Relation of Smoking With Carotid Artery Wall Thickness and Stenosis in Older Adults

The Cardiovascular Health Study

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Background Cigarette smoking has been associated with increased risk of atherosclerotic diseases in hospital-based studies and in studies of middle-aged populations but not in population-based studies of older adults with and without clinical cardiovascular disease. 

Methods and Results We investigated the relation of smoking to carotid artery atherosclerotic disease, expressed as intimal-medial wall thickness and arterial lumen narrowing (stenosis) measured by ultrasound. Subjects were 5116 older adults participating in the baseline examination of the Cardiovascular Health Study, a community-based study of cardiovascular diseases in older age. With increased smoking there was significantly greater internal and common carotid wall thinning and internal carotid stenosis: current smokers>former smokers>never-smokers; for instance, the unadjusted percent stenosis was 24%, 20%, and 16%, respectively (P<.0001). A significant dose-response relation was seen with pack-years of smoking. These findings persisted after adjusting for other cardiovascular risk factors and were also confirmed when analyses were restricted to those without prevalent cardiovascular disease. The difference in internal carotid wall thickness between current smokers and nonsmokers was greater than the difference associated with 10 years of age among never-smoking participants (0.39 mm versus 0.31 mm). Among all participants, the prevalence of clinically significant (>50%) internal carotid stenosis increased from 4.4% in never-smokers to 7.3% in former smokers to 9.5% in current smokers (P<.0001). 

Conclusions These findings extend previous reports of a positive relation between smoking and carotid artery disease to a population-based sample of older adults using several different indicators of atherosclerotic disease. (Circulation. 1994;90:2905-2908.)

Key Words • atherosclerosis • stenosis • smoking • carotid arteries

Cigarette smoking is firmly established as a risk factor for coronary heart disease, peripheral vascular disease, and stroke.1,2 One possible explanation for this relation is that smoking increases the formation of atherosclerosis. Indeed, chronic cigarette smoking has been associated with an increased risk of atherosclerotic diseases of the coronary, aortic, abdominal, and peripheral arteries3 and, more recently, of the extracranial carotid arteries.4-6 Most previous studies relating smoking to carotid artery disease have been performed as hospital-based studies3,4 or in studies of middle-aged populations.5,8 No studies have related smoking to carotid artery disease in population-based samples of older adults and in people with and without clinical cardiovascular disease.

The purpose of this study is to report the cross-sectional associations between cigarette smoking and carotid artery atherosclerotic disease in a population-based sample of older adults. While previous studies have used either carotid artery wall thickness or lumen stenosis as the only indicator of atherosclerotic disease, we have examined the association of smoking to wall thickness in both the internal and common carotid arteries as well as to degree of narrowing of the arterial lumen (stenosis), thus including a wider range of expression of atherosclerotic disease. Data were obtained from 5116 individuals over age 64 years who participated in the baseline examination of the Cardiovascular Health Study (CHS).

Methods

The CHS cohort was selected from Medicare eligibility lists from four geographic areas in the United States: Allegheny County (Pittsburgh), Pa; Forsyth County, NC; Sacramento County, Calif; and Washington County, Md. Details of the study objectives and design9 and recruitment of the study cohort10 have been described previously. The collection of all data was performed according to standard protocols by personnel trained and certified by the CHS Coordinating Center. All subjects gave informed consent to participate, and the study protocol was approved by each institution's committee on human research.

Carotid Ultrasound

Carotid ultrasound was performed at all four centers using Toshiba SSA-270A imaging units (Toshiba America Medical Systems). The four machines were identically equipped with a phased-array imaging probe having a characteristic -3-dB cutoff point of 6.7 MHz. The pulsed Doppler frequency was 4.0 MHz. The imaging protocol has been described in detail previously.11 It involved obtaining a single longitudinal lateral view of the distal 10 mm of the right and left common carotid

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arteries and three longitudinal views in different imaging planes of each internal carotid artery. The internal carotid artery was defined as including the carotid bulb, identified by the loss of the parallel wall present in the common carotid artery, and the 10-mm segment of the internal carotid artery distal to the tip of the flow divider that separates the external and internal carotid arteries. Studies were recorded and read at the Ultrasound Reading Center. The high-resolution images of the common and internal carotid arteries were analyzed to calculate the average intimal-medial-thickness of the near and far walls. All measurements of wall thickness were calculated using a specially designed computer program.

The reader estimated percent diameter stenosis for each internal carotid artery using both image and Doppler data. Doppler peak systolic flow velocities below 1.5 m/s were assumed to indicate the absence of significant (50%) lumen stenosis. Gray-scale imaging data alone were then used to estimate percent diameter stenosis as absent (0%), mild (1% to 24%), or moderate (25% to 49%). Doppler peak flow velocities of 1.5 to 2.5 m/s were taken to represent stenosis of 50% to 74%; Doppler flow velocities of 2.5 m/s or greater indicated 75% to 99% stenosis. The last category included totally occluded internal carotid arteries. In all the analyses presented here, studies coded by the reader as having normal Doppler flow velocities but uninterpretable gray-scale images were included in the 0% stenosis category. For analysis, the midpoint of each category was used, that is, 0%, 12%, 37%, 67%, 87%, and 100%, respectively.

To quantify the degree of thickening of the carotid artery walls, the multiple measures of wall thickness were summarized into two variables, one for the common carotid and one for the internal carotid artery. The maximum wall thickness of the common carotid artery was defined as the mean of the maximum wall thicknesses from each view of the near and far walls on both the left and right sides. The maximum wall thickness variable of the internal carotid artery was defined in the same way.

**Smoking**

Smoking behavior was ascertained by self-report. Ages at initiation and quitting (if applicable) were obtained. Participants were classified as never-smokers if they responded that they had smoked fewer than 100 cigarettes or 5 packs of cigarettes during their lifetime. Former smokers were those who reported having smoked at least 100 cigarettes or 5 packs of cigarettes during their lifetime and had not smoked during the previous 30 days. Among never-smokers, a question was asked about whether anyone living with them smoked cigarettes regularly, an indicator of exposure to passive smoking. One hundred eighty-three participants answered "yes" to this question.

**Prevalent Cardiovascular Disease**

Prevalent cardiovascular disease (CVD) was defined as confirmed history of myocardial infarction, angina pectoris, stroke, or congestive heart failure or a history of coronary angioplasty or bypass surgery. Algorithms for classification of prevalent disease in CHS have been published.\(^\text{12}\)

**Statistical Analysis**

Univariate and multivariate analyses were performed using the srs program for personal computers. Adjustments were done using ANCOVA. These analyses are based on participants who had complete data on smoking and common carotid wall thickness (5080), internal carotid wall thickness (5035), and stenosis (5031).

**Results**

Of the 5201 individuals enrolled in CHS, 2919 (57.1%) were women and 2197 (42.9%) were men. The cohort was largely white (94.8%), with blacks accounting for 4.6% and other races for 0.6%. Mean age was 72.7 years.

The distribution of the CHS population by smoking categories is shown in the Table. A larger proportion of women than men were never-smokers or current smokers, whereas more men were former smokers. For both sexes, the proportion of current smokers decreased with increasing age, and the proportion of never-smokers generally increased with age. Mean age for never-smokers was 73.4 years, for former smokers 72.5 years, and for current smokers 70.8 years.

Smoking was positively and significantly related to carotid artery wall thickness and to degree of stenosis. After adjustment for age, sex, and race, mean wall thickness and percent stenosis by smoking status are displayed in Fig 1. Since no significant differences were observed between never-smokers exposed to and not exposed to passive smoking, these two groups were combined in the analysis. Former smokers had thicker carotid walls and higher degrees of stenosis than never-smokers. The same was true of current smokers compared with former smokers. These differences persisted after further adjustment for total and high-density lipoprotein (HDL) cholesterol, fasting glucose and fac-
tor VII, and hypertension and diabetes status. When we examined the relation between smoking and carotid artery disease in the low and high percentiles of the carotid artery disease distribution rather than using the mean values, we observed similar patterns. Also, when analyses were repeated using average rather than maximum wall thicknesses, similar results were obtained.

Because people who have been diagnosed with CVD may have quit smoking because of their disease, we reexamined the relation between smoking and carotid artery disease among participants without prevalent CVD. Although, as expected, mean wall thicknesses and degree of stenosis were smaller in this healthy group than in the total group, similar patterns were observed, with a gradient of disease from never-smokers to former smokers to current smokers. For instance, mean values for maximum internal carotid artery wall thicknesses, adjusted for age, sex, and race, were, respectively, 1.33 mm, 1.48 mm, and 1.71 mm (P<.0001) compared with 1.39 mm, 1.59 mm, and 1.72 mm for all participants.

Among former and current smokers, dose-response relations were seen between pack-years of smoking and carotid artery disease. Mean carotid artery wall thicknesses and degree of stenosis increased with increasing quartiles of pack-years of smoking, significantly for all three outcome measures (Fig. 2). Adjustment for the same covariates as above did not change these findings (P<.0001). Pack-years of smoking ranged from 0 to 240 years (median, 29 pack-years).

The difference in mean maximum internal carotid artery wall thickness between current smokers and nonsmokers was 0.390 mm after adjustment for age, sex, and race. This difference was greater than the difference associated with 10 years of age among never-smoking CHS participants, 0.310 mm, and points to the powerful effect of smoking on carotid artery disease. As previously reported from CHS, maximum stenosis and maximum internal and common carotid artery wall thicknesses all increased significantly with age (P<.0001).13

The prevalence of clinically significant (≥50%) internal carotid artery stenosis increased from never-smokers (4.4%) to former smokers (7.3%) to current smokers (9.5%) (χ²=27.7, P<.0001).

Discussion

Smoking has been reported to be a risk factor for carotid artery wall thickening or stenosis in hospital-based studies and in population-based studies of middle-aged populations.3-8,12,13 This study confirms that smoking in the elderly is also strongly associated with atherosclerotic disease, assessed in three different ways: internal and common carotid artery wall thickening and narrowing of the arterial lumen. The associations included thicker walls and higher degrees of stenosis from never-smokers to former smokers to current smokers. There was also a dose-response effect of pack-years of smoking, confirming previous reports of smoking and wall thickness in studies of younger persons.3,6,14 These findings could not be explained by the effect of potential confounders, including other risk factors for atherosclerosis. Since some participants may have quit smoking because of illness such as heart disease, it is important to note that the associations were also strong and consistent among those without prevalent cardiovascular disease as among the entire cohort. As previously reported in hospital-based studies,6 the strength of the associations differ between different segments of the carotid distribution and are generally stronger in the internal than in the common carotid. The reasons for these site differences are not known.

To put the strength of the association between smoking and wall thickness in perspective, we compared smoking with perhaps the strongest risk factor for wall thickening, namely, age. When current smokers are compared with never-smokers, the difference is greater than the difference between participants who are 10 years different in age.

Cigarette smoking is a risk factor for clinical cardiovascular events, possibly partly through its association with higher fibrinogen levels, hemoglobin concentration, and reduced myocardial oxygen supply.15-17 The association of smoking with atherosclerosis also indicates an atherogenic role. However, the mechanisms whereby cigarette smoking influences the atherosclerotic process is not known. Over 4000 constituents have been identified in cigarette smoke,18 and the effect of smoking is superimposed on a very complex atherogenic process. Smoking may be involved in the atherogenic process through its influence on other factors including elevated plasma total cholesterol and low-density lipoprotein cholesterol and reduced HDL cholesterol.16,19 Changes that favor a net flux of cholesterol into the arterial wall. Elevation in plasma fibrinogen concentration and elevation in white blood cell count may also contribute to accelerated atherosclerosis formation.16 It has also been suggested that cigarette smoking increases arterial wall stiffness and alters the pattern of arterial blood flow.20 This effect on compliance may be another mechanism explaining the atherogenic effect of smoking since the pattern of blood flow may affect the development of arteriosclerosis.

Our findings of smaller degrees of wall thickening and stenosis among former smokers compared with current smokers suggest that smoking cessation either reverses or slows the progression of atherosclerosis. This latter observation corroborates previous findings of the benefits of quitting smoking in terms of reduced risks of total and cardiovascular mortality, even among those who stop smoking after age 65 years.21 This reduced risk suggests that some of the processes by which smoking causes atherosclerosis may be reversible.

During early phases of atherosclerotic plaque buildup, the arterial lumen usually enlarges to maintain an adequate lumen size.22 While the presence of wall thickening without significant stenosis represents early disease, the
presence of discernable stenosis usually represents somewhat more advanced disease. Because the associations with smoking were consistent both with regard to wall thickening and to degree of stenosis, smoking may be associated with both early and later stages of the atherosclerotic process. Although intimal-medial thickening measured by ultrasound cannot be unequivocally attributed to atherosclerosis, it is a plausible estimate of atherosclerotic changes in the arterial wall. As reviewed by Heiss et al., atrtherosclerotic structural changes of the arterial wall are known to progress through the stage of diffuse thickening of the tunica intima, which in turn represents the principal site of localized atherosclerotic lesions.

Summary

Our findings in this population-based study of older adults confirm previously reported associations between cigarette smoking and carotid atherosclerosis observed in younger and sometimes select populations. In addition, the findings are consistent for different measures of the atherosclerotic process. Thus, there is now abundant evidence for a strong, graded, and biologically plausible association between cigarette smoking and extracranial carotid artery atherosclerosis across diverse study designs and populations, all of which support a causal interpretation of this relation.

Appendix

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