Effects of Cumulative Smoking Exposure and Duration of Smoking Cessation on Carotid Artery Structure

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Background: While prior epidemiological studies have examined the association between cigarette smoking and carotid atherosclerosis, few studies have evaluated the association of both cumulative smoking exposure and the duration of smoking cessation with carotid artery structure.

Methods and Results: The study population consisted of 2,503 community-dwelling Korean males aged 50 years and older. Common carotid artery intima-media thickness (CCA-IMT), carotid plaque, and the internal diameter of the common carotid artery (CCA-diameter) were determined by high-resolution B-mode ultrasonography. Data on the characteristics of the subjects, including smoking status, pack-years of smoking, and years since quitting smoking, were collected using a standardized questionnaire. The current smokers had significantly greater CCA-IMT and CCA-diameter and a significantly higher risk of carotid plaque than did the subjects who had never smoked ($P=0.009$, <0.001 , and 0.036 , respectively). Dose-response relationships between pack-years and CCA-IMT and CCA-diameter were found among the current smokers ($P=0.001$ and <0.001 , respectively); however, no significant association between pack-years and the carotid artery parameters was observed among the former smokers. For the former smokers, CCA-IMT and CCA-diameter tended to decrease with increasing years since quitting smoking ($P=0.009$ and 0.012 , respectively), whereas no significant association with carotid plaque was found.

Conclusions: Cumulative smoking exposure in current smokers and the duration of smoking cessation in former smokers are significant risk factors for carotid atherosclerosis. (*Circ J* 2012; **76**: 2041–2047)

Key Words: Atherosclerosis; Carotid arteries; Smoking; Smoking cessation

Intima-media thickness (IMT) and carotid artery plaque, which are markers of subclinical atherosclerosis, are used as surrogate endpoints of cardiovascular disease, myocardial infarction, and stroke.^{1,2} Carotid diameter correlates with conventional cardiovascular risk factors, and carotid arterial enlargement has been suggested as a useful indicator of carotid atherosclerosis.³ Atherosclerosis is the underlying condition that leads to the increased risk of cardiovascular disease mortality, and cigarette smoking is one of the most important risk factors for atherosclerosis.

A number of epidemiological studies have examined the as-

sociation between cigarette smoking and atherosclerosis using carotid IMT or carotid plaque.^{4–11} Although most studies have reported a positive association between smoking status (ie, never, former, and current smokers) with carotid atherosclerosis, few studies have examined the cumulative effects of smoking (eg, pack-years) on carotid atherosclerosis. A few epidemiological studies have investigated the association between years since smoking cessation and carotid atherosclerosis,^{7,10,12} but results are inconsistent across studies. Moreover, it remains undetermined whether cigarette smoking is significantly associated with carotid enlargement in the general population.

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We investigated the effects of cumulative cigarette smoking exposure on carotid artery structure, such as carotid IMT, plaque, and luminal diameter, among community-dwelling adults aged 50 years and older. We also examined whether there is an inverse association between the time since smoking cessation and carotid artery parameters.

Methods

Subjects

The study population consisted of community-dwelling Korean males aged 50 years and older. The subjects were participants in baseline surveys (2007–2009) as part of the Dong-gu Study, an ongoing population-based prospective study designed to investigate the prevalence, incidence, and risk factors for chronic disease in community-dwelling persons aged 50 years and older. Only males were included in the analysis because of the extremely low prevalence of female smokers (1.9% of current smokers in this study and 1.8% of former smokers). Of the 2,644 participants, 131 were excluded from analysis because of incomplete information regarding their medical history, lifestyle characteristics, and anthropometric and biochemical measurements; an additional 10 subjects with missing information or poor images on carotid ultrasonography were excluded. A total of 2,503 subjects were included in the final analyses. This study was conducted in accordance with the Declaration of Helsinki guidelines. The study protocol was approved by the institutional review board of Chonnam National University Hospital, and written informed consent was given by all the study subjects.

Definitions of Smoking

Information on smoking habits was collected using a standardized questionnaire administered by well-trained research staff. Participants were classified according to their smoking status as never, former, or current smoker. Never smokers were defined as participants who had never smoked a cigarette or had smoked fewer than 100 cigarettes in their lifetime. Former smokers were defined as participants who had smoked at least 100 cigarettes in their lifetime, but did not currently smoke. Current smokers were defined as participants who had smoked at least 100 cigarettes during their lifetime, including at the time of the interview. For subjects who reported former or current smoking, pack-years, which is an indication of cumulative smoking exposure, was calculated by multiplying the number of years smoked with the average number of packs per day (1 pack=20 cigarettes). Based on their pack-years, participants were assigned to the following categories: 0 (never smoked), 0.1–20.0, 20.1–40.0, or >40 pack-years. According to additional information regarding the number of years that had passed since they quit smoking, former smokers were classified as ≤3, 4–10, 11–20, and ≥21 years and compared with the current smokers.

Carotid Ultrasonography

Carotid ultrasonography, image analysis, and assessments of reproducibility were performed as described previously.¹³ Briefly, 2 well-trained ultrasonographers evaluated the carotid artery structure of all participants using a high-resolution B-mode ultrasound (SONOACE 9900; Medison, Seoul, Korea) equipped with a 7.5-MHz linear array transducer. IMT was determined as the distance from the media-adventitia interface to the intima-lumen interface on the far wall between the carotid bulb origin and a point 10 mm proximal to the common carotid artery (CCA) on the longitudinal view in a plaque-free region.

The CCA-IMT was determined as the average of the maximum IMT of the left and right CCAs. The presence of carotid plaque, defined as focal structures that encroached into the lumen by at least 100% of the surrounding IMT value, was determined from scans of the carotid artery segments, including the common, bulb, and internal carotid artery. The luminal diameter of the CCA (CCA-diameter) was determined as the mean of the luminal diameter of the left and right CCAs at a point 10 mm proximal to the carotid bulb origin.

Covariates

Demographic data detailing the lifestyle, medical history, and medications used by the subjects were collected using a standardized questionnaire administered by trained staff. Alcohol consumption was assessed using a structured interview; the amount of ethanol consumed per day was calculated from the average number of alcoholic beverages consumed. Physical exercise was categorized as none, irregular or regular. Body mass index (BMI) was calculated as the weight of the subject in kilograms divided by the height in meters squared. Blood pressure was measured using a mercury sphygmomanometer and the average of 3 consecutive systolic and diastolic readings was used in the analysis. After a 12-h overnight fast, venous blood samples were collected for measurement of serum total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and fasting blood glucose levels by enzymatic methods. Low-density lipoprotein cholesterol was calculated by Friedewald's formula. All samples were analyzed using an automatic analyzer (model 7600 chemical analyzer; Hitachi Ltd, Tokyo, Japan).

Statistical Analysis

The baseline characteristics of the subjects based on smoking status are expressed as either means±standard deviation or numbers (percentage). These values were compared using an analysis of variance for continuous variables and a chi-square test for categorical variables. An analysis of covariance and multiple logistic regressions were used to evaluate the association between smoking status, cumulative smoking exposure, and duration of smoking cessation with carotid artery parameters. Bonferroni's method was used for multiple comparisons (never vs. former, never vs. current, and former vs. current). In the analysis of smoking status and cumulative smoking exposure among current smokers, model 1 was adjusted for age; model 2 was adjusted for age, BMI, systolic blood pressure, fasting blood glucose, total cholesterol, HDL-cholesterol, uric acid, alcohol consumption, physical exercise, and the use of medications for hypertension, diabetes, and hyperlipidemia; and model 3 was adjusted for the other 2 carotid artery parameters in model 2. In the analysis of cumulative smoking exposure among current smokers, model 4 was further adjusted for the duration of smoking cessation. Pack-years was additionally adjusted in models 2 and 3 for an analysis of years since quitting smoking. Unadjusted and adjusted means±standard errors and adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated. A linear trend in the association between smoking status, extent of cigarette exposure, and duration of smoking cessation with carotid artery parameters was determined by treating smoking categories as a continuous variable.

All statistical analyses were performed using the SPSS 15.0 software package (Chicago, IL, USA). $P<0.05$ was considered statistically significant.

Table 1. Baseline Characteristics of the Study Population According to Smoking Status (n=2,503)

	Never smoker (n=617)	Former smoker (n=1,288)	Current smoker (n=598)	P- difference*	Bonferroni's method for multiple comparisons		
					P value†	P value‡	P value§
Age, years	66.9±7.8	66.7±7.9	63.8±7.6	<0.001	1.000	<0.001	<0.001
BMI, kg/m ²	24.1±2.9	24.0±2.7	23.4±2.8	<0.001	1.000	<0.001	<0.001
SBP, mmHg	125.1±15.9	125.7±16.5	123.1±16.7	0.005	1.000	0.105	0.004
DBP, mmHg	76.0±10.1	75.7±10.5	75.3±10.9	0.438	1.000	0.606	1.000
Antihypertensive medications, n (%)	223 (36.1)	477 (37.0)	165 (27.6)	<0.001	0.706	0.001	<0.001
Fasting blood glucose, mg/dl	113.8±27.2	113.1±26.3	113.9±29.5	0.810	1.000	1.000	1.000
Antidiabetic medications, n (%)	97 (15.7)	199 (15.5)	98 (16.4)	0.873	0.879	0.752	0.603
Total cholesterol, mg/dl	186.4±35.1	188.2±37.6	188.3±40.3	0.562	0.931	1.000	1.000
LDL-cholesterol, mg/dl	113.1±31.1	111.7±32.9	109.6±35.5	0.187	1.000	0.210	0.596
HDL-cholesterol, mg/dl	48.8±11.2	49.5±12.0	48.9±13.0	0.375	0.669	1.000	0.886
Triglycerides, mg/dl¶	127.2±88.1	145.9±127.7	155.7±111.9	<0.001	0.003	<0.001	0.262
Lipid-lowering medications, n (%)	33 (5.3)	87 (6.8)	37 (6.2)	0.493	0.237	0.530	0.644
Uric acid, mg/dl	5.6±1.4	5.9±1.4	5.8±1.5	0.002	0.002	0.320	0.364
Alcohol consumption, g/day	7.4±15.9	15.0±23.4	20.8±28.2	<0.001	<0.001	<0.001	<0.001
Regular exercise, n (%)	129 (20.9)	283 (22.0)	98 (16.4)	0.017	0.647	0.037	0.005
Age at starting smoking	–	22.3±5.3	22.8±6.3	–	–	–	0.062
Total years of smoking, years	–	28.3±13.8	40.6±9.9	–	–	–	<0.001
No. of cigarettes per day	–	18.5±12.5	16.1±8.2	–	–	–	<0.001
Pack-years of smoking	–	27.5±22.9	32.5±18.1	–	–	–	<0.001

Data are means±standard deviation or n (percentage).

*P value obtained by ANOVA for CCA-IMT and CCA-Diameter, or by chi-square test for carotid plaques; †P value obtained by comparing never smokers and former smokers; ‡P value obtained by comparing never smokers and current smokers; §P value obtained by comparing former smokers and current smokers; ¶P value obtained after log-transformation.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Table 2. Carotid Artery Parameters According to Smoking Status (n=2,503)

	Never smoker (n=617)	Former smoker (n=1,288)	Current smoker (n=598)	P- difference*	Bonferroni's method for multiple comparisons		
					P value†	P value‡	P value§
CCA-IMT, mm							
Model 1	0.759±0.006	0.761±0.004	0.777±0.006	0.043	1.000	0.075	0.075
Model 2	0.755±0.006	0.760±0.004	0.784±0.006	0.001	1.000	0.002	0.003
Model 3	0.757±0.006	0.760±0.004	0.782±0.006	0.003	1.000	0.009	0.007
CCA-diameter, mm							
Model 1	6.360±0.031	6.513±0.021	6.531±0.032	<0.001	<0.001	<0.001	1.000
Model 2	6.361±0.027	6.488±0.019	6.583±0.028	<0.001	<0.001	<0.001	0.015
Model 3	6.364±0.027	6.488±0.019	6.579±0.028	<0.001	0.001	<0.001	0.024
Carotid plaque							
Model 1	1.00	1.29 (1.06–1.57)	1.66 (1.31–2.10)	<0.001	0.012	<0.001	0.015
Model 2	1.00	1.17 (0.95–1.44)	1.41 (1.10–1.81)	0.025	0.144	0.007	0.077
Model 3	1.00	1.14 (0.93–1.41)	1.31 (1.02–1.69)	0.112	0.220	0.036	0.203

Data are means±standard error of mean or odds ratios (95% confidence interval).

Model 1 was adjusted for age; model 2 was adjusted for age, BMI, SBP, fasting blood glucose, total cholesterol, HDL-cholesterol, uric acid, alcohol consumption, regular exercise, and use of medications for hypertension, diabetes, and dyslipidemia; model 3 was additionally adjusted for other two carotid artery parameters in model 2.

*P value obtained by ANCOVA for CCA-IMT and CCA-Diameter, or by logistic regression for carotid plaque; †P value obtained by comparing never smokers and former smokers; ‡P value obtained by comparing never smokers and current smokers; §P value obtained by comparing former smokers and current smokers.

CCA-IMT, common carotid artery intima-media thickness; CCA-diameter, internal diameter of common carotid artery. Other abbreviations as in Table 1.

Results

Of the 2,503 subjects examined, 617 (24.7%) were never smokers, 1,288 (51.5%) were former smokers, and 598 (23.8%) were current smokers. The baseline characteristics of the study pop-

ulation according to smoking status are shown in **Table 1**. Compared to the never and former smokers, the current smokers were younger, had lower BMI, used fewer antihypertensive medications, did less regular exercise, and consumed more alcohol.

Table 3. Relationship Between Cumulative Smoking Exposure (Pack-Years) and Carotid Artery Parameters in Current Smokers

	Cumulative smoking exposure (pack-years)				P trend [§]
	0 (never smoker) (n=617)	0.1–20.0 (n=162)	20.1–40.0 (n=270)	>40.0 (n=166)	
CCA-IMT, mm					
Model 1	0.753±0.006	0.752±0.011	0.776±0.009*	0.788±0.011†	0.002
Model 2	0.749±0.006	0.758±0.011	0.780±0.009†	0.791±0.011†	<0.001
Model 3	0.750±0.006	0.758±0.011	0.779±0.009†	0.789±0.011†	0.001
CCA-diameter, mm					
Model 1	6.349±0.031	6.422±0.061	6.536±0.047†	6.594±0.060‡	<0.001
Model 2	6.321±0.028	6.510±0.054†	6.543±0.042‡	6.600±0.054‡	<0.001
Model 3	6.325±0.028	6.511±0.054†	6.538±0.042‡	6.594±0.054‡	<0.001
Carotid plaque					
Model 1	1.00	1.28 (0.90–1.83)	1.65 (1.22–2.23)†	1.79 (1.26–2.55)†	<0.001
Model 2	1.00	1.15 (0.79–1.68)	1.38 (1.00–1.91)*	1.41 (0.96–2.06)	0.024
Model 3	1.00	1.10 (0.75–1.61)	1.26 (0.91–1.74)	1.24 (0.84–1.83)	0.146

Data are means±standard error of mean or odds ratios (95% confidence interval).

Model 1 was adjusted for age; model 2 was adjusted for age, BMI, SBP, fasting blood glucose, total cholesterol, HDL-cholesterol, uric acid, alcohol consumption, regular exercise, and use of medications for hypertension, diabetes, and dyslipidemia; model 3 was additionally adjusted for the other 2 carotid artery parameters in model 2.

*P<0.05, †P<0.01, ‡P<0.001: compared with '0 pack-years' group (never smoker).

§P value for trend obtained by ANCOVA for CCA-IMT and CCA-diameter, or by logistic regression using the categories of smoking amount as a continuous variable (0–3) for carotid plaque.

Abbreviations as in Tables 1,2.

Table 4. Relationship Between Cumulative Smoking Exposure (Pack-Years) and Carotid Artery Parameters in Former Smokers

	Cumulative smoking exposure (pack-years)				P trend [§]
	0 (never smoker) (n=617)	0.1–20.0 (n=589)	20.1–40.0 (n=424)	>40.0 (n=275)	
CCA-IMT, mm					
Model 1	0.764±0.006	0.758±0.006	0.767±0.007	0.785±0.009*	0.030
Model 2	0.763±0.006	0.760±0.006	0.768±0.007	0.783±0.009*	0.031
Model 3	0.763±0.006	0.761±0.006	0.768±0.007	0.781±0.009	0.067
Model 4	0.774±0.008	0.759±0.006	0.761±0.008	0.771±0.010	0.875
CCA-diameter, mm					
Model 1	6.371±0.027	6.486±0.027†	6.525±0.032†	6.601±0.040‡	<0.001
Model 2	6.390±0.027	6.499±0.027†	6.523±0.032†	6.534±0.040†	0.003
Model 3	6.391±0.027	6.500±0.027†	6.522±0.032†	6.531±0.040†	0.004
Model 4	6.431±0.039	6.494±0.027	6.495±0.037	6.495±0.047	0.407
Carotid plaque					
Model 1	1.00	1.09 (0.86–1.37)	1.33 (1.03–1.72)*	1.81 (1.34–2.44)‡	<0.001
Model 2	1.00	1.02 (0.80–1.30)	1.19 (0.91–1.56)	1.59 (1.16–2.18)†	0.004
Model 3	1.00	1.01 (0.79–1.29)	1.17 (0.89–1.53)	1.51 (1.10–2.07)*	0.012
Model 4	1.00	0.68 (0.37–1.26)	0.79 (0.42–1.51)	1.00 (0.51–1.96)	0.114

Data are means±standard error of mean or odds ratios (95% confidence interval).

Model 1 was adjusted for age; model 2 was adjusted for age, BMI, SBP, fasting blood glucose, total cholesterol, HDL-cholesterol, uric acid, alcohol consumption, regular exercise, and use of medications for hypertension, diabetes, and dyslipidemia; model 3 was additionally adjusted for the other 2 carotid artery parameters in model 2; model 4 was additionally adjusted for years since quitting smoking in model 3.

*P<0.05, †P<0.01, ‡P<0.001: compared with '0 pack-years' group (never smokers).

§P value for trend obtained by ANCOVA for CCA-IMT and CCA-diameter, or by logistic regression using the categories of smoking amount as a continuous variable (0–3) for carotid plaque.

Abbreviations as in Tables 1,2.

The carotid artery parameters according to smoking status are presented in **Table 2**. The current smokers had a significantly greater CCA-IMT than the never and former smokers in models 2 and 3. The former and current smokers had significantly greater CCA-diameters than the never smokers in all adjusted models, and significant differences were observed

between the former and current smokers in models 2 and 3. Although the former and current smokers had a significantly higher risk of carotid plaque than the never smokers in model 1, only the current smokers had a significantly higher risk of carotid plaque in models 2 and 3.

The relationship between cumulative smoking exposure

Table 5. Relationship Between Years Since Quitting Smoking and Carotid Artery Parameters (n=1,832)

	Years since quitting smoking					P trend [§]
	Current smoker (n=598)	≤3 years (n=185)	4–10 years (n=395)	11–20 years (n=301)	≥21 years (n=353)	
CCA-IMT, mm						
Model 1	0.775±0.006	0.772±0.010	0.769±0.007	0.755±0.008*	0.747±0.008†	0.002
Model 2	0.779±0.006	0.766±0.010	0.766±0.007	0.752±0.008†	0.750±0.008†	0.004
Model 3	0.778±0.006	0.765±0.010	0.766±0.007	0.754±0.008*	0.750±0.008†	0.009
CCA-diameter, mm						
Model 1	6.526±0.032	6.560±0.057	6.529±0.039	6.431±0.045	6.532±0.042	0.375
Model 2	6.578±0.029	6.551±0.052	6.522±0.035	6.386±0.040‡	6.492±0.040	0.007
Model 3	6.574±0.029	6.550±0.052	6.523±0.035	6.390±0.040‡	6.495±0.040	0.012
Carotid plaque						
Model 1	1.00	0.99 (0.70–1.39)	0.80 (0.61–1.04)	0.68 (0.51–0.91)*	0.74 (0.56–0.99)*	0.006
Model 2	1.00	1.06 (0.74–1.52)	0.84 (0.64–1.11)	0.74 (0.55–1.01)	0.89 (0.65–1.22)	0.137
Model 3	1.00	1.09 (0.76–1.57)	0.87 (0.66–1.15)	0.80 (0.58–1.09)	0.95 (0.69–1.30)	0.300

Data are means±standard error of mean or odds ratios (95% confidence interval).

Model 1 was adjusted for age; model 2 was adjusted for age, BMI, SBP, fasting blood glucose, total cholesterol, HDL-cholesterol, uric acid, alcohol consumption, regular exercise, use of medications for hypertension, diabetes, and dyslipidemia, and pack-years of smoking; model 3 was additionally adjusted for the other 2 carotid artery parameters in model 2.

*P<0.05, †P<0.01, *P<0.001: compared with current smokers.

§P value for trend obtained by ANCOVA for CCA-IMT and CCA-diameter, or by logistic regression using the categories of smoking amount as a continuous variable (0–4) for carotid plaque.

Abbreviations as in Tables 1,2.

(pack-years) and carotid artery parameters for the current smokers is shown in [Table 3](#). Increasing trends of CCA-IMT according to pack-years of smoking were observed in models 1, 2, and 3 (P=0.002, <0.001, and 0.001, respectively). Compared to the never smokers (0 pack-years), heavy smokers with 20.1–40.0 and >40.0 pack-years had a significantly higher CCA-IMT in all models. There was a significant, dose-dependent association between pack-years of smoking and CCA-diameter in all adjusted models (P<0.001), and all smokers with 0.1–20.0, 20.1–40.0, and >40.0 pack-years had significantly higher CCA-diameters than the never smokers. The risk of carotid plaque was significantly increased with pack-years of smoking in models 1 and 2 (P<0.001 and 0.024, respectively); however, no significant trend was observed in model 3 (P trend=0.146).

The relationship between cumulative smoking exposure and carotid artery parameters for the former smokers is shown in [Table 4](#). CCA-IMT tended to increase according to pack-years of smoking in all adjusted models (P=0.030, 0.031, and 0.067, respectively). Additionally, increasing trends of CCA-diameter according to cumulative smoking exposure were observed in models 1, 2, and 3 (P<0.001, 0.003, and 0.004, respectively). A significant linear trend in the presence of carotid plaque was observed in all adjusted models (P<0.001, 0.004, and 0.012, respectively). However, after adjusting for years since quitting smoking in model 4, no significant association between pack-years of smoking and carotid artery parameters was found for the former smokers. Further stratified analyses by medication for hypertension and/or diabetes and/or dyslipidemia were examined. However, after adjustment for ‘years since quitting smoking’, no significant relationships between cumulative smoking exposure and carotid artery parameters were observed in either the medication group or the no-medication group.

The relationship between years since quitting smoking and carotid artery parameters is shown in [Table 5](#). CCA-IMT decreased with increasing years since quitting smoking in all adjusted analyses (P=0.002, 0.004, and 0.009 for models 1, 2, and 3, respectively). The adjusted CCA-IMT values for sub-

jects who had quit 11–20 and ≥21 years ago were significantly less than for the current smokers in all adjusted models. Although no significant association between smoking cessation and CCA-diameter was observed in model 1, a significant inverse correlation was found between years since quitting smoking and CCA-diameter in models 2 and 3 (P=0.007 and 0.012, respectively). The risk of carotid plaque was negatively associated with years since quitting smoking in model 1 (P=0.006); however, this correlation was not statistically significant in models 2 and 3 (P=0.137 and 0.300, respectively).

Discussion

The results of our cross-sectional study of community-dwelling Korean males indicate that cumulative cigarette smoking exposure is a significant risk factor for carotid atherosclerosis, and that smoking cessation has significant beneficial effects that can circumvent this risk.

Cigarette smoking is a major risk factor for total and cardiovascular mortality.¹⁴ It is estimated that 4.83 million premature deaths worldwide in 2000 were attributable to smoking, and that the leading cause of death from smoking was cardiovascular disease (1.69 million deaths).¹⁵ Cigarette smoking is the leading cause of preventable death in the United States,¹⁶ accounting for approximately 443,000 deaths and 5.1 million years of potential life lost annually in the United States during 2000–2004.¹⁷ Smoking increases the risk and death of ischemic heart disease by 1.4–3-fold in Japan.¹⁸ In addition, it has been reported that the 3 leading causes of death attributable to smoking are cardiovascular disease, cancer, and respiratory disease in the United States¹⁹ and China.²⁰ Compared to life-long nonsmokers, the relative risk (95% CI) of smoking for cardiovascular mortality was 1.17 (1.09–1.26) for males and 1.21 (1.10–1.34) for females in a large, prospective cohort study of a nationally representative sample of Chinese adults.²⁰ A significant dose-response association was found between the number of cigarettes smoked per day and the risk of total cardiovascular disease events in Japanese men.¹⁸

Atherosclerosis is the underlying condition leading to the increased risk of cardiovascular disease mortality, and cigarette smoking is one of the most important risk factors for atherosclerosis. Although a number of epidemiological studies have examined the association between cigarette smoking and carotid atherosclerosis in Western populations,^{4-8,11} few studies have investigated this association in Asian populations.¹⁰ Recently, Liang et al reported that smoking was associated with an increased CCA-IMT both cross-sectionally and longitudinally among Chinese middle-aged and older adults.⁹ Our results are consistent with those of previous studies showing a positive association between cigarette smoking and carotid atherosclerosis.⁴⁻¹¹ In our study, there was a significant difference between never smokers and current smokers in all carotid artery parameters. Our observations are confirmed by previous data.^{4-9,11} Moreover, we found differences in CCA-IMT and CCA-diameter between former and current smokers, suggesting that the effects of smoking on carotid artery structure are reversible. Although no significant difference in carotid IMT was found in some previous studies, suggesting that the effects of smoking are irreversible,^{21,22} a significant difference was observed in others.^{6,10,11,23} The classification of smoking status into never, former, and current smokers has been questioned because lifelong smokers who have recently stopped smoking are categorized as former smokers, whereas smokers who started smoking only a few months ago are categorized as current smokers. Thus, cumulative smoking exposure, such as pack-years, should be taken into account to properly evaluate the effects of cigarette smoking on carotid atherosclerosis. Liang et al reported a significant dose-dependent relationship between pack-years and CCA-IMT with the risk of carotid plaque.⁹ Further, Baldassarre et al found that carotid IMT was positively related to pack-years in former and current smokers.¹¹ In our study, we found a significant increasing trend between pack-years of smoking and carotid atherosclerosis in current smokers, confirming that the effects of cumulative smoking exposure on carotid artery structure are dose-dependent.²⁴⁻²⁶ However, after adjusting for years since quitting smoking, the association between pack-years of smoking and carotid artery parameters among the former smokers was not statistically significant. These results suggest that the duration of smoking cessation rather than cumulative smoking exposure might have more significant effects on carotid atherosclerosis in former smokers.

Only a few epidemiological studies have reported that the duration of smoking cessation is inversely associated with CCA-IMT and the risk of carotid plaques.^{7,10} The Guangzhou Biobank Cohort Study found a significant inverse association between the duration of smoking cessation and both carotid IMT and carotid plaque,¹⁰ suggesting that smoking cessation can delay or stop the progression of carotid atherosclerosis. In accordance with previous studies,¹⁰ smoking cessation had beneficial effects on CCA-IMT and CCA-diameter in our study, whereas no significant negative correlation was observed between years since quitting smoking and carotid plaque. Some possible explanations for these differences include variation in smoking prevalence and adjusted confounding variables across studies. In addition, carotid plaque was defined as focal structures that encroached into the lumen by at least 100% of the surrounding IMT value, whereas in a previous Chinese study they were defined as a distinct area protruding at least 1.2 mm into the lumen.¹⁰

Study Limitations

There are some limitations to our study that need to be dis-

cussed. First, our study design was cross-sectional, so we cannot make causal inferences between cigarette smoking and carotid arterial structure. However, because we are planning to perform follow-up checks of our participants, the longitudinal effects of smoking and smoking cessation on the progression of carotid atherosclerosis will be evaluated. Second, information about smoking based on a questionnaire does not always reflect actual smoking exposure; it is possible that under-reporting of smoking exists. Also, accurate information regarding secondhand smoke exposure was not collected in this study. Misclassification of smoking status and cumulative smoking exposure due to measurement error might have attenuated the relationship between cigarette smoking and carotid atherosclerosis. Third, although this study used the presence of carotid plaque as an outcome variable, more precise analyses using plaque characteristics (volume, height, and echogenicity) are needed. The use of plaque presence as an outcome might have resulted in a weak or non-significant association between cigarette smoking and carotid plaque. Fourth, unmeasured confounding variables in our study could affect the association between cigarette smoking and smoking cessation with carotid artery parameters. However, to minimize the effects of confounding variables, a number of key potential cardiovascular risk factors, including carotid artery parameters, were adjusted. Fifth, we measured office blood pressure only, not 24-h ambulatory blood pressure. Therefore, the findings that CCA-IMT and CCA-diameter decreased since quitting smoking in former smokers might only reflect the reduction of 24-h ambulatory blood pressure, not remodeling of the carotid artery.

Despite these limitations, our study has several strengths. First, a large proportion of the community-dwelling population participated in this study. Second, the measurement CCA-IMT, carotid plaque, and CCA-diameter enabled us to more precisely evaluate the effects of smoking on carotid artery structure. Third, few studies have evaluated the association between cumulative smoking exposure and the duration of smoking cessation with carotid atherosclerosis.

Conclusions

Cumulative smoking exposure in current smokers and the duration of smoking cessation in former smokers are significant risk factors for carotid atherosclerosis. Considering the high prevalence of current smokers (52.3% of males) in Korea,²⁷ these findings have important public health implications.

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