 (37)	165 (27)	0.0006	49 (29)	116 (26)	0.4903
	<30	293 (63)	439 (73)		118 (71)	321 (74)	
Oral contraceptives	Yes	69 (15)	66 (11)	0.0581	13 (8)	53 (12)	0.1259
	No	397 (85)	538 (89)		154 (92)	384 (88)	

* χ^2 .[†] Controls only.

Table 2
Odds Ratio for Ischemic Stroke by Smoking Status and, in Current Smokers, by Cigarettes Smoked Daily

	Cases (n)	Controls (n)	Model 1 [†]			Model 2 [‡]		
			OR	95% CI	P	OR	95% CI	P
Never smokers*	177	323
Former smokers	70	114	1.0	0.7–1.4	0.9138	1.0	0.6–1.4	0.8291
Current smokers	219	167	2.3	1.7–3.0	<0.0001	2.6	1.9–3.6	<.0001
1–10 cig/d	92	77	2.1	1.5–3.0	<0.0001	2.2	1.5–3.3	<.0001
11–20 cig/d	80	67	2.0	1.4–2.9	0.0004	2.5	1.6–3.8	<.0001
21–39 cig/d	18	10	3.2	1.4–7.1	0.0045	4.3	1.8–10	0.0009
40+ cig/d	25	7	5.7	2.4–14	<0.0001	9.1	3.2–26	<.0001

* Reference is never smokers.

[†]Model 1 is adjusted for age only.

[‡]Model 2 is adjusted for study period, age, race, education, HTN, DM, CAD, hyperlipidemia, OC use, and BMI.