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

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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\(^{15}\) and quality control criteria established by the Asymptomatic Carotid Atherosclerosis Study.\(^{19}\)

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.\(^{20}\) 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%) showing only a lesser degree of stenosis (n \(< 60\%)\) carotid artery stenosis* 101 (21%) 62 (14%)

Diabetes mellitus* 131 (27%) 156 (36%)

Hypertension* 267 (55%) 280 (65%)

High-grade (\(\geq 60\%\)) carotid artery stenosis* 101 (21%) 62 (14%)

History of cigarette smoking 200 (41%)‡ 187 (43%)§

\(\geq 20\) pack-years† 200 (41%)‡ 187 (43%)§

1–19 pack-years† 120 (25%) 55 (13%)

Race/ethnicity

Hispanic 190 (44%)

Black 154 (36%)

White 483 (100%) 83 (19%)

Other 4 (1%)

*Significant \((P<0.05, \chi^2)\) difference between BCID and NOMASS samples. †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. ‡Current regular cigarette smoking or former regular cigarette smoking stopped within 5 years from study inclusion. §History of past or current cigarette smoking.

Additional regression models were set up to test the effect of smoking in strata of different degrees of carotid stenosis/occlusion. Finally, a regression analysis of a merged data set from both samples was done. 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 regression model of the merged data set.

**Results**

In NOMASS, 43% of the patients had a history of current or reformatted 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 (\(\geq 60\%\) 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; \( P < 0.1 \)). 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 (≤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></th>
<th>NOMASS (n=431)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High-Grade Carotid Stenosis (n=101)</td>
<td>Normal or Low-Grade Stenosis (n=382)</td>
<td>High-Grade Carotid Stenosis (n=62)</td>
<td>Normal or Low-Grade Stenosis (n=369)</td>
</tr>
<tr>
<td>Mean±SD age, y</td>
<td>65±9</td>
<td>65±13</td>
<td>71±12</td>
<td>69±12</td>
</tr>
<tr>
<td>Female sex</td>
<td>32 (31%)</td>
<td>168 (43%)</td>
<td>30 (48%)</td>
<td>199 (53%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>58 (57%)</td>
<td>209 (54%)</td>
<td>40 (64%)</td>
<td>240 (65%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>33 (32%)</td>
<td>98 (25%)</td>
<td>25 (40%)</td>
<td>131 (35%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>53 (52%)</td>
<td>144 (37%)</td>
<td>25 (40%)</td>
<td>148 (40%)</td>
</tr>
<tr>
<td>History of cigarette smoking</td>
<td>67 (66%)†</td>
<td>133 (34%)‡</td>
<td>34 (54%)‡</td>
<td>153 (41%)#</td>
</tr>
<tr>
<td>≥20 pack-years</td>
<td>...</td>
<td>...</td>
<td>22 (35%)</td>
<td>98 (27%)</td>
</tr>
<tr>
<td>1–19 pack-years*</td>
<td>...</td>
<td>...</td>
<td>9 (15%)</td>
<td>46 (12%)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td></td>
<td>23 (37%)</td>
<td>167 (45%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td></td>
<td>17 (27%)</td>
<td>137 (37%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>101 (100%)</td>
<td>382 (100%)</td>
<td>21 (33%)</td>
<td>62 (16%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1%)</td>
<td>3 (1%)</td>
<td></td>
<td></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 without cigarette 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.

### TABLE 4. Multivariate Logistic Regression Model Estimating the Effect of Pack-Year Cigarette Consumption on High-Grade Carotid Artery Stenosis (Data From NOMASS)

<table>
<thead>
<tr>
<th>Cigarette Smoking</th>
<th>OR (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \geq 20 ) pack-years of smoking</td>
<td>2.0 (1.1–3.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>1–19 pack-years of smoking</td>
<td>1.8 (0.8–4.2)</td>
<td>0.17</td>
</tr>
<tr>
<td>Race/ethnicity*</td>
<td>2.5 (1.2–5.0)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Additional variables in the regression model (hypertension, diabetes, hypercholesterolemia, age, sex) are not shown in the table and had no significant effect.

*White vs nonwhite.

In BCID, the association between smoking and high-grade carotid stenosis was stronger than in NOMASS. Most likely, this can be explained by the racial composition of the purely white Berlin sample and possibly also by the more restricted definition of smoking in the Berlin study. The effect of smoking was similar in the BCID sample and the white subgroup of NOMASS (ORs of 3.9 and 3.2, respectively). In NOMASS (and in the merged analysis), white smokers showed a stronger association with carotid stenosis than blacks, and no effect was found for Hispanic smokers. This may indicate an important, yet unexplained, racial/ethnic difference in the effect of cigarette smoking. In support of these findings, other analyses from NOMASS\(^{27}\) have found significantly less carotid plaques in stroke-free Hispanics than in other racial/ethnic groups.

Studies analyzing the effect of smoking on carotid artery plaques in mixed samples of symptomatic and asymptomatic patients have already suggested an independent link of this particular risk factor with carotid arteriosclerosis.\(^{13–16}\) Our results further establish this association for ischemic stroke and TIA patients with high-grade carotid stenosis of potential surgical relevance. However, the analysis was not restricted to cases of clinically defined symptomatic stenosis and did include stroke (or TIA) patients with carotid stenosis unrelated to the actual clinical pathology. An analysis of strictly symptomatic stenoses would imply sample sizes beyond the scope of any database presently available.

Our results are also restricted to a sample of patients with TIA or stroke and do not include a stroke-free comparison group. Therefore, the cross-sectional association between cigarette smoking and carotid stenosis implies that smoking may be more strongly related to atherogenic strokes rather than nonatherogenic causes such as cardioembolism and small-vessel disease.

Our results not only showed a similar effect of cigarette smoking on high-grade carotid stenosis but furthermore indicated against a significant relevance of other major risk factors of arteriosclerosis. In a selected sample of 240 patients undergoing cerebral angiography, Homer et al\(^{15}\) found a strong association of smoking with luminal narrowing of the carotid arteries. Unlike the results of our studies, however, hypertension and LDL cholesterol were also shown to have an impact. On the basis of 752 cases with cerebral angiography, Whisnant et al\(^{14}\) confirmed the importance of cigarette smoking and also a less strong effect of other risk factors. Both investigations did not represent prospective studies in unselected stroke samples and therefore may not lend themselves to direct comparisons. Nevertheless, in conjunction with our findings they support the growing evidence of the major role of cigarette smoking in the etiology of carotid stenosis.

Clearly, not all carotid stenoses can be attributed to smoking. Given the prevalence of cigarette exposure in our two samples and the size of the effect of cigarette smoking on carotid stenosis, we found that the attributable risk for our white stroke patients can be estimated at 45% (NOMASS) and 53% (BCID) or 50% when NOMASS and BCID whites are combined. In contrast, the attributable risk for our black
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. 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 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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