CLINICAL STUDY

Risk Factors for Subclinical Carotid Atherosclerosis Among Current Smokers

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This study characterized the determinants of carotid atherosclerosis in a large contemporary sample of current smokers. Associations between risk factors, carotid intima-media thickness (CIMT), and carotid plaque presence were determined by multivariable regression. Participants included 1504 current smokers (58% female) who were a median (interquartile range) of 44.7 (38–53) years old and smoked 25 (15–40) pack-years; 55% had plaque. Pack-years, age, male sex, nonwhite race, body mass index, systolic blood pressure, small low-density lipoproteins (LDLs), and total high-density lipoproteins were independently associated with CIMT (model R^2=0.434, P<.001). Pack-years (odds ratio [OR], 1.14 per 10 pack-years; P=.001), age (OR, 1.75 per 10 years; P<.001), body mass index (OR, 0.91 per 5 kg/m^2; P=.035), and small LDLs (OR, 1.11 per 100 nmol/L; P<.001) were independently associated with carotid plaque presence (model χ^2=210.7, P<.001). The association between pack-years and carotid plaque was stronger in women (OR, 1.09 per 10 pack-years, $P_{interaction}$=.018). **Prev Cardiol. 2010;13:166–171.** ©2010 Wiley Periodicals, Inc.

Epidemiologic studies have established a strong, direct relationship between cigarette smoking and the development of cardiovascular disease (CVD).[1] Vasomotor dysfunction, vascular inflammation, and lipid oxidation are key pathways by which cigarette smoking influences the initiation and progression of atherosclerotic vascular disease.[2,3] Carotid intima-media thickness (CIMT) and carotid plaque are noninvasive measures of atherosclerotic vascular disease that also predict CVD events.[4,5] Smoking is associated with higher CIMT.[6–8] Cigarette smoking independently increases atherosclerotic burden and acts synergistically with other risk factors to increase CVD risk.[1] However, there is a paucity of data as to which risk factors are the most important predictors of atherosclerosis among smokers and how they interact with each other. It also is not known whether smoking-related parameters such as the duration of smoking, degree of nicotine dependence, and patient's personality and affect (mood) influence atherosclerotic burden in current smokers.

The purpose of this study was to identify and characterize the determinants of carotid atherosclerosis in a large cross-sectional sample of current smokers participating in a longitudinal study of the effects of continued smoking and smoking cessation on CVD risk factors and atherosclerosis progression.

METHODS

Study Participants and Design

The institutional review board at the University of Wisconsin School of Medicine and Public Health approved this study. All participants provided written informed consent. The study was a longitudinal, randomized, double-blind, placebo-controlled smoking cessation trial to evaluate the efficacy of several smoking cessation pharmacotherapies and examine the natural history of continued smoking and smoking cessation.[9] Each participant's consent for the randomized clinical trial included permission to evaluate the physiologic effects of active cigarette use and smoking cessation on atherosclerosis by ultrasonographic evaluation of CIMT and carotid plaque presence at baseline and after 3 years. As the long-term study is ongoing, this manuscript describes the independent risk factors for CIMT

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and plaque burden in current smokers prior to randomization to the smoking cessation intervention. Inclusion and exclusion criteria were based on participation in the clinical trial. Inclusion criteria were age $\geq$18 years, current smoking of $\geq$10 cigarettes/day for the previous 6 months, an expired carbon monoxide level of $>$9 ppm, and stated motivation to try to quit smoking. Major exclusion criteria were uncontrolled hypertension (blood pressure $>$160/100 mm Hg) and myocardial infarction in the previous 4 weeks. Details of other exclusion criteria are described in the smoking cessation efficacy study.[9]

STUDY PROCEDURES

All participants were recruited from communities in and around Madison and Milwaukee, Wisconsin. Adult smokers were recruited via television, radio, and newspaper advertisements, flyers, and earned media including press conferences and interviews from January 2005 to June 2007. At the baseline visit, anthropometric data, fasting laboratory tests, validated questionnaires, and interviews were completed. Blood pressure levels were taken with calibrated mercury sphygmomanometers after participants were seated for a minimum of 5 minutes The bare upper right arm was used unless contraindicated. The appropriate size cuff was placed and blood pressures were obtained by trained personnel using standardized procedures. The waist circumference was measured with participants standing, feet shoulder-width apart. A plastic measuring tape was placed horizontally around the bare waist, at the level of the iliac crest, with measurements taken at the end of normal exhalation by trained technicians using a standardized protocol. Advanced lipoprotein testing was performed via nuclear magnetic resonance spectroscopy by LipoScience, Inc. (Lipoprofile-2; LipoScience, Inc., Raleigh, NC).[10] A total of 9 subclasses were measured. Low-density lipoproteins (LDLs) and high-density lipoproteins (HDLs) were defined as follows: large LDLs, 21.2–23.0 nm; small LDLs, 18.0–21.2 nm; large HDLs, 8.8–13.0 nm; medium HDLs, 8.2–8.8 nm; and small HDLs, 7.3–8.2 nm.

Carotid Ultrasonography

Before the initial quit attempt, baseline digital images of the right and left common carotid, bulb, and internal carotid artery segments were acquired using a high-resolution linear array transducer (L10-5) and a cardiovascular ultrasound system (CV70; Siemens Medical Solutions, Mountain View, WA). The CIMT imaging protocol has been described previously.[11,12] Images were transferred via the Internet to a secure Web server at the University of Wisconsin Atherosclerosis Imaging Program, the core ultrasound laboratory. All scanners were trained and certified by the core lab.

The mean far wall CIMT of the distal 1 cm of each common carotid artery was measured in triplicate at the electrocardiographic R-wave by a single reader using a semiautomated border detection program. Images were obtained on each side from 3 angles of interrogation.[11–13] Longitudinal and cross-sectional images of the common carotid, bulb, and internal carotid artery segments were evaluated for the presence or absence of plaque (focal thickness of the intimal-medial layer of $\geq$1.2 cm).[5] The coefficient of variation for repeatability of mean common carotid artery measurements in this study was 1.7%.

Statistical Analysis

Analyses were performed with SPSS software (SPSS, Inc., Chicago, IL). The average of the mean right- and left-sided far wall CIMT measurements of the common carotid artery was used to define the mean composite CIMT (“mean-mean”). Cardiovascular risk factors and CIMT were described by medians and interquartile ranges, unless noted otherwise. Multivariable linear regression models were created to determine associations between CVD risk factors and CIMT. Multivariable logistic regression models were used to identify independent risk factors for carotid plaque presence and to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Age, sex, race, and smoking burden (pack-years) were included in all models of CIMT and plaque presence. Other variables that were evaluated included body mass index (BMI), waist circumference, total cholesterol, HDL cholesterol (HDL-C), triglycerides, LDL cholesterol (LDL-C), total/HDL-C ratio, glucose, systolic blood pressure, diastolic blood pressure, hemoglobin A_{1c}, high-sensitivity C-reactive protein, serum creatinine, total LDL particles, small LDL particles, mean LDL particle size, total HDL particles, small HDL particles, mean HDL particle size, current use of antihypertensive and/or lipid-lowering medication, serum cotinine level, alcohol consumption (number of drinks per month), and 3 psychometric evaluations: the Fagerström Test of Nicotine Dependence, Positive and Negative Affect Schedule, and the Multidimensional Personality Questionnaire.[14–16] Because of collinearity, separate models were used to determine which smoking-related parameters and which LDL- and HDL-related cholesterol and lipoprotein measures were most strongly associated with CIMT and carotid plaque presence; the strongest associations were included in the final models. Interactions between smoking burden and the significant variables in the final models for CIMT and plaque presence were formally tested. Evaluation of histograms of residuals, residual plots vs predicted values, and normal quartile–quartile plots (Q–Q plots) did not demonstrate significant violations of linear regression assumptions of errors and linearity.

Table I. Participant Baseline Characteristics

Variable	Median	25th Percentile	75th Percentile
Age (y)	45	37.8	53
Number of cigarettes smoked per day	20	15	25.3
Current pack-years smoking	25	15	40
Peak pack-years smoking	31	19.8	52.5
Fagerström Test for Nicotine Dependence	6	4	7
Serum cotinine (ng/mL)	214	150	282
Carotid intima-media thickness (mm)	0.700	0.633	0.778
Male (mm)	0.711	0.649	0.817
Female (mm)	0.672	0.614	0.739
Total cholesterol (mg/dL)	183.1	159.9	207.9
High-density lipoprotein cholesterol (mg/dL)	39.2	30.8	49.3
Triglycerides (mg/dL)	116.0	82.4	173.9
Low-density lipoprotein cholesterol (mg/dL)	119.0	99.5	140.8
Total/high-density lipoprotein cholesterol ratio	2.9	1.8	5.2
Low-density lipoproteins (nmol/L)	1276	1054.5	1517.5
Small low-density lipoproteins (nmol/L)	676	403.2	968.3
Mean low-density lipoprotein diameter (nm)	21.2	20.6	21.8
High-density lipoproteins (μmol/L)	29.6	25.8	33.9
Large high-density lipoproteins (μmol/L)	4.6	2.6	6.9
Mean high-density lipoprotein diameter (nm)	8.6	8.3	9.0
Systolic blood pressure (mm Hg)	120	109.5	128.0
Diastolic blood pressure (mm Hg)	76	68	82
Body mass index (kg/m^2)	28.3	24.5	32.6
Waist circumference (in)	37.7	33.7	42.1
Fasting glucose (mg/dL)	91.5	86	98
Hemoglobin A_{1c} (%)	5.5	5.3	5.8
Framingham Risk Score %/10 y	3.1	1.1	8.2
C-reactive protein (mg/L)	1.2	0.4	3.7
Alcohol consumption (drinks per month)	2	0	6

RESULTS

Participant Characteristics

Participant characteristics are provided in Table I. There were 1504 current smokers in this study (58% female, 84% white, 14% black, 2% American Indian/Alaskan/Asian/Pacific). The median age was 45.0 (37.8–53.0) years. Participants smoked approximately 1 pack of cigarettes daily with a total smoking burden of 25 (15–40) current pack-years. Men (30 [16.2–45] pack-years) had a significantly greater smoking burden than women (23 [14.2–35] pack-years) ($P<.001$). The median CIMT was 0.700 (0.633–0.778) mm, which was higher than expected compared to the general population.[17] Fifty-five percent had carotid plaque. The cohort had low HDL-C and an elevated total/HDL-C ratio, with increased small LDL particles. In this cohort, 529 patients (35.6%) had the metabolic syndrome. The presence of plaque among participants with the metabolic syndrome (39.1%) was significantly higher than in those without (31.4%) ($\chi^2=9.1$, $P=.002$). The mean (standard deviation) Framingham Risk Score was 5.6% (0.1%)/10 years. The Framingham Risk Score in participants with plaque (6.7%/10 years) was significantly higher than in those without plaque (4.2%/10 years) ($P<.001$).

Risk Factors Associated With Higher CIMT

The baseline and all subsequent models included age, sex, and race. Separate multivariable regression models were created to determine which smoking variables were most strongly associated with CIMT. The smoking-related variables evaluated were number of cigarettes smoked per day ($P=.266$), peak pack-years (peak cigarette packs per day × years smoked; $P=.660$), current pack-years (current cigarette packs per day × years smoked; $P<.001$), Fagerström Test of Nicotine Dependence score ($P=.212$), and serum cotinine value ($P=.170$). Of the smoking-related variables, current pack-years had the strongest independent associations with the markers of subclinical atherosclerosis and was used in subsequent models. Male sex ($P<.001$) and nonwhite race ($P<.001$) were associated with CIMT, as was BMI ($P<.001$), as opposed to waist circumference ($P=.115$). Fasting glucose ($P=.119$) and hemoglobin A_{1c} ($P=.368$) were not independently associated with CIMT. Systolic and diastolic blood pressures were analyzed in multivariable models and demonstrated a collinear relationship ($r=0.68$, $P<.001$). Systolic blood pressure had a stronger association with CIMT ($r=0.34$, $P<.001$) than diastolic blood pressure ($r=0.15$, $P<.001$), so systolic

Table II. Independent Risk Factors for Carotid Intima-Media Thickness (Model R^2=0.434, P<.001)

Variable	Standardized Coefficient	t	P Value
Age (y)	0.468	17.73	<.001
Sex	−0.126	−5.73	<.001
Race	0.083	3.99	<.001
Current pack-years smoking	0.095	3.60	<.001
Body mass index (kg/m^2)	0.155	7.15	<.001
Systolic blood pressure (mm Hg)	0.125	5.62	<.001
Small low-density lipoproteins (nmol/L)	0.053	2.44	.015
Total high-density lipoproteins (μmol/L)	−0.074	−3.45	.001

Table III. Independent Risk Factors for Carotid Plaque Presence (Model χ^2=210.7, P<.001)

Variable	Odds Ratio	95% Confidence Interval	P Value
Age (per 10 y)	1.75	1.53–2.00	<.001
Body mass index (per 5 kg/m^2)	0.91	0.83–0.99	.035
Small low-density lipoproteins (per 100 nmol/L)	1.11	1.08–1.13	<.001
Current pack-years (per 10 pack-years)	1.14	1.05–1.23	.001

Table IV. Significant Interactions of Carotid Plaque Risk Factors (Model χ^2=216.3, P<.001)

Variable	Odds Ratio	95% Confidence Interval	P Value
Age (per 10 y)	1.72	1.50–1.97	<.001
Body mass index (per 5 kg/m^2)	0.90	0.82–0.98	.025
Small low-density lipoproteins (per 100 nmol/L)	1.11	1.08–1.13	<.001
Current pack-years (per 10 pack-years)	1.12	1.03–1.21	.007
Pack-years × sex (per 10 pack-years)	1.09	1.01–1.18	.018

blood pressure was used in all models. Alcohol consumption was not associated with CIMT (P=.325). The Positive and Negative Affect Schedule (positive P=.694; negative P=.072) and the Multidimensional Personality Questionnaire analyses (positive emotionality P=.696; negative emotionality P=.565; constraint P=.894) were not associated with CIMT.

In regard to lipids, HDL-C (P<.001), triglycerides (P=.005), and total/HDL-C ratio (P<.001) were independently associated with CIMT, but total cholesterol (P=.835) and LDL-C (P=.090) were not. Among the lipoprotein measurements, small LDLs (P=.006) and total HDL particles (P=.002) were more associated with CIMT than were total LDL particles (P=.620) and small HDL particles (P=.389). Mean LDL (P=.077) and HDL particle diameters (P=.094) were not independently associated with CIMT. Triglycerides were not independently associated with CIMT in any model that included HDL-C or HDL particles. The final model for CIMT is in Table II. A model that included HDL-C rather than total HDL particles had the same contributors and an equivalent adjusted R^2. The models were not notably changed after adjustment for use of lipid-lowering (n=168, 11.1%) and antihypertensive n=205, 13.6%) medications. Interaction testing was performed between each of the significant variables and smoking burden (current pack-years). However, no significant interactions were identified.

Risk Factors for Carotid Plaque Presence

In the best multivariable model (model χ^2=210.7, P<.001), variables that were independently associated with carotid plaque presence were age (OR, 1.75; 95% CI, 1.53–2.00 per 10 years; P<.001), BMI (OR, 0.91; 95% CI, 0.83–0.99 per 5 kg/m^2; P=.035), small LDL particles (OR, 1.11; 95% CI, 1.08–1.13 per 100 nmol/L; P<.001), and smoking burden (OR, 1.14; 95% CI, 1.05–1.23 per 10 pack-years, P=.001) (Table III).

Additional analyses were performed to evaluate the apparent but unsuspected inverse relationship between BMI and carotid plaque presence. We observed that the prevalence of carotid plaque was consistent across quintiles of BMI (data not shown). BMI was significantly correlated with small LDL particles (r=0.215, P<.001), which also predicted plaque presence. These findings suggest that the weak, inverse relationship between BMI and plaque presence most likely is confounded by small LDL particles. The presence of the metabolic syndrome (P=.969) and the Framingham Risk Score were not independent predictors of carotid plaque presence (P=.103).

Interaction testing between smoking burden and the other significant variables (model χ^2=216.3, P<.001) demonstrated that the effect of pack-years on carotid plaque presence was stronger in women (OR, 1.09; 95% CI, 1.01–1.18 per 10 pack-years; $P_{interaction}$=.018) than men (Table IV). There was no interaction between age and sex ($P_{interaction}$=.257). Addition of an interaction term for age and sex in the model did not significantly affect the observed

interaction between pack-years and female sex, demonstrating that the sex difference in the effect of pack-years on carotid plaque was not due to age differences. No other significant interactions were identified.

DISCUSSION

In this study of more than 1500 active smokers, both carotid plaque and CIMT were associated with increasing age, BMI, small LDLs, and pack-years of smoking. The association between smoking burden and carotid plaque presence was stronger in women than in men. Increasing CIMT additionally was associated with male sex, nonwhite race, systolic blood pressure, and total HDL-C. The relationship between smoking burden (pack-years) and higher CIMT is consistent with a previous report from the Atherosclerosis Risk in Communities (ARIC) study.[6] However, data regarding smoking in ARIC were ascertained 2 decades ago and participants in the ARIC study on average were a decade older than in our study and were in a narrower age range (45–65 years). We studied a modern set of active smokers across a wide range of ages (18–79 years) and looked at the effect of smoking burden after controlling for lipoprotein measurements, which are more strongly associated with CIMT than are lipids.[18] Furthermore, we evaluated physiologic markers of smoking such as cotinine and measures of nicotine dependence, alcohol consumption, personality, and affect disorders, which may be more common among current smokers.

Several of the findings in this study are unique. Because of the large sample size and evaluation of multiple descriptors of smoking burden, we were able to determine that of the smoking-related variables, current pack-years was most strongly associated with both carotid plaque presence and CIMT, even after controlling for the effects of age. In this cohort, current pack-years and age were the strongest predictors of both CIMT and carotid plaque presence, supporting the dose-response relationship previously observed between cigarette smoking and CVD incidence, suggesting that increased atherosclerotic burden contributes to the increased CVD risk observed in smokers.[1,3]

Several studies have supported the hypothesis that smoking interacts with other risk factors in a multiplicative fashion, further increasing CVD risk, even in young adults.[1,19] In our study, another important finding was the interaction between smoking burden and female sex. Although men had a significantly higher smoking burden, the effect of increasing pack-years of smoking on the development of carotid plaque was stronger in women than in men. The observation that female smokers are at increased CVD risk is supported by previous research that demonstrated that smoking had a stronger association with coronary heart disease incidence in women compared to men.[20] This study emphasizes the importance of targeting smoking cessation interventions and avoidance messages toward women.

Smoking is associated with low HDL-C and hypertriglyceridemia.[21] However, this study demonstrated that direct lipoprotein measurements were more strongly associated with subclinical carotid atherosclerosis than their corresponding lipid measurements and lipid ratios. Small LDL and total HDL particle concentrations were independently associated with higher CIMT, and small LDL particles were independently associated with carotid plaque presence, a more advanced stage of subclinical atherosclerosis. LDL-C levels tend not to be increased in smokers, but smoking does shift the LDL particle size to the smaller, more atherogenic lipoprotein subtype.[21] As expected, small LDLs, rather than LDL-C, total LDL particles, or LDL size had the strongest association with carotid atherosclerosis of the LDL-related variables. In this context, BMI also was associated with increasing CIMT and carotid plaque presence. The relationship of BMI to CIMT is an expected finding, since obesity also is associated with low HDL and small LDL particles.[22] Although BMI was an inverse predictor of carotid plaque presence in the multivariable model, the relationship was weak, was of borderline statistical significance, and added only a minimal amount of predictive value to the regression model (adjusted $R^2=0.184$ without BMI, adjusted $R^2=0.188$ with BMI). Furthermore, the area under the curve for BMI was only 0.499. Because the presence of plaque was consistent across all quintiles of BMI and BMI was positively correlated with small LDL particles ($r=0.215$, $P<.001$) which strongly predicted carotid plaque presence, we believe that the relationship between BMI and carotid plaque in smokers is confounded by small LDL particles. If small LDL particles are not present, then the negative metabolic effects of increased BMI on atherosclerosis are less likely to be seen.

Inventories regarding personality and affect were not associated with carotid atherosclerosis in our study. Previous research has not shown a direct relationship between positive and negative affect and coronary artery disease.[23] However, certain emotions may be confounders of atherosclerosis development and CVD events.[24]

Limitations

This was a cross-sectional study of individuals who chose to participate in a smoking cessation intervention study; therefore, our findings may not be generalizable to all smokers. However, more than 70% of current smokers plan to quit smoking in the next year.[25] Although significant efforts were made to target recruitment of nonwhite participants, nonwhites represented only approximately 16% of the study cohort. It is possible that there are racial differences in associations with carotid atherosclerosis

among smokers. Data about family history of premature CVD and physical activity were not available for analysis. Uncontrolled hypertension was an exclusion criterion, which restricted the range to evaluate blood pressure and its relationship to carotid atherosclerosis. Inclusion of individuals with higher blood pressures may have demonstrated a stronger association of blood pressure with CIMT and/or plaque. Menopausal status was not known; however, 69% of the women were younger than 50, and <1% were on estrogen therapy. Therefore, the use of hormone replacement therapy should not affect the results of this study. Finally, data were not available for biomarkers that may affect atherosclerosis among smokers, such as fibrinogen and inflammatory cytokines.

CONCLUSIONS

Among current smokers, increasing smoking burden, systolic blood pressure, BMI, and small LDL and total HDL particles are associated with the presence and extent of subclinical carotid atherosclerosis. Smoking burden was more strongly associated with carotid plaque presence among women than men. In addition to supporting the importance of smoking cessation for the prevention of CVD, this study highlights the importance of other risk factors for atherosclerosis and CVD among current smokers.

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