Cigarette Smoking as a Determinant of High-Grade Carotid Artery Stenosis in Hispanic, Black, and White Patients With Stroke or Transient Ischemic Attack

Henning Mast, MD; John L.P. Thompson, PhD; I-Feng Lin, MS; Christoph Hofmeister; Andreas Hartmann, MD; Peter Marx, MD; Jay P. Mohr, MD; Ralph L. Sacco, MD

Background and Purpose—We sought to investigate the association of cigarette smoking with high-grade carotid artery stenosis in Hispanic, black, and white patients with cerebral ischemia in two independent samples.

Methods—Prospectively collected data from the Northern Manhattan Stroke Study (NOMASS) (n=431) and the Berlin Cerebral Ischemia Databank (BCID) (n=483) were used separately for a cross-sectional study estimating the association between cigarette smoking and high-grade carotid stenosis (defined as a luminal narrowing of ≥60%, diagnosed by duplex and/or Doppler ultrasound). In both studies, cerebral ischemia patients with normal sonographic findings or nonstenosing plaques of their carotid arteries served as a comparison group. Multivariate logistic regression models were used for statistical tests to determine the association between smoking and the dependent variable for high-grade carotid stenosis. Age, sex, hypertension, diabetes, hypercholesterolemia, and race/ethnicity were considered potential confounders. Further analyses of the NOMASS data estimated the effect of the amount of cigarette use and the impact of race/ethnicity.

Results—High-grade carotid stenoses were found in 14% of the NOMASS and in 21% of the Berlin patients. In Berlin the entire sample was white, whereas in New York only 19% of the cohort were white. In both samples, smoking was independently associated with severe carotid stenosis (NOMASS: odds ratio [OR], 1.5; 95% confidence interval [CI], 1.1 to 2.0; BCID: OR, 3.9; 95% CI, 2.4 to 6.4). Patients smoking 20 pack-years or more showed a significant association (OR, 2.0; 95% CI, 1.1 to 3.9), whereas no significant effect was found for lower amounts of cigarette use. In NOMASS, white smokers displayed a significant (OR, 3.2; 95% CI, 1.1 to 8.9) association with high-grade carotid stenosis, the association for black smokers was less strong, and no association was found among Hispanics.

Conclusions—Smoking is an independent determinant of severe carotid artery stenosis in patients with focal cerebral ischemia. The association differs by race/ethnicity, with the greatest effect observed among whites. (Stroke. 1998;29:908-912.)

Key Words: carotid stenosis ■ cigarette smoking ■ stroke

Recent carotid endarterectomy trials have demonstrated the clinical importance of high-grade carotid artery stenosis. Cigarette smoking is an established risk factor for arteriosclerosis and ischemic stroke.1–16 However, prior stroke epidemiological studies evaluating the relationship between cigarette smoking and carotid stenosis have enrolled predominantly white subjects or had insufficient sample sizes of black or Hispanic patients. We investigated the effect of cigarette smoking on carotid stenosis of 60% luminal narrowing or more in two separate prospective samples of patients from Berlin and northern Manhattan with ischemic stroke and TIA. The combination of the two data sets, in addition, allowed for an adequate sample size to address the relationship of cigarette smoking in three different racial/ethnic groups.

Subjects and Methods

The Northern Manhattan Stroke Study (NOMASS) is a prospective study of stroke patients aged over 39 years who are residents of the northern Manhattan community.17 For the present investigation 431 consecutive cases of ischemic infarction with completed duplex Doppler ultrasound studies enrolled between January 1, 1990, and April 21, 1994, and treated in the Milstein Hospital wing of the Columbia-Presbyterian Medical Center were analyzed: 62 (14%) with common/internal carotid artery stenosis of 60% or more (including occlusion) and, serving as a reference group, 369 (86%) with bilaterally normal findings (n=78) or only low-grade (<60%) stenosing carotid plaques (n=291) diagnosed by duplex Doppler ultrasound.
ultrasound investigations (Siemens Quantum 2000 machine). Classification of degree of stenosis was based on generally accepted definitions and quality control criteria established by the Asymtomatic Carotid Atherosclerosis Study. Smoking was defined as history of current or past regular cigarette use (nonsmoking was defined as never having smoked regularly), and the amount of cigarette consumption was measured by the average number of packs per day and the duration of smoking in years. For this analysis hypertension was assumed to be present under the following conditions: (1) the patient or the patient’s family reported that they had been informed of the diagnosis by a physician before the classifying stroke event or antihypertensive medication had been recommended, or (2) the patient’s medical documents showed that hypertension requiring treatment had been diagnosed by a physician before the classifying event. Diabetes was defined as chronic hyperglycemia requiring diet, oral medication, or insulin treatment, diagnosed before stroke onset. Hypercholesterolemia was diagnosed when patients had a history of increased blood cholesterol levels requiring diet or medication or increased blood cholesterol levels of 240 mg/dL or more measured after admission. Race/ethnicity was defined by self-identification as Hispanic, white non-Hispanic, black non-Hispanic, or “other” non-Hispanic.

The Berlin Cerebral Ischemia Data Bank (BCID) is a prospective, hospital-based registry for consecutive TIA and ischemic stroke patients. For the present study the 483 consecutive cases with complete Doppler ultrasound studies were analyzed: 101 (21%) showing unilateral or bilateral carotid stenosis of 60% or more (including occlusion) and, serving as a reference group, 382 (79%) revealing no pathological findings (n = 303) or flow changes indicating only a lesser degree of stenosis (n = 79). The degree of carotid stenosis was assessed by conventional Doppler ultrasound investigations (4- and 8-MHz probe studies, EME TC 2000 machine) of the extracranial neck vessels, following generally accepted definitions and validated against gold-standard conventional angiography. Unlike duplex Doppler ultrasound, conventional Doppler ultrasound does not detect nonstenosing plaque. Therefore, the number of BCID patients with no pathological Doppler results was 574.

In BCID, smoking was classified into two categories: (1) nonsmokers/former smokers (never smoked regularly or stopped regular smoking ≥5 years ago) and (2) smokers (regular smoking within the last 5 years). The BCID definitions of other risk factors (hypertension, diabetes, hypercholesterolemia) were similar to the ones used in NOMASS. All BCID subjects were white.

In NOMASS, two multivariate logistic regression models controlling for age, sex, race/ethnicity (white versus nonwhite), hypertension, diabetes mellitus, and hypercholesterolemia were used to determine whether (1) history and (2) amount of cigarette consumption measured in pack-years (dichotomized into 1 to 19 pack-years and ≥20 pack-years) were independent predictors of high-grade carotid artery stenosis. Three further univariate regression models estimated the effect of history of current or past cigarette smoking in three different racial/ethnic groups: Hispanics, blacks, and whites. To test for the significance of a difference in the effect of smoking on carotid stenosis among whites and nonwhites, an interaction term was introduced into the first regression model.

In BCID, one multivariate logistic regression model controlling for age, sex, hypertension, diabetes, hypercholesterolemia, and coronary heart disease was applied to determine whether regular cigarette smoking within the last 5 years was an independent predictor of high-grade carotid artery stenosis.

### Results

In NOMASS, 43% of the patients had a history of current or reformulated cigarette smoking. Of all NOMASS cases, 28% had smoked for 20 or more pack-years. In BCID, 41% of the patients were cigarette smokers (Table 1). The two samples differed significantly with regard to sex, risk factors, and frequency of carotid stenosis (Table 1). The frequencies of independent variables (cigarette smoking, hypertension, diabetes, hypercholesterolemia, age, sex, and race/ethnicity) in study groups with carotid stenosis (≥60% or occlusion) and reference cases are shown in Table 2. Despite similar frequencies of cigarette smoking across Hispanic, black, and white race subgroups, the frequency of severe carotid artery stenosis was greater among whites (25% NOMASS, 21% BCID) than in Hispanics (12%) or blacks (11%).

Both NOMASS and BCID studies revealed that smoking was significantly associated with high-grade carotid artery stenosis, and this effect was independent of other risk factors (Table 3). In contrast, hypertension, diabetes, and hypercholesterolemia had no significant relationship with high-grade carotid stenosis. NOMASS data also showed that smoking of 20 or more pack-years (Table 4) and white race (Tables 3 to 5) determined severe carotid artery stenosis. The association for black smokers was less strong, and no association was found among Hispanic cigarette smokers (Table 5). In NO-
The difference of the effect of smoking on carotid stenosis between whites and nonwhites was not significant (OR, 2.5; 95% CI, 0.8 to 7.5; \( P \approx 0.1 \)).

The impact of smoking was further analyzed in subgroups of different degrees of arterial luminal narrowing. In BCID, the point estimates for subgroups of 60% to 79% stenosis (38 patients), 80% or more stenosis (27 patients), and carotid occlusion (36 patients) showed increasing ORs of 2.8 (95% CI, 1.4 to 5.6), 3.7 (95% CI, 1.6 to 8.5), and 4.8 (95% CI, 2.2 to 10.3), respectively (ORs and CIs are from univariate regression models). In NOMASS, the number of patients in corresponding subgroups was too small (only 9 cases in the group of patients with 60% to 79% stenosis, and only 21 whites with carotid stenosis) for a meaningful statistical analysis.

The final meta-analysis of a merged data set from both samples repeated the previous results of a significant association of high-grade carotid stenosis with cigarette smoking (OR, 2.2; 95% CI, 1.6 to 3.1; adjusted for race/ethnicity). The effect of smoking was again stronger when the analysis was restricted to white smokers (OR, 3.5; 95% CI, 2.3 to 5.4).

Reclassifying the stenosis group to include patients with low-grade stenosing plaques (NOMASS) and flow accelerations indicating low-grade (\( \leq 60\% \)) stenosis (BCID) from the reference group such that the comparison sample now comprised only patients with normal ultrasound findings of their carotid arteries reduced the OR but did not alter the significance of the association between carotid stenosis and cigarette smoking (OR, 1.5; 95% CI, 1.1 to 2.0; adjusted for race/ethnicity). Finally, in the merged data set analysis the

### Table 2. Age, Sex, Risk Factors, and Race/Ethnicity in Patients With High-Grade Carotid Artery Stenosis and Reference Cases With Normal Findings or Low-Grade Stenosis

<table>
<thead>
<tr>
<th></th>
<th>BCID (n=483)</th>
<th>NOMASS (n=431)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High-Grade Carotid Stenosis (n=101)</td>
<td>Normal or Low-Grade Stenosis (n=382)</td>
</tr>
<tr>
<td>Mean±SD age, y</td>
<td>65±9</td>
<td>65±13</td>
</tr>
<tr>
<td>Female sex</td>
<td>32 (31%)</td>
<td>168 (43%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>58 (57%)</td>
<td>209 (54%)</td>
</tr>
<tr>
<td>Diabetes mellit</td>
<td>33 (32%)</td>
<td>98 (25%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>53 (52%)</td>
<td>144 (37%)</td>
</tr>
<tr>
<td>History of cigarette smoking</td>
<td>67 (66%)†</td>
<td>133 (34%)‡</td>
</tr>
<tr>
<td>( \geq 20 ) pack-years</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>1–19 pack-years*</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Race/ethnicity

<table>
<thead>
<tr>
<th></th>
<th>BCID (n=483)</th>
<th>NOMASS (n=431)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic</td>
<td>23 (37%)</td>
<td>167 (45%)</td>
</tr>
<tr>
<td>Black</td>
<td>17 (27%)</td>
<td>137 (37%)</td>
</tr>
<tr>
<td>White</td>
<td>101 (100%)</td>
<td>382 (100%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1%)</td>
<td>3 (1%)</td>
</tr>
</tbody>
</table>

*In NOMASS, 12 patients with a history of cigarette smoking had missing data on pack-years, and pack-years were not recorded in the Berlin sample.
†Regular cigarette smoking within the last 5 years.
‡History of past or current cigarette smoking.

### Table 3. Multivariate Logistic Regression Model Estimating the Effect of Cigarette Smoking on High-Grade Carotid Artery Stenosis

<table>
<thead>
<tr>
<th></th>
<th>BCID</th>
<th>NOMASS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>3.9</td>
<td>2.4–6.4</td>
</tr>
<tr>
<td>Race/ethnicity*</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.1</td>
<td>0.7–1.8</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.4</td>
<td>0.9–2.4</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>1.5</td>
<td>0.9–2.4</td>
</tr>
<tr>
<td>Age</td>
<td>1.0</td>
<td>1.0–1.0</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>1.6</td>
<td>0.9–2.8</td>
</tr>
</tbody>
</table>

Race/ethnicity was not included in the model of the Berlin sample because all cases were white. Because of missing data values, 5 BCID and 9 NOMASS patients were omitted from the analysis.

*White vs nonwhite.
difference of the effect of smoking on carotid stenosis between whites and nonwhites became significant (OR, 2.7; 95% CI, 1.6 to 4.5; \( P = 0.0002 \)).

### Discussion

In our analysis an independent association of smoking with high-grade carotid artery stenosis was demonstrated. This finding, showing consistency over two studies, may strengthen the notion of a causal role of cigarette smoking in stenosing arteriosclerotic carotid disease. Comparisons between two studies with the use of nonuniform definitions for their main variables (smoking and degree of carotid stenosis) can lead to difficulty with generalizing the results. However, the stability of the findings across our two independent samples supports the assumption of a robust effect.

In principle, data from patient histories on cigarette consumption may be questioned for their validity. The reported rate and amount of smoking are likely to be biased by underestimation. The effect of such misclassification error would most likely be nondifferential because the patients were unaware of the study hypothesis. Therefore, an attenuation of the OR toward the null value could be expected, which implies that the true association may be stronger than shown (we assume that underestimation affects patients with and without carotid stenosis evenly and a systematic error of underreported cigarette smoking in patients without severe carotid stenosis is not a plausible option). Categorizing former smokers and nonsmokers together, as has been done in the BCID, may also raise concerns. Prior studies have suggested a similar and lower stroke risk for nonsmokers and reformed smokers compared with current smokers.\(^1,10-12,24-26\) Therefore, the BCID classification may be reasonable, and any error introduced would result in an underestimation of the effect of cigarette smoking on carotid stenosis.

### TABLE 5. Univariate Logistic Regression Models Estimating the Effect of History of Cigarette Smoking on Carotid Artery Stenosis in Different Racial/Ethnic Groups (Data From NOMASS)

<table>
<thead>
<tr>
<th>Cigarette smoking</th>
<th>OR</th>
<th>95% CI</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whites</td>
<td>3.2</td>
<td>1.1–8.9</td>
<td>0.03</td>
</tr>
<tr>
<td>Blacks</td>
<td>1.4</td>
<td>0.9–1.8</td>
<td>0.07</td>
</tr>
<tr>
<td>Hispanics</td>
<td>1.4</td>
<td>0.6–3.3</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Four cases with self-identified race/ethnicity “other” (Table 1) are not listed.
stroke patients was only 15%, and that for Hispanics was even less (13%).

Stroke databanks have estimated that approximately 9% of all ischemic strokes are of carotid origin.\textsuperscript{17,28} This suggests that a substantial proportion of the costs of both stroke treatment and prevention can be allocated to stenosing carotid disease. Unlike other risk factors, cigarette smoking is modifiable in a radical fashion. There is ample evidence that this could positively influence the risk of stroke\textsuperscript{11} and reduce the burden on healthcare resources.

We conclude that cigarette smoking is an independent determinant of high-grade carotid artery stenosis in patients with cerebral ischemia. The association differs by race/ethnicity, with the greatest effect observed among whites.

**Acknowledgments**

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