ORIGINAL RESEARCH

Smoking, Smoking Cessation, and Measures of Subclinical Atherosclerosis in Multiple Vascular Beds in Japanese Men

Takashi Hisamatsu, MD, PhD; Katsuyuki Miura, MD, PhD; Hisatomi Arima, MD, PhD; Aya Kadota, MD, PhD; Sayaka Kadowaki, MD, PhD; Sayuki Torii, MD, PhD; Sentaro Suzuki, MD; Naoko Miyagawa, PhD; Atsushi Sato; Masahiro Yamazoe, MD; Akira Fujiyoshi, MD, MPH, PhD; Takayoshi Ohkubo, MD, PhD; Takashi Yamamoto, MD, PhD; Kiyoshi Murata, MD, PhD; Robert D. Abbott, PhD; Akira Sekikawa, MD, MPH, PhD; Minoru Horie, MD, PhD; Hirotsugu Ueshima, MD, PhD; for the Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA) Research Group*

***Background*—**Smoking is an overwhelming, but preventable, risk factor for cardiovascular diseases (CVD), although smoking prevalence remains high in developed and developing countries in East Asia.

***Methods and Results*—**In a population-based sample of 1019 Japanese men aged 40 to 79 years, without CVD, we examined cross-sectional associations of smoking status, cumulative pack-years, daily consumption, and time since cessation, with subclinical atherosclerosis at 4 anatomically distinct vascular beds, including coronary artery calcification, carotid intima-media thickness (CIMT) and plaque, aortic artery calcification (AoAC), and ankle-brachial index. Current, former, and never smoking were present in 32.3%, 50.0%, and 17.7%, respectively. Compared to never smokers, current smokers had significantly higher risks of subclinical atherosclerosis in all 4 circulations (eg, odds ratios for coronary artery calcification >0, 1.79 [95% CIs, 1.16–2.79]; CIMT >1.0 mm, 1.88 [1.02–3.47]; AoAC >0, 4.29 [2.30–7.97]; and ankle-brachial index <1.1, 1.78 [1.16–2.74]) and former smokers did in carotid and aortic circulations (CIMT >1.0 mm, 1.94 [1.13–3.34]; and AoAC >0, 2.55 [1.45–4.49]). Dose–response relationships of pack-years and daily consumption, particularly with CIMT, carotid plaque, AoAC, and ankle-brachial index, were observed among both current and former smokers, and even a small amount of pack-years or daily consumption among current smokers was associated with coronary artery calcification and AoAC, whereas time since cessation among former smokers was linearly associated with lower burdens of all atherosclerotic indices.

***Conclusions*—**Cigarette smoking was strongly associated with subclinical atherosclerosis in multiple vascular beds in Japanese men, and these associations attenuated with time since cessation. **(*J Am Heart Assoc*. 2016;5:e003738 doi: 10.1161/JAHA.116.003738)**

Key Words: atherosclerosis • coronary artery calcification • cumulative pack-years exposure • prevention • smoking • smoking cessation

Smoking remains the number 1 preventable cause of death worldwide, and it contributes significantly to cardiovascular diseases (CVD).[1] Despite a recent decline in smoking rates in Western industrialized countries, tobacco use is still very high in developing Asian countries as well as in industrialized ones, including Japan, with ≈30% of the male population lighting up.[1] Among many contributors for CVD, smoking is one of the leading avoidable causes, and therefore advancing a tobacco-free world is a key strategic priority in preventive medicine.

The evidence linking smoking exposure with various CVD, including myocardial infarction, stroke, and aortic and

From the Department of Environmental Medicine and Public Health, Faculty of Medicine, Shimane University, Izumo, Japan (T.H.); Departments of Public Health (T.H., K. Miura, H.A., A.K., S.K., S.T., S.S., N.M., A. Sato, M.Y., A.F., H.U.), Cardiovascular and Respiratory Medicine (T.H., S.T., T.Y., M.H.), and Radiology (K. Murata) and Center for Epidemiologic Research in Asia (K. Miura, A.K., R.D.A., H.U.), Shiga University of Medical Science, Otsu, Japan; Department of Preventive Medicine and Public Health, Faculty of Medicine, Fukuoka University, Fukuoka, Japan (H.A.); Department of Hygiene and Public Health, Teikyo University School of Medicine, Tokyo, Japan (T.O.); Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, PA (A. Sekikawa).

Accompanying Tables S1 through S4 are available at http://jaha.ahajournals.org/content/5/9/e003738/DC1/embed/inline-supplementary-material-1.pdf

*A complete list of the SESSA Research Group members can be found in the Appendix at the end of the article.

Correspondence to: Takashi Hisamatsu, MD, PhD, Department of Environmental Medicine and Public Health, Faculty of Medicine, Shimane University, 89-1 Enya-cho, Izumo, Shimane 693-8501, Japan. E-mail: hisataka@med.shimane-u.ac.jp

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peripheral vascular diseases, is clearly present, although the mechanisms accounting for these associations have not been fully elucidated.[2] Atherosclerosis is considered to be a critical player in the pathophysiology of smoking-induced CVD,[2] and these adverse effects would be reduced by smoking cessation.[3] Accordingly, in the view of public health and clinical resources, determining which measures of subclinical atherosclerosis are most influenced by smoking, and whether any of the relationship between smoking and these subclinical measures decrease with longer time since smoking cessation is of utmost importance.

Precise and valid measures of subclinical atherosclerosis are available for coronary, carotid, aortic, and peripheral circulations; however, few population-based studies have assessed the associations of both smoking and smoking cessation with subclinical atherosclerosis,[4,5] and no studies, to date, have examined the association of smoking and smoking cessation with subclinical atherosclerosis in all 4 circulations.

In a general sample of Japanese men with a high smoking burden, but low atherosclerotic risk,[6–8] we aimed to cross-sectionally investigate the influence of smoking on these 4 anatomically distinct vascular beds, using coronary artery calcification (CAC), carotid intima-media thickness (CIMT) and plaque, aortic artery calcification (AoAC), and ankle-brachial index (ABI), by examining the following: (1) the strength of association between smoking status and each vascular bed; (2) whether there are dose-response relationships with cumulative smoking exposure by pack-years and with smoking intensity by daily cigarette consumption in these associations; and (3) whether these associations attenuate with length of time since smoking cessation in former smokers.

Methods

Study Participants and Measurements

The Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA) is an ongoing prospective, population-based study of a random sample from a general Japanese population as described elsewhere.[9,10] Participants eligible for the present study were 1094 men aged 40 to 79 years enrolled at baseline (May 2006–March 2008) in the SESSA. After excluding 75 participants with a history of myocardial infarction or stroke (n=66) and with missing information (n=9), including variables related to smoking, a total of 1019 participants were analyzed in the present study. Of the 1019 participants, 987 underwent carotid ultrasound examination to assess CIMT and plaque. The present study was approved by the Institutional Review Board of Shiga University of Medical Science (No. 17–19, 17–83; Otsu, Japan), and all participants provided written informed consent.

A self-administered questionnaire was used to obtain information on demography, smoking habits, alcohol drinking, physical activity, socioeconomic status, medication use (hypertension, dyslipidemia, and diabetes mellitus), and medical history. After the participants completed the questionnaires, trained nurses confirmed them with the participants. Smoking status was categorized into 3 groups: current, former, and never smokers. Participants who smoked in the last 30 days were defined as current smokers, whereas participants who had never smoked before were defined as never smokers. Based on the information, daily cigarette consumption was calculated in former and current smokers. Pack-years were estimated by multiplying the average number of packs smoked daily by the number of smoking years. Time since smoking cessation was calculated by subtracting age at cessation from age at the baseline survey.

Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Using an automated sphygmomanometer (BP-8800; Omron Health Care Co. Ltd, Tokyo, Japan), the mean of 2 consecutive measurements on the right arm with participants in a seated position after a 5-minute rest were used to determine blood pressure. Diabetes mellitus was defined as a hemoglobin A1c $\geq$6.1% (per the Japan Diabetes Society protocol; equivalent to $\geq$6.5% in the National Glycohemoglobin Standardization Program),[11] a fasting blood glucose $\geq$126 mg/dL, or the use of antidiabetic medications. Total cholesterol and triglycerides were measured using enzymatic assays, and high-density lipoprotein (HDL) cholesterol (HDL-C) was determined using a direct method. Low-density lipoprotein cholesterol was estimated using Friedewald's formula[12] in the 1003 participants with triglycerides <400 mg/dL. Lipid measurements were standardized according to the protocol for the US Centers for Disease Control and Prevention/Cholesterol Reference Method Laboratory Network. C-reactive protein (CRP) was measured by nephelometry using a BN II Analyzer with a threshold of 0.16 mg/L. Alcohol intake was estimated as the total weekly amount of alcohol consumption (g/week). Participants who exercised were defined as those who regularly did either brisk walking or more-active exercise $\geq$1 h/week.[13,14]

Assessment of Subclinical Atherosclerosis

We assessed CAC and AoAC either by electron-beam computed tomography (EBCT) using a C-150 scanner (Imatron, South San Francisco, CA) or 16-channel multidetector-row computed tomography (MDCT) using an Aquilion scanner (Toshiba, Tokyo, Japan).[9,15] EBCT and MDCT images accounted for 69.8% and 30.2%, respectively, of coronary and aortic scans. Images were obtained from the level of the aortic root through the heart every 3-mm slice to evaluate CAC and from the aortic arch to the iliac bifurcation every

6-mm slice to evaluate AoAC, with a scan time of 100 (EBCT) or 320 ms (MDCT). Presence of CAC and AoAC was defined as a minimum of 3 contiguous pixels (area=1 mm^2) with a density of ≥130 HU using the AcculmageAccul software (Accul-mage Diagnostics, South San Francisco, CA). One trained physician interpreted coronary and aortic scanning using the widely accepted Agatston method.[16] The physician was blinded to the participants' characteristics. Protocols for CAC and AoAC measurement were developed from a separate cohort study by our research group,[17] in which the repro-ducibility of coronary and aortic scans was very high (intraclass correlations of 0.99 and 0.98, respectively).[18] Because a stratified analysis by computed tomography (CT) type showed similar results, images by EBCT and MDCT were considered equivalent. Other studies have also reported comparable findings for CAC and AoAC assessment by EBCT and MDCT.[19,20]

As previously described,[10,21] high-resolution B-mode ultra-sound (Xario-660A; Toshiba Medical Systems, Tokyo, Japan) was used to scan both right and left carotid arteries with a 7.5-MHz probe according to a standardized method estab-lished by the Ultrasound Research Laboratory of University of Pittsburgh (Pittsburgh, PA).[22] Images from the following segments were digitized: both near and far walls of common carotid arteries (CCA; 1 cm proximal to the carotid bulb); far wall of the bulb; and far wall of the internal carotid arteries (ICAs; 1 cm distal to the bulb). Intima-media thickness in each image was traced with an automatic image-reading program (AMS; Chalmers University of Technology, Gothenburg, Swe-den). Mean CIMT comprised the mean of all averages across the 8 locations (4 in each artery) from CCAs, bulb, and ICAs.[10,21] Carotid plaque was defined as a focal thickening lesion (≥50% protrusion compared to adjacent areas) with CIMT >1 mm.[21] The total number of plaques in CCAs, bulb, and ICAs on both left and right sides was counted.

ABI was estimated separately for each leg, with the numerator being the higher of the dorsalis pedis or posterior tibial systolic pressures in each leg and the denominator being the higher of the right versus left brachial systolic pressures, using an automatic waveform analyzer (Form I PWV/ABI; Omron Health Care Co. Ltd, Tokyo, Japan), while participants were in a supine position after a 5-minute rest.[10] The select ABI for participants was the smaller of the right versus left ABI.

Statistical Analysis

Characteristics were analyzed according to smoking status. Differences in characteristics were evaluated using the ANOVA, χ^2 test, or Kruskal–Wallis test. All outcomes were analyzed in a cross-sectional fashion. For dichotomous outcomes, including CAC, AoAC, CIMT, and ABI, logistic regression was used. Cut-off points for CAC were defined as CAC score >0, ≥100, and ≥400 according to their clinical significance and consistency with previous studies.[23,24] Similarly, AoAC was defined as AoAC score >0, ≥100,[18,25,26] and ≥1000; CIMT was defined as CIMT >1.0 mm; and ABI was defined as ABI <1.1.[27–29] Because of the low prevalence of ABI <1.0 (n=44 [4%]), this cut-off point was not chosen. For carotid plaque, because the distribution showed overdispersion, negative binomial regres-sion was used. In all analyses, the adjusted model included age, BMI, systolic blood pressure, total cholesterol, HDL-C, medication for hypertension and dyslipidemia (yes/no), diabetes mellitus (yes/no), alcohol intake (g/week), exercise (yes/no), and CRP. CT type was further included concomi-tantly when CAC and AoAC were analyzed. Further adjust-ment for occupation status and education years did not substantially affect the findings, and therefore these variables were not included in the model. For cumulative exposure or intensity analyses, the associations of measures of subclinical atherosclerosis with tertiles of pack-years or daily cigarette consumption were estimated in both former and current smokers compared to never smokers. For smoking cessation analyses, the association of subclinical atherosclerosis with tertiles of time since cessation was estimated in former smokers compared to current smokers. Similarly, cessation analyses were conducted compared to never smokers. As a sensitivity analysis, daily cigarette consumption was taken into account in the adjusted model for smoking cessation analyses. Tertiles were used for pack-years, daily cigarette consumption, and time since cessation because (1) there are no established cut-off points for these measures; (2) these measures were not normally distributed (their distribution were likely to be right-skewed); and (3) a sufficient sample size was obtained in each group. Tests for trend across categories were also based on assigning median value for each category of pack-years, cigarettes smoked daily, and years since quitting and modeling this variable as a contin-uous variable. Analyses were performed using SPSS (version 22.0; SPSS, Inc., Chicago, IL) and SAS software (version 9.4; SAS Institute Inc., Cary, NC). Two-tailed P values of <0.05 were considered statistically significant.

Results

Of the 1019 participants, 329 (32.3%) were current, 509 (50.0%) were former, and 181 (17.7%) were never smokers. Character-istics based on smoking status are shown in Table 1. Current smokers were younger and had lower levels of systolic blood pressure and HDL-C, a higher level of CRP, less medication for hypertension, higher alcohol intake, less exercise, and a lower unemployment rate than former or never smokers.

Compared to never smokers, both former and current smokers had higher burdens of CIMT (adjusted odds ratio

Table 1. Characteristics of Participants According to Smoking Status in 1019 Men Aged 40 to 79 Years (SESSA, Shiga, Japan, 2006–2008)

	Smoking Status		
	Never (n=181)	Former (n=509)	Current (n=329)
Age, y	63.7 (10.2)	65.4 (9.5)	60.8 (9.7)*†
BMI, kg/m^2	23.7 (2.8)	23.5 (3.0)	23.4 (3.1)
Systolic blood pressure, mm Hg	135.4 (17.2)	138.0 (19.7)	134.0 (18.5)†
Diastolic blood pressure, mm Hg	79.8 (9.7)	80.3 (11.3)	78.8 (11.1)
Diabetes mellitus, %	21.0	19.8	23.1
Total cholesterol, mg/dL	207.6 (33.8)	209.3 (32.2)	208.8 (35.4)
High-density lipoprotein cholesterol, mg/dL	59.9 (17.0)	60.2 (17.5)	56.0 (15.7)*†
Low-density lipoprotein cholesterol, mg/dL‡	125.0 (30.7)	125.5 (29.5)	125.4 (34.6)
Medication for hypertension, %	27.6	33.8	21.6†
Medication for dyslipidemia, %	17.1	13.4	10.0
Alcohol intake, g/week	105.9 (167.1)	165.9 (179.4)§	196.0 (218.8)*
Exercise, %	45.9	51.5	28.9*†
Occupation status, %			
Self-employed including agriculture	12.2	12.0	17.3
Company employees	45.3	41.1	48.3
Unemployed	32.0	38.5	25.8†
Others	10.5	8.4	8.6
Education years, y	12.5 (3.2)	12.5 (3.2)	12.3 (2.9)
CRP, mg/L	0.37 (0.17, 0.65)	0.43 (0.23, 0.90)§	0.49 (0.25, 1.11)*
Pack-years exposure	NA	25.0 (11.3, 42.3)	38.7 (24.3, 51.8)†
Daily cigarettes/day	NA	20 (15, 30)	20 (15, 25)

Values are expressed as mean (standard deviation), median (25th, 75th), or percentage. Differences in characteristics were evaluated using the analysis of variance, χ^2 test, or Kruskal–Wallis test. BMI indicates body mass index; CRP, C-reactive protein; NA, not applicable; SESSA, Shiga Epidemiological Study of Subclinical Atherosclerosis.
*P<0.01 between never and current smokers.
†P<0.01 between former and current smokers.
‡Estimated using Friedewald's formula in 1003 (never, 179; former, 503; current, 321) men with triglycerides <400 mg/dL.
§P<0.01 between never and former smokers.

[OR] for CIMT >1.0 mm, 1.94; 95% CI, 1.13–3.34, and 1.88; 95% CI, 1.02–3.47, respectively), carotid plaque (adjusted ratio of expected counts, 1.30; 95% CI, 1.10–1.53, and 1.40; 95% CI, 1.17–1.67, respectively), and AoAC (eg, adjusted OR for AoAC >0, 2.55; 95% CI, 1.45–4.49, and 4.29; 95% CI, 2.30–7.97, respectively; Table 2). Current smoking, but not former smoking, was also significantly associated with a higher level of CAC (eg, adjusted OR for CAC ≥400, 2.64; 95% CI, 1.20–5.79) and lower level of ABI (adjusted OR for ABI <1.1, 1.78; 95% CI, 1.16–2.74) compared to never smoking (Table 2).

Graded associations were observed between cumulative smoking exposure by pack-years and subclinical atherosclerosis, including CIMT, carotid plaque, CAC >0, ABI, and all indices of AoAC in current smokers (all P for trend <0.05; Table 2), whereas increases in ORs for CAC ≥100 and ≥400 were not statistically significant with higher pack-year cumulative exposure among current smokers. Similar results were observed among former smokers (Table S1). Even the lowest pack-years among current smokers was also significantly associated with CAC ≥100, ≥400, and all indices of AoAC as compared to never smokers (Table 2). Similar findings were observed in smoking intensity analyses by daily cigarette consumption in both current and former smokers (Table S2).

Compared to current smokers, burdens of subclinical atherosclerosis in all 4 circulations linearly decreased among former smokers with length of time since cessation (all P for trend, <0.05; Table 3). These reductions became significant at ≥10.4 cessation years for CAC >0, AoAC >0 and ≥100, and at ≥24.4 cessation years for carotid plaque, CAC ≥100, ≥400, ABI, and AoAC ≥1000. After further adjustment for daily cigarette consumption in addition to the adjusted model, the associations of time since cessation with atherosclerotic

Table 2. Association of Smoking Status and Cumulative Smoking Exposure by Pack-Years With Measures of Subclinical Atherosclerosis in Carotid, Coronary, Aortic, and Peripheral Vascular Beds in 1019 Men Aged 40 to 79 Years (SESSA, Shiga, Japan, 2006–2008)

	Smoking Status			Pack-Years in Current Smokers			
	Never (n=181)	Former (n=509)	Current (n=329)	<29.1 (n=109)	29.1 to 46.7 (n=110)	≥46.8 (n=110)	*P* for Trend
CIMT >1.0 mm, n (%)*	22 (12.6)	105 (21.1)	45 (14.3)	10 (9.6)	12 (11.5)	23 (21.5)	
OR	1 (Ref)	1.94 (1.13–3.34)†	1.88 (1.02–3.47)†	1.46 (0.62–3.47)	1.54 (0.67–3.54)	2.47 (1.21–5.05)†	0.024
Carotid plaque, median (25th, 75th)*	2 (0, 3)	2 (1, 4)	2 (0, 4)	1 (0, 3)	2 (0, 4)	3 (1, 5)	
Ratio of expected counts	1 (Ref)	1.30 (1.10–1.53)‡	1.40 (1.17–1.67)§	1.06 (0.84–1.34)	1.45 (1.16–1.80)‡	1.67 (1.35–2.06)§	<0.001
CAC >0, n (%)	108 (59.7)	332 (65.2)	211 (64.1)	56 (51.4)	73 (66.4)	82 (74.5)	
OR	1 (Ref)	1.13 (0.75–1.69)	1.79 (1.16–2.79)‡	1.30 (0.74–2.29)	2.05 (1.17–3.60)†	2.16 (1.20–3.89)†	0.006
CAC ≥100, n (%)	34 (18.8)	124 (24.4)	81 (24.6)	22 (20.2)	27 (24.5)	32 (29.1)	
OR	1 (Ref)	1.33 (0.83–2.13)	2.06 (1.23–3.45)‡	2.15 (1.09–4.23)†	2.18 (1.14–4.18)†	1.89 (1.01–3.53)†	0.117
CAC ≥400, n (%)	11 (6.1)	46 (9.0)	36 (10.9)	10 (9.2)	11 (10.0)	15 (13.6)	
OR	1 (Ref)	1.45 (0.70–3.03)	2.64 (1.20–5.79)†	3.07 (1.14–8.27)†	2.61 (0.98–6.93)	2.43 (0.98–6.01)	0.155
ABI <1.1, n (%)	45 (24.9)	166 (32.6)	120 (36.5)	35 (32.1)	36 (32.7)	49 (44.5)	
OR	1 (Ref)	1.36 (0.92–2.03)	1.78 (1.16–2.74)‡	1.58 (0.91–2.73)	1.53 (0.89–2.65)	2.29 (1.35–3.90)‡	0.002
AoAC >0, n (%)	132 (72.9)	442 (86.8)	276 (83.9)	80 (73.4)	96 (87.3)	100 (90.9)	
OR	1 (Ref)	2.55 (1.45–4.49)‡	4.29 (2.30–7.97)§	3.64 (1.69–7.88)‡	5.21 (2.33–11.64)§	3.90 (1.61–9.44)‡	<0.001
AoAC ≥100, n (%)	98 (54.1)	348 (68.4)	217 (66.0)	58 (53.2)	73 (66.4)	86 (78.2)	
OR	1 (Ref)	1.81 (1.16–2.82)‡	3.50 (2.10–5.82)§	2.89 (1.49–5.62)‡	3.73 (1.99–7.00)§	3.97 (2.02–7.84)§	<0.001
AoAC ≥1000, n (%)	30 (16.6)	171 (33.6)	103 (31.3)	25 (22.9)	34 (30.9)	44 (40.0)	
OR	1 (Ref)	2.61 (1.58–4.30)§	4.02 (2.31–6.99)§	3.20 (1.55–6.59)‡	4.75 (2.40–9.41)§	4.14 (2.15–7.99)§	<0.001

Pack-years groups were categorized according to tertiles of pack-years in current smokers. All values are expressed as ORs and ratios of expected counts with 95% CIs. For dichotomous outcomes, logistic regression was used. For carotid plaque, negative binomial regression was used. Adjusted covariates included age, body mass index, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, medication for hypertension and dyslipidemia (yes/no), diabetes mellitus (yes/no), alcohol intake (g/week), exercise (yes/no), and C-reactive protein. The CT type was further included concomitantly when CAC and AoAC were analyzed. ABI indicates ankle-brachial index; AoAC, aorta artery calcification; CAC, coronary artery calcification; CIMT, carotid intima-media thickness; OR, odds ratio; SESSA, Shiga Epidemiological Study of Subclinical Atherosclerosis.
*A total of 987 (never, 174; former, 498; current, 315 [pack-years <29.1, 104; 29.1–46.7, 104; ≥46.8, 107]) men underwent measurement of carotid atherosclerosis.
†$P<0.05$; ‡$P<0.01$; §$P<0.001$.

burdens in all 4 circulations were somewhat attenuated, but still statistically significant except for that with CIMT (Table S3). Additionally, by 24.4 years for CIMT, carotid plaque, and AoAC, by 10.4 years for ABI, and even less than 10.4 years for CAC, ORs or ratios of expected counts were not statistically different for former smokers compared to never smokers (Table S4).

Discussion

In this community-based, cross-sectional study of Japanese men without apparent CVD, of which about 30% are current and 50% are former smokers, significant associations were observed between current smoking and subclinical atherosclerosis in all 4 vascular beds, including coronary, carotid, aortic, and peripheral arteries, and between former smoking and that in carotid and aortic arteries. These associations, particularly with carotid, aortic, and peripheral atherosclerosis, also became stronger with increasing cumulative exposure and intensity of smoking in both former and current smokers compared to never smokers. Even the lowest amount of pack-years or cigarettes smoked daily among current smokers was associated with CAC, particularly CAC ≥100 or ≥400, and AoAC. Furthermore, longer time since smoking cessation was associated with lower degrees of atherosclerosis in all 4 circulations in former smokers, with somewhat differences among anatomically distinct sites.

Our results support past demonstrations with respect to the adverse effect of smoking in multiple vascular beds, including CAC. McEvoy et al showed that among participants aged 45–84 years with a smoking rate of 14% and a cessation rate of 38% in the Multi-Ethnic Study of Atherosclerosis

Table 3. Association of Smoking Cessation Interval With Subclinical Atherosclerosis in Carotid, Coronary, Aortic, and Peripheral Vascular Beds in 1019 Men Aged 40 to 79 Years (SESSA, Shiga, Japan, 2006–2008)

		Cessation Interval in Former Smokers				
	Current (n=329)	<10.4 Years (n=169)	10.4 to 24.3 Years (n=170)	≥24.4 Years (n=170)	Never (n=181)	*P* for Trend
CIMT >1.0 mm, n (%)*	45 (14.3)	32 (19.4)	40 (24.0)	33 (19.9)	22 (12.6)	
OR	1 (Ref)	1.10 (0.63–1.91)	1.23 (0.72–2.10)	0.81 (0.46–1.41)	0.53 (0.29–0.98)†	0.013
Carotid plaque, median (25th, 75th)*	2 (0, 4)	2 (1, 4)	2 (1, 4)	2 (1, 4)	2 (0, 3)	
Ratio of expected counts	1 (Ref)	1.08 (0.92–1.27)	0.89 (0.75–1.05)	0.81 (0.68–0.96)†	0.71 (0.59–0.84)§	<0.001
CAC >0, n (%)	211 (64.1)	112 (66.3)	108 (63.5)	112 (65.9)	108 (59.7)	
OR	1 (Ref)	0.84 (0.53–1.32)	0.54 (0.34–0.86)‡	0.52 (0.33–0.82)‡	0.55 (0.35–0.85)‡	0.005
CAC ≥100, n (%)	81 (24.6)	40 (23.7)	42 (24.7)	42 (24.7)	34 (18.8)	
OR	1 (Ref)	0.71 (0.44–1.17)	0.65 (0.40–1.06)	0.58 (0.35–0.95)†	0.48 (0.29–0.81)‡	0.008
CAC ≥400, n (%)	36 (10.9)	15 (8.9)	21 (12.4)	10 (5.9)	11 (6.1)	
OR	1 (Ref)	0.59 (0.29–1.18)	0.80 (0.42–1.52)	0.29 (0.13–0.66)‡	0.37 (0.17–0.82)†	0.008
ABI <1.1, n (%)	120 (36.5)	63 (37.3)	54 (31.8)	49 (28.8)	45 (24.9)	
OR	1 (Ref)	0.99 (0.66–1.48)	0.71 (0.47–1.08)	0.60 (0.39–0.93)†	0.55 (0.36–0.85)‡	0.002
AoAC >0, n (%)	276 (83.9)	145 (85.8)	145 (85.3)	152 (89.4)	132 (72.9)	
OR	1 (Ref)	1.05 (0.53–2.11)	0.48 (0.23–0.98)†	0.33 (0.16–0.67)‡	0.21 (0.11–0.41)§	<0.001
AoAC ≥100, n (%)	217 (66.0)	119 (70.4)	119 (70.0)	110 (64.7)	98 (54.1)	
OR	1 (Ref)	0.97 (0.56–1.67)	0.55 (0.32–0.95)†	0.25 (0.15–0.43)§	0.26 (0.16–0.44)§	<0.001
AoAC ≥1000, n (%)	103 (31.3)	57 (33.7)	69 (40.6)	45 (26.5)	30 (16.6)	
OR	1 (Ref)	0.78 (0.48–1.26)	0.92 (0.57–1.48)	0.37 (0.22–0.61)§	0.24 (0.14–0.42)§	<0.001

The reference category is current smokers. Cessation interval groups were categorized according to tertiles of years since smoking cessation. All values are expressed as ORs and ratios of expected counts with 95% CIs. For dichotomous outcomes, logistic regression was used. For carotid plaque, negative binomial regression was used. Adjusted covariates included age, body mass index, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, medication for hypertension and dyslipidemia (yes/no), diabetes mellitus (yes/no), alcohol intake (g/week), exercise (yes/no), and C-reactive protein. The CT type was further included concomitantly when CAC and AoAC were analyzed. ABI indicates ankle-brachial index; AoAC, aorta artery calcification; CAC, coronary artery calcification; CIMT, carotid intima-media thickness; OR, odds ratio; SESSA, Shiga Epidemiological Study of Subclinical Atherosclerosis.
*A total of 987 (current, 315; former, 498 [cessation interval <10.4 years, 165; 10.4–24.3 years, 167; ≥24.4 years, 166]; never, 174) men underwent measurement of carotid atherosclerosis.
†$P<0.05$; ‡$P<0.01$; §$P<0.001$.

(MESA), current and former smoking were associated with subclinical atherosclerosis at 3 anatomically distinct sites, including CAC, CIMT, and ABI.[5] A significant relationship of current or former smoking to CAC has also been previously reported from other cohorts.[4,30–32] Similarly, CIMT[33–36] and AoAC[18] findings associated with smoking have been confirmed in previous studies. Our findings of CAC, CIMT, AoAC, and ABI related to smoking in a Japanese population in addition to these pieces of past evidence in the Western ones indicate that both current and former smoking is strongly associated with subclinical atherosclerosis in multiple vascular beds.

The present study revealed significant dose-response relationships between cumulative exposure and intensity of smoking and carotid, aortic, and peripheral atherosclerosis in both current and former smokers. MESA examined the relationships, resulting in almost null associations of measures of subclinical atherosclerosis with pack-years smoking, particularly in current smokers.[5] This inconsistency between studies may be explained by the fact that the relative impact of cumulative smoking exposure for atherosclerosis was not evaluated, compared to never smokers, in MESA.[5] Another reason for the discrepancy between studies may be because of the difference in the study sample demographics, such as smoking rate, pack-years exposure, and atherosclerotic distribution. For example, cumulative pack-years exposure among current smokers in the present study seems to be higher than that in MESA.[5] The higher pack-years exposure in the present study could contribute to increased risks of atherosclerosis among current smokers, particularly in the highest group of pack-years. For the present study, significant dose–response relationships were not also confirmed in the associations particularly with CAC, although almost all ORs for CAC among current smokers were statistically significant even in the lowest groups of cumulative exposure and intensity, suggesting that cumulative exposure and intensity of smoking may not be important, but current smoking

behavior itself may be harmful for coronary atherosclerosis. To our knowledge, only 2 studies, including our study,[5] have investigated the dose-response relationship with cumulative pack-years exposure for atherosclerosis, including CAC, whereas, according to another MESA report,[37] cumulative pack-years among current smokers was an important determinant of CVD. Therefore, further research is necessary to confirm these associations in other populations and identify mechanisms underlying these inconsistencies among studies.

The present study is one of the first to comprehensively reveal the association between smoking cessation and subclinical atherosclerosis, including all 4 vascular beds. The associations of smoking with CAC, CIMT, and ABI decreased with time since quitting in former smokers in MESA.[5] A similar result between smoking cessation and CAC was also observed in a German population-based study.[4] Given that the present study is cross-sectional, our findings of lower odds for subclinical atherosclerosis with longer time since quitting do not represent that these risks are decreasing over time in former smokers, rather that the accumulation of these markers slows down after smoking cessation. Thus, a shorter interval from cessation and a higher pack-year total could be associated with increased atherosclerotic burdens in former smokers. Additionally, the present analyses, which were performed on time since cessation, do not address how long after quitting smoking cardiovascular health returns to the state of never smokers. Importantly, however, we extend the past knowledge by demonstrating linear reductions on atherosclerotic burdens in all 4 vascular beds with length of time since smoking cessation, even though with some differences among vascular sites and with slight attenuation after further adjusting for amount of smoking.

Our study has several limitations. The study design was cross-sectional. Therefore, causal and longitudinal relationships were not addressed. However, cumulative pack-years exposure and time since cessation themselves provide information in the past to present; thus, these time frames would support the causality. Also, smoking parameters were based on self-report, rather than an objective marker, such as cotinine, which could lead to the underestimation of the true associations. Third, although we carefully controlled for the major known confounders, our findings may, in part, be explained by differences in unknown confounders. Finally, because only Japanese men were included for analyses, our results are restricted to men of a single ethnic group. However, population homogeneity reduces possible confounding from cultural and environmental variation.

In conclusion, in a community-based sample of Japanese men without clinical CVD, the present study demonstrated strong associations with subclinical atherosclerosis in multiple vascular beds among both current and former smokers, with dose-dependent relationships with cumulative exposure or intensity. These harmful associations also attenuated with time since smoking cessation. The subclinical atherosclerosis in carotid, coronary, aortic, and peripheral arteries are all strong predictors for CVD.[38–41] Therefore, the new findings in Japanese men, with high rates of smoking and smoking cessation, support evidence for the negative impact of smoking and benefit for CVD prevention by smoking cessation as early as possible and provide important implications for the tobacco regulatory science on cardiovascular health worldwide.

Appendix

Members of the SESSA Research Group

Chairperson: Hirotsugu Ueshima (Center for Epidemiologic Research in Asia, Department of Public Health, Shiga University of Medical Science, Otsu, Shiga).

Co-chairpersons: Katsuyuki Miura (Department of Public Health, Shiga University of Medical Science, Otsu, Shiga).

Research members: Minoru Horie, Yasutaka Nakano, Takashi Yamamoto (Department of Cardiovascular and Respiratory Medicine, Shiga University of Medical Science, Otsu, Shiga), Emiko Ogawa (Health Administration Center, Shiga University of Medical Science, Otsu, Shiga), Hiroshi Maegawa, Itsuko Miyazawa (Division of Endocrinology and Metabolism, Department of Medicine, Shiga University of Medical Science, Otsu, Shiga), Kiyoshi Murata (Department of Radiology, Shiga University of Medical Science, Otsu, Shiga), Kenichi Mitsunami (Shiga University of Medical Science, Otsu, Shiga), Kazuhiko Nozaki (Department of Neurosurgery, Shiga University of Medical Science, Otsu, Shiga), Akihiko Shiino (Biomedical MR Science Center, Shiga University of Medical Science, Otsu, Shiga), Isao Araki (Kusatsu Public Health Center, Kusatsu, Shiga), Teruhiko Tsuru (Department of Urology, Shiga University of Medical Science, Otsu, Shiga), Ikuo Toyama (Unit for Neuropathology and Diagnostics, Molecular Neuroscience Research Center, Shiga University of Medical Science, Otsu, Shiga), Hisakazu Ogita, Souichi Kurita (Division of Medical Biochemistry, Department of Biochemistry and Molecular Biology, Shiga University of Medical Science, Otsu, Shiga), Toshinaga Maeda (Central Research Laboratory, Shiga University of Medical Science, Otsu, Shiga), Naomi Miyamatsu (Department of Clinical Nursing Science Lecture, Shiga University of Medical Science, Otsu, Shiga), Toru Kita (Kobe City Medical Center General Hospital, Kobe, Hyogo), Takeshi Kimura (Department of Cardiovascular Medicine, Kyoto University, Kyoto), Yoshihiko Nishio (Department of Diabetes, Metabolism, and Endocrinology, Kagoshima University, Kagoshima), Yasuyuki Nakamura (Department of Food Science and Human Nutrition, Faculty of Agriculture, Ryukoku University, Otsu, Shiga), Tomonori Okamura (Department of Preventive

Medicine and Public Health, School of Medicine, Keio University, Tokyo), Akira Sekikawa, Emma J.M. Barinas-Mitchell (Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA), Daniel Edmundowicz (Department of Medicine, Section of Cardiology, School of Medicine, Temple University, Philadelphia, PA, USA), Takayoshi Ohkubo (Department of Hygiene and Public Health, Teikyo University School of Medicine, Tokyo), Atsushi Hozawa (Preventive Medicine, Epidemiology Section, Tohoku University, Tohoku Medical Megabank Organization, Sendai, Miyagi), Nagako Okuda (Department of Health and Nutrition, University of Human Arts and Sciences, Saitama), Aya Higashiyama (Research and Development Initiative Center, National Cerebral and Cardiovascular Center, Suita, Osaka), Shinya Nagasawa (Department of Epidemiology and Public Health, Kanazawa Medical University, Kanazawa, Ishikawa), Yoshikuni Kita (Faculty of Nursing Science, Tsuruga Nursing University, Tsuruga, Fukui), Yoshitaka Murakami (Division of Medical Statistics, Department of Social Medicine, Toho University, Tokyo), Aya Kadota (Center for Epidemiologic Research in Asia, Department of Public Health, Shiga University of Medical Science, Otsu, Shiga), Akira Fujiyoshi, Naoyuki Takashima, Takashi Kadowaki, Sayaka Kadowaki (Department of Public Health, Shiga University of Medical Science, Otsu, Shiga), Robert D. Abbott, Seiko Ohno (Center for Epidemiologic Research in Asia, Shiga University of Medical Science, Otsu, Shiga), Hisatomi Arima (Department of Preventive Medicine and Public Health, Faculty of Medicine, Fukuoka University, Fukuoka), Takashi Hisamatsu (Department of Environmental Medicine and Public Health, Faculty of Medicine, Shimane University, Izumo, Shimane), Naoko Miyagawa, Keiko Kondo, Sayuki Torii, Yoshino Saito, Maryam Zaid, Sentaro Suzuki, Takahiro Ito, Masahiro Yamazoe, Takeshi Shibukawa, and Masaki Sumi (Department of Public Health, Shiga University of Medical Science, Otsu, Shiga).

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Association of cumulative smoking exposure by pack-years with subclinical atherosclerosis in the carotid, coronary, aortic, and peripheral vascular beds in 509 former smokers (SESSA, Shiga, Japan, 2006–2008)

	Never	Pack-years in former smokers			*P* for trend
	(n = 181)	<16.1 (n = 171)	16.1–36.2 (n = 169)	≥36.3 (n = 169)	
CIMT >1.0 mm, n (%)§	22 (12.6)	20 (11.9)	40 (24.2)	45 (27.3)	
OR	1 (ref)	1.27 (0.63–2.54)	2.2 (1.18–4.10)*	2.28 (1.24–4.21)†	0.003
Carotid plaque, median (25th, 75th)§	2 (0, 3)	1 (0, 3)	2 (1, 4)	3 (2, 5)	
Ratio of expected counts	1 (ref)	1.02 (0.84–1.25)	1.31 (1.08–1.58)†	1.57 (1.30–1.88)‡	<0.001
CAC >0, n (%)	108 (59.7)	96 (56.1)	110 (65.1)	126 (74.6)	
OR	1 (ref)	1.00 (0.61–1.62)	1.07 (0.65–1.75)	1.37 (0.82–2.28)	0.175

CAC ≥100, n (%)	34 (18.8)	28 (16.4)	47 (27.8)	49 (29.0)	
OR	1 (ref)	1.06 (0.58–1.94)	1.49 (0.85–2.60)	1.41 (0.82–2.44)	0.149
CAC ≥400, n (%)	11 (6.1)	8 (4.7)	16 (9.5)	22 (13.0)	
OR	1 (ref)	1.04 (0.39–2.82)	1.32 (0.56–3.11)	1.89 (0.83–4.30)	0.048
ABI <1.1, n (%)	45 (24.9)	46 (26.9)	53 (31.4)	67 (39.6)	
OR	1 (ref)	1.15 (0.7–1.87)	1.26 (0.78–2.03)	1.76 (1.09–2.82)*	0.013
AoAC >0, n (%)	132 (72.9)	134 (78.4)	146 (86.4)	162 (95.9)	
OR	1 (ref)	1.84 (0.95–3.56)	2.36 (1.13–4.93)*	5.57 (2.16–14.39)‡	<0.001
AoAC ≥100, n (%)	98 (54.1)	83 (48.5)	119 (70.4)	146 (86.4)	
OR	1 (ref)	0.88 (0.52–1.49)	1.96 (1.12–3.46)*	4.44 (2.37–8.30)‡	<0.001
AoAC ≥1000, n (%)	30 (16.6)	33 (19.3)	56 (33.1)	82 (48.5)	
OR	1 (ref)	1.58 (0.85–2.95)	2.18 (1.21–3.92)†	4.38 (2.48–7.75)‡	<0.001

Pack-years groups were categorized according to tertiles of pack-years in former smokers. All abbreviations are shown in Table 2. All values are expressed as ORs and ratios of expected counts with 95% confidence intervals. For dichotomous outcomes, logistic regression was used. For carotid plaque, negative binomial regression was used. Adjusted covariates are shown in Table 2.

*P <0.05; †P <0.01, ‡P <0.001.

§987 (never, 174; former, 498 [pack-years <16.1, 168; 16.1–36.2, 165; ≥36.3, 165]) men underwent measurement of carotid atherosclerosis.

Table S2. Association of smoking intensity by daily cigarette consumption with subclinical atherosclerosis in the carotid, coronary, aortic, and peripheral vascular beds in 1019 men (SESSA, Shiga, Japan, 2006–2008)

	Never (n = 181)	Daily cigarette consumption in former smokers				Daily cigarette consumption in current smokers			
		<20 (n = 167)	20 (n = 194)	≥21 (n = 148)	*P* for trend	<16 (n = 111)	16–20 (n= 123)	≥21 (n = 95)	*P* for trend
CIMT >1.0 mm, n (%)§	22 (12.6)	34 (20.7)	40 (21.3)	31 (21.2)		15 (14.4)	15 (12.7)	15 (16.1)	
OR	1 (ref)	1.64 (0.87–3.11)	2.18 (1.17–4.06)*	2.04 (1.06–3.95)*	0.019	1.55 (0.71–3.36)	1.74 (0.80–3.79)	2.76 (1.23–6.20)*	0.016
Carotid plaque, median (25th, 75th)§	2 (0, 3)	2 (1, 3)	2 (1, 4)	2 (1, 5)		1 (0, 4)	2 (0, 4)	2 (1, 4)	
Ratio of expected counts	1 (ref)	1.03 (0.85–1.26)	1.33 (1.11–1.60)†	1.57 (1.29–1.90)‡	<0.001	1.23 (0.98–1.53)	1.41 (1.13–1.75)†	1.67 (1.33–2.09)‡	<0.001

CAC >0, n (%)	108 (59.7)	108 (64.7)	121 (62.4)	103 (69.6)		74 (66.7)	75 (61.0)	62 (65.3)	
OR	1 (ref)	1.03 (0.62–1.71)	1.04 (0.65–1.68)	1.38 (0.82–2.31)	0.335	1.85 (1.04–3.27)*	1.65 (0.96–2.84)	1.98 (1.09–3.59)*	0.028
CAC ≥100, n (%)	34 (18.8)	38 (22.8)	49 (25.3)	37 (25.0)		31 (27.9)	27 (22.0)	23 (24.2)	
OR	1 (ref)	1.12 (0.63–1.99)	1.46 (0.85–2.52)	1.42 (0.79–2.54)	0.144	2.18 (1.17–4.08)*	1.88 (0.99–3.56)	2.18 (1.09–4.36)*	0.103
CAC ≥400, n (%)	11 (6.1)	10 (6.0)	20 (10.3)	16 (10.8)		14 (12.6)	11 (8.9)	11 (11.6)	
OR	1 (ref)	0.88 (0.34–2.25)	1.71 (0.75–3.93)	1.84 (0.77–4.39)	0.055	2.86 (1.14–7.13)*	2.21 (0.84–5.82)	2.99 (1.11–8.09)*	0.084
ABI <1.1, n (%)	45 (24.9)	52 (31.1)	56 (28.9)	58 (39.2)		39 (35.1)	50 (40.7)	31 (32.6)	
OR	1 (ref)	1.20	1.19	1.83	0.032	1.60	2.20	1.57	0.025

		(0.74–1.96)	(0.75–1.91)	(1.12–2.99)*		(0.94–2.74)	(1.31–3.70)†	(0.88–2.80)	
AoAC >0, n (%)	132 (72.9)	139 (83.2)	168 (86.6)	135 (91.2)		92 (82.9)	103 (83.7)	81 (85.3)	
OR	1 (ref)	1.46 (0.71–3.00)	2.55 (1.26–5.13)†	5.05 (2.18–11.67)‡	<0.001	3.82 (1.66–8.79)†	4.15 (1.93–8.90)‡	5.40 (2.31–12.63)‡	<0.001
AoAC ≥100, n (%)	98 (54.1)	103 (61.7)	129 (66.5)	116 (78.4)		73 (65.8)	82 (66.7)	62 (65.3)	
OR	1 (ref)	0.95 (0.55–1.66)	1.69 (0.99–2.89)	4.44 (2.36–8.34)‡	<0.001	2.91 (1.49–5.68)†	4.27 (2.25–8.10)‡	4.22 (2.10–8.47)‡	<0.001
AoAC ≥1000, n (%)	30 (16.6)	46 (27.5)	71 (36.6)	54 (36.5)		34 (30.6)	42 (34.1)	27 (28.4)	
OR	1 (ref)	1.57 (0.86–2.86)	3.39 (1.92–6.00)‡	3.31 (1.80–6.07)‡	<0.001	2.95 (1.51–5.76)†	6.04 (3.08–11.83)‡	4.02 (1.91–8.45)‡	<0.001

Groups were divided according to tertiles of daily cigarette consumption in each smoker. All abbreviations are shown in Table 2. All values are expressed as ORs and ratios of expected counts with 95% confidence intervals. For dichotomous outcomes, logistic regression was used. For carotid plaque, negative binomial regression was used. Adjusted covariates are shown in Table 2.

*P <0.05; †P <0.01, ‡P <0.001.

§987 (never, 174; former, 498 [daily cigarette consumption <20, 164; 20, 188; ≥21, 146]; current, 315 [daily cigarette consumption <16, 104; 16–20, 118; ≥21, 93]) men underwent measurement of carotid atherosclerosis.

Table S3. Association of smoking cessation interval with subclinical atherosclerosis in carotid, coronary, aortic, and peripheral vascular beds in 1019 men aged 40–79 years (SESSA, Shiga, Japan, 2006–2008)

	Current	Cessation interval in former smokers			Never (n = 181)	*P* for trend
	(n = 329)	<10.4 years (n = 169)	10.4–24.3 years (n = 170)	≥24.4 years (n = 170)		
CIMT >1.0 mm, n (%)§	45 (14.3)	32 (19.4)	40 (24.0)	33 (19.9)	22 (12.6)	
OR	1 (ref)	1.06 (0.61–1.86)	1.17 (0.68–2.02)	0.82 (0.47–1.43)	0.62 (0.31–1.24)	0.143
Carotid plaque, median (25th, 75th)§	2 (0, 4)	2 (1, 4)	2 (1, 4)	2 (1, 4)	2 (0, 3)	
Ratio of expected counts	1 (ref)	1.03 (0.88–1.21)	0.84 (0.71–0.99)*	0.82 (0.69–0.97)*	0.86 (0.72–1.05)	0.046
CAC >0, n (%)	211 (64.1)	112 (66.3)	108 (63.5)	112 (65.9)	108 (59.7)	
OR	1 (ref)	0.82 (0.52–1.29)	0.54 (0.34–0.85)†	0.53 (0.33–0.83)†	0.61 (0.36–1.04)	0.020

CAC ≥100, n (%)	81 (24.6)	40 (23.7)	42 (24.7)	42 (24.7)	34 (18.8)	
OR	1 (ref)	0.71 (0.43–1.17)	0.65 (0.39–1.07)	0.58 (0.35–0.95)*	0.49 (0.27–0.88)*	0.012
CAC ≥400, n (%)	36 (10.9)	15 (8.9)	21 (12.4)	10 (5.9)	11 (6.1)	
OR	1 (ref)	0.58 (0.28–1.17)	0.78 (0.40–1.52)	0.29 (0.13–0.67)†	0.39 (0.16–0.97)*	0.016
ABI <1.1, n (%)	120 (36.5)	63 (37.3)	54 (31.8)	49 (28.8)	45 (24.9)	
OR	1 (ref)	0.97 (0.65–1.45)	0.70 (0.46–1.06)	0.61 (0.40–0.94)*	0.62 (0.37–1.03)	0.016
AoAC >0, n (%)	276 (83.9)	145 (85.8)	145 (85.3)	152 (89.4)	132 (72.9)	
OR	1 (ref)	0.95 (0.47–1.94)	0.48 (0.23–0.99)*	0.37 (0.18–0.76)†	0.43 (0.19–0.97)*	0.017
AoAC ≥100, n (%)	217 (66.0)	119 (70.4)	119 (70.0)	110 (64.7)	98 (54.1)	
OR	1 (ref)	0.86 (0.49–1.50)	0.51 (0.29–0.88)*	0.27 (0.16–0.46)†	0.44 (0.23–0.82)*	<0.001
AoAC ≥1000, n (%)	103 (31.3)	57 (33.7)	69 (40.6)	45 (26.5)	30 (16.6)	
OR	1 (ref)	0.74 (0.45–1.22)	0.87 (0.54–1.42)	0.37 (0.23–0.62)‡	0.29 (0.15–0.55)‡	<0.001

The reference category is current smokers. Cessation interval groups were categorized according to tertiles of years since smoking cessation. All abbreviations are shown in Table 2. All values are expressed as ORs and ratios of expected counts with 95% confidence intervals. The statistical analyses are shown in Table 2. Adjusted covariates included age, body mass index, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, medication for hypertension and dyslipidemia (yes/no), diabetes mellitus (yes/no), alcohol intake (g/week), exercise (yes/no), C-reactive protein, and daily cigarette consumption (for current smokers, daily amount of smoking; for former smokers, daily amount of prior smoking). The CT type was further included concomitantly when CAC and AoAC were analyzed.

*P <0.05; †P <0.01, ‡P <0.001.

§987 (current, 315; former, 498 [cessation interval <10.4 years, 165; 10.4–24.3 years, 167; ≥24.4 years, 166]; never, 174) men underwent measurement of carotid atherosclerosis.

Table S4. Association of smoking cessation interval with subclinical atherosclerosis in the carotid, coronary, aortic, and peripheral vascular beds in 509 former smokers (SESSA, Shiga, Japan, 2006–2008)

	Never	Cessation interval in former smokers			*P* for
		≥24.4 years	10.4–24.3 years	<10.4 years	
	(n = 181)	(n = 170)	(n = 170)	(n = 169)	trend
CIMT >1.0 mm, n (%)§	22 (12.6)	33 (19.9)	40 (24.0)	32 (19.4)	
OR	1 (ref)	1.53 (0.81–2.90)	2.32 (1.24–4.34)†	2.08 (1.08–3.98)*	0.013
Carotid plaque, median (25th, 75th)§	2 (0, 3)	2 (1, 4)	2 (1, 4)	2 (1, 4)	
Ratio of expected counts	1 (ref)	1.14 (0.94–1.39)	1.25 (1.03–1.52)*	1.53 (1.26–1.85)‡	<0.001
CAC >0, n (%)	108 (59.7)	112 (65.5)	108 (63.5)	112 (66.3)	
OR	1 (ref)	0.94 (0.58–1.55)	0.99 (0.60–1.63)	1.53 (0.92–2.53)	0.005

CAC ≥100, n (%)	34 (18.8)	34 (18.8)	42 (24.7)	42 (24.7)	
OR	1 (ref)	1.20 (0.69–2.10)	1.35 (0.77–2.36)	1.48 (0.83–2.62)	0.008
CAC ≥400, n (%)	11 (6.1)	10 (5.9)	21 (12.4)	15 (8.9)	
OR	1 (ref)	0.79 (0.31–2.04)	2.15 (0.94–4.91)	1.58 (0.65–3.79)	0.008
ABI <1.1, n (%)	45 (24.9)	49 (28.8)	54 (31.8)	63 (37.3)	
OR	1 (ref)	1.09 (0.67–1.77)	1.29 (0.80–2.09)	1.80 (1.12–2.90)*	0.002
AoAC >0, n (%)	132 (72.9)	152 (89.4)	145 (85.3)	145 (85.8)	
OR	1 (ref)	1.51 (0.74–3.10)	2.23 (1.06–4.70)†	4.90 (2.27–10.59)‡	<0.001
AoAC ≥100, n (%)	98 (54.1)	110 (64.7)	119 (70.0)	119 (70.4)	
OR	1 (ref)	0.96 (0.56–1.63)	2.10 (1.18–3.72)†	3.69 (2.02–6.75)‡	<0.001
AoAC ≥1000, n (%)	30 (16.6)	45 (26.5)	69 (40.6)	57 (33.7)	
OR	1 (ref)	1.51 (0.84–2.73)	3.77 (2.11–6.73)‡	3.18 (1.75–5.77)‡	<0.001

The reference category is never smokers. Cessation interval groups were categorized according to tertiles of years since smoking cessation. All abbreviations are shown in Table 2. All values are expressed as ORs and ratios of expected counts with 95% confidence intervals. For dichotomous outcomes, logistic regression was used. For carotid plaque, negative binomial regression was used. Adjusted covariates are shown in Table 2.

*P <0.05; †P <0.01, ‡P <0.001.

§987 (never, 174; 498 [cessation interval ≥24.4 years, 166; 10.4–24.3 years, 167; <10.4 years, 165]) men underwent measurement of carotid atherosclerosis.