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

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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.

Key Words: stroke ■ women ■ smoking
were 2-sided and on the standard error of the model coefficients. All probability values were computed using logistic regression. Model parameter estimates were computed using 386) were defined as those who had smoked greater than 100 cigarettes or 5 packs of cigarettes in their lifetime. Current smokers (n = 184) 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/interview (cases/controls). 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<0.002). 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).

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.

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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). \( ^* \)Significant (P<0.05) for all tests. \( ^\dagger \)Controls only. ***Statistical analyses were conducted using SAS v9 (SAS Institute). \( ^* \)Significant (P<0.05) for all tests. \( ^\dagger \)Controls only. **Statistical analyses were conducted using SAS v9 (SAS Institute). \( ^* \)Significant (P<0.05) for all tests. \( ^\dagger \)Controls only. *

| 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  |
|                 | \( \geq 12 \)   | 404 (87)    | 540 (89)      |         | 134 (80)          | 406 (93)      |          |
| Hypertension    | Yes             | 160 (34)    | 83 (14)       | <.0001 | 29 (17)           | 54 (12)       | 0.1098   |
|                 | No              | 306 (66)    | 521 (86)      |         | 138 (83)          | 383 (88)      |          |
| Diabetes Mellitus| Yes             | 66 (14)     | 22 (4)        | <.0001 | 8 (5)             | 14 (3)        | 0.3518   |
|                 | No              | 400 (86)    | 382 (96)      |         | 159 (95)          | 423 (97)      |          |
| Coronary artery disease | Yes | 58 (13) | 19 (3) | <.0001 | 7 (4) | 12 (3) | 0.3626 |
|                 | No              | 408 (87)    | 585 (97)      |         | 160 (96)          | 425 (97)      |          |
| Hyperlipidemia  | 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 | \( \geq 30 \)   | 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)      |          |

\( ^* \)Significant (P<0.05) for all tests. \( ^\dagger \)Controls only.
Inflammatory markers. Smoking also increases fibrinogen dysfunction with associated alteration in hemostatic and coagulant state. 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, suggesting that induction of a procoagulant state is the primary mechanism. Cigarette smoking causes vascular endothelial dysfunction with associated alteration in hemostatic and inflammatory markers. Smoking also increases fibrinogen concentration, reduces fibrinolytic activity, increases platelet aggregability, and causes polycythemia. 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.

Discussion

There is prior evidence for a dose-response between amount of smoking in middle-aged to older adults and stroke risk but few data to document a dose-response in young adults. 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 Love 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 with OR of 2.3 for 1 to 10 cigarettes/d and 3.2 for 21–39 cigarettes/d.

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-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. Despite the evidence that smoking is a risk factor for many diseases, including stroke, 20.9% (45.1 million) of the United States population defined themselves as current smokers in 2005 and every year, nearly 750,000 young people become regular smokers. 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.

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.

Stroke risk decreases significantly 3 years after cessation of cigarette smoking and is at the level of nonsmokers by 5 years. Although smoking cessation has major and immediate health benefits for men and women of all ages, 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. 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.

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.

Appendix

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Disclosures

None.

References


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