Amount of Smoking Independently Predicts Carotid Artery Atherosclerosis Severity

Robert J. Dempsey, MD, and Robert W. Moore, PhD

**Background and Purpose:** Cigarette smoking is correlated with extracranial carotid artery plaque thickness. Our aim in the present study was to determine whether the level of prior cigarette use is a significant predictor of carotid artery plaque thickness when age, history of hypertension, and history of diabetes are controlled.

**Methods:** We studied a continuous sample of 790 patients with a history of smoking referred for diagnostic ultrasound imaging of the carotid arteries. Subjects (mean age 61 years) had an average of 51 pack-years of cigarette use. History of hypertension was present in 44% and history of diabetes in 18%.

**Results:** Right and left maximum carotid artery plaque thicknesses were averaged for each patient; the average of this value for all 790 subjects was 1.9 mm. In bivariate analysis, age ($p<0.0001$), pack-years ($p<0.0001$), history of hypertension ($p=0.0003$), and history of diabetes ($p=0.037$) were each positively associated with carotid artery plaque thickness. In multiple regression analysis, age ($p<0.0001$), pack-years ($p=0.0005$), and history of hypertension ($p=0.0644$) were statistically significant independent predictors of carotid artery plaque thickness, but history of diabetes ($p=0.2451$) was not.

**Conclusions:** In smokers, the level of cigarette use is associated with an acceleration of carotid artery atherosclerosis development. This effect is independent of age, hypertension, and diabetes. These results support smoking abatement as an important element to stroke prevention in clinical practice. (Stroke 1992;23:693–696)

**KEY WORDS** • arteriosclerosis • carotid arteries • cigarette smoking • ultrasonics
Subjects, and 40.5% had an average of 2.5 mm or more of plaque in both sides.

Plaque thickness was correlated with age (r=0.41, p<0.0001), pack-years of cigarette smoking (r=0.21, p<0.0001), history of hypertension (r=0.13, p=0.0003), and history of diabetes (p=0.03). Age was correlated with pack-years of cigarette smoking (r=0.15, p<0.0001) but not with history of diabetes or hypertension. History of diabetes was associated with history of hypertension (r=0.18, p<0.0001), but neither of these was associated with pack-years of smoking. Data were converted to standard scores, and multivariate analysis was performed using a general linear model (GLM) program.13

Results

Regression analysis was used to examine the relation between carotid plaque thickness and age. A curvilinear pattern is evident in which each decade of increase in age is associated with smaller increases in plaque thickness. Lower levels of carotid plaque are found in subjects over age 80 than in those who are 1–2 decades younger. A polynomial regression equation in which a quadratic function of age is included indicated that the downward curving pattern in the data is statistically significant (p<0.0001). Similarly, there is a curvilinear relation between carotid plaque thickness and smoking. The polynomial regression of plaque thickness on pack-years of smoking also had a statistically significant negative quadratic predictor (p=0.0003).

Figure 1 shows the age-adjusted carotid plaque thick-

ness of light (1–30 pack-years), moderate (31–60 pack-
years), and heavy (61 or more pack-years) smokers who have various combinations of hypertension and diabetes histories. For example, of 385 smokers with neither hypertension nor diabetes, 131 light smokers had a carotid plaque thickness averaging 1.65 mm, compared with 1.80 mm for 142 moderate smokers and 1.97 mm for 112 heavy smokers in this group (p<0.0001). Similar patterns are seen regardless of the presence of diabetes, hypertension, or both. After adjusting for age, there is a positive and significant association between pack-years of cigarette use and carotid artery plaque thickness, regardless of the presence or absence of the other conditions.

Table 1 shows the results of unstandardized and standardized multiple regression analysis of carotid artery plaque thickness. Age, pack-years of smoking, and history of hypertension are positive, independent, statistically significant predictors of carotid plaque thickness among these smokers. The negative quadratic functions indicate that in multiple regression, the curvilinear patterns described above remain statistically significant. History of diabetes is not a statistically significant independent predictor of carotid plaque thickness among these subjects.

All possible two-, three-, and four-way interactions among independent variables were examined and found to be statistically insignificant in the multiple regression model. They are therefore omitted from the analysis. The overall proportion of variance accounted for (R²) was 21.8%. Stepwise regression was used to examine the incremental contribution of each variable to the explanation of variance in carotid plaque thickness. Figure 2 shows the contribution of each of the independent variables to the explanation of variation in carotid plaque thickness. Age explained 17.7%, followed by pack-years of smoking (which explained 2.6%), and history of hypertension (which explained 1.3%). History of diabetes explained a statistically insignificant 0.2% of the variation in plaque thickness among these subjects. Overall, nearly four fifths (78.2%) of the variation in carotid plaque thickness remains unexplained in this model.

Discussion

Determining the causes of accelerated carotid artery atherosclerosis is important in the understanding of stroke risk factors. Age is generally regarded as the most important risk factor for carotid artery atherosclero-

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**TABLE 1. Unstandardized and Standardized Multiple Regression Coefficients for Average Carotid Artery Plaque Thickness Regressed on Age, History of Hypertension, History of Diabetes, Pack-Years of Cigarette Use, and Quadratic Functions of Age and Pack-Years of Cigarette Use**

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>Regression coefficient estimates</th>
<th>t test</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unstandardized</td>
<td>Standardized</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.1433</td>
<td>0.973</td>
<td>4.11</td>
</tr>
<tr>
<td>Age*age</td>
<td>0.00057</td>
<td>-0.596</td>
<td>-2.53</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>0.23652</td>
<td>0.093</td>
<td>2.86</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>0.12362</td>
<td>0.038</td>
<td>1.16</td>
</tr>
<tr>
<td>Pack-years of smoking</td>
<td>0.01224</td>
<td>0.310</td>
<td>3.51</td>
</tr>
<tr>
<td>Pack-years*pack-years</td>
<td>0.00005</td>
<td>-0.186</td>
<td>-2.13</td>
</tr>
<tr>
<td>Intercept</td>
<td>-3.21871</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
sive as well as for all types of stroke combined.
It is not clear, however, whether aging itself has direct effects on the atherosclerotic process or, rather, is a correlate of duration of exposure to factors such as smoking, hypertension, or diabetes that alter the relation between increasing years of life and the probability of suffering a stroke. In the present study we found that age, hypertension, and increased smoking exposure were each independent predictors of advancing carotid artery atherosclerosis.

The discovery of a negative curvilinear component to the associations between plaque thickness and both age and smoking lends itself to more than one explanation. Initially we believed that it was best explained by a survival selection process. As years of age or pack-years of smoking increase in association with carotid atherosclerosis, the probability of high-plaque patients remaining alive to be referred into such a sample as ours decreases. Examination of the data suggests another explanation, however. The presence of a curvilinear relation between age and plaque thickness is only evident for subjects in the light smoking category (1–30 pack-years). In the higher age groups, these subjects are more likely to be former smokers than are subjects with moderate and heavy levels of tobacco use. If smoking cessation by patients produces the benefit of reducing the rate of atherosclerotic plaque formation (compared with that in patients who continue to smoke), a pattern similar to the one we observed might be expected. Ignoring such negative curvilinear aspects of a relation between smoking and plaque progress among patient populations will tend to result in underestimations of its true magnitude. Prospective studies based on representative samples of community-based populations in which current and former smokers can be separated for analysis are needed to determine which explanation is correct.

The magnitude of the proportion of variation explained by each of the variables in the model should not be accepted uncritically. By sampling patients, we have restricted the range of variation in health in our sample compared with community-based populations. By studying only those patients with a history of cigarette smoking, we similarly restrict the range of variation in that variable (by omitting nonsmokers) and underesti-
tion of the plaque is that the noninvasive nature of duplex ultrasound allows its application to prospective studies based on representative samples of community-based populations.

We conclude that in smokers, the level of cigarette use is associated with an acceleration of the normal age-related development of carotid artery atherosclerosis as measured by thickness of intra-arterial plaques. This effect is independent of age, hypertension, and diabetes. In clinical practice, smoking abatement should be included as a component of stroke prevention strategies. Future studies are needed to determine whether cessation of smoking results in normalization or in deceleration of the normal age-related development of carotid plaque formation.

References
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