Smoking habits and progression of coronary and aortic artery calcification: A 5-year follow-up of community-dwelling Japanese men.

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ABSTRACT

***Background and aims*:** To examine whether smoking habits, including smoking amount and cessation duration at baseline, are associated with atherosclerosis progression.

***Methods*:** At baseline (2006-08, Japan), we obtained smoking status, amount of smoking and time since cessation for quitters in a community-based random sample of Japanese men initially aged 40-79 years and free of cardiovascular disease. Coronary artery calcification (CAC) and aortic artery calcification (AAC) as biomarker of atherosclerosis was quantified using Agatston's method at baseline and after 5 years of follow-up. We defined progression of CAC and AAC (yes/no) using modified criteria by Berry.

Results: A total of 781 participants was analyzed. Multivariable adjusted odds ratios (ORs) of CAC and AAC progression for current smokers were 1.73 (95% CI, 1.09−2.73) and 2.47 (1.38−4.44), respectively, as compared to never smokers. In dose-response analyses, we observed a graded positive relationship of smoking amount and CAC progression in current smokers (multivariable adjusted ORs: 1.23, 1.72, and 2.42 from the lowest to the highest tertile of pack-years). Among the former smokers, earlier quitters (≥10.7 years) had similar ORs of the progression of CAC and AAC to that of participants who had never smoked.

Conclusions: Compared with never smokers, current smokers especially those with greater pack-years at baseline had higher risk of atherosclerosis progression in community-dwelling Japanese men. Importantly, the residual adverse effect appears to be present for at least ten years after smoking cessation. The findings highlight the importance of early avoidance or minimizing smoking exposure for the prevention of atherosclerotic disease.

Key Words: atherosclerosis, coronary artery calcification, aortic artery calcification, smoking, prevention, smoking cessation

INTRODUCTION

Cigarette smoking is a major preventable risk factor for cardiovascular diseases (CVD). Recent estimates reported that approximately 29.6% of Japanese men smoke, although the rates of smoking have declined since 1960s, and this proportion is higher than those of Western populations [1, 2]. The adverse effects of smoking continuation relative to smoking cessation on CVD risk have been reported [3, 4]. However, it is still unclear how smoking amount and duration of cessation affect the progression of atherosclerosis, a process which silently leads to CVD events. This investigation is important for consolidating evidence with hard outcomes for emphasizing prevention in earlier stages of CVD.

Some earlier studies have sought to cross-sectionally evaluate the effect of smoking and smoking cessation on prevalence of coronary artery calcification (CAC), a robust measure of coronary atherosclerosis [5-11]. In the current study, we aimed to examine whether smoking habits, including amount of smoking and duration of cessation (for quitters) at baseline, are associated with progression of coronary and aortic artery calcification in a 5-year follow-up of community-dwelling Japanese men.

METHODS

Study population

The Shiga Epidemiological Study of Subclinical Atherosclerosis study (SESSA) is a study of subclinical atherosclerosis and its determinants on a community-based sample of Japanese residents. Details as described previously [12, 13]. In brief, between 2006 and 2008, we randomly selected and invited 2379 Japanese men aged 40 to 79 years who were residents of Kusatsu City, Shiga, based on the Basic Residents' Register of the city. The Register contains information on name, sex, birth date, and address of residents. A total of 1094 men agreed to participate (The participation rate was 46%). All the participants provided informed consent and the study has been approved by the Institutional Review Board of Shiga University of Medical Science.

Data on medical history, use of medications, smoking, and other lifestyle factors were collected from each participant using a self-administered questionnaire. Trained technicians confirmed the completed questionnaire with participants.

Follow-up

Participants in the baseline survey were then recruited for a follow-up examination between 2010 and 2014. A total of 853 participants completed both the baseline and the follow-up diagnostic imaging exam [14]. We excluded participants with missing data on AAC score due to incomplete slice coverage of the aorta, smoking status at baseline and participants with history of stroke, myocardial infraction, or revascularization at baseline. Consequently, 781 men were analyzed.

Ascertainment of smoking habits

All the variables pertinent to smoking was based on self-report obtained at baseline [13]. Such variables include smoking status (never, former, current), cumulative smoking exposure (pack-years of smoking) and cessation interval (among former smoker). Current smokers were participants who smoked in the last 30 days, whereas former smokers were those with past history of smoking but no consumption of cigarettes within the previous 30 days. Participants who had never smoked were defined as never smokers. Pack-years are the daily dose (in 20 cigarettes per day) multiplied by the duration of smoking (in years). Time since smoking cessation was calculated by subtracting age at cessation from age at baseline.

Ascertainment of atherosclerosis

Atherosclerosis was assessed by radiographic detection of calcific deposits in the coronary artery and aortic artery. At the baseline, each participant was scanned once by either electron-beam computed tomography (EBCT) using a C-150 scanner (Imatron South San Francisco, CA, USA) or 16-channel multi-detector row computed tomography (MDCT) using an Aquilion scanner (Toshiba, Tokyo, Japan).

In follow-up, all participants were scanned by 64-channel MDCT. The detailed methodology for acquisition and interpretation of the scans has been described [5, 14]. In brief, images of every 3 mm level from the level of the root of the aorta through the heart were used for measurement of CAC; and every 6 mm level from the aortic arch to the iliac bifurcation were used for measurement of AAC. A focus of calcification score was defined as the presence of minimum of three contiguous pixels (area = 1 mm^2) with density >130 Hounsfield units (HU) using a DICOM workstation and AccuImage software (AccuImage Diagnostics, South San Francisco, CA, USA), then CAC and AAC score was calculated according to the Agatston method [15].

Atherosclerosis progression in our study is included development and progression of atherosclerosis. We defined CAC progression (yes/no) using modified criteria by Berry [16] as follows: for those with CAC = 0 at baseline, defined as CAC ≥10 at follow-up; for those with 0<CAC <100 at baseline, defined as annualized change of ≥10 Agatston units at follow-up; for those with CAC ≥100 at baseline, defined as annualized percentage change of ≥10% at follow-up. Due to only one time imaging at each exam, we used a threshold of CAC ≥10 for those with CAC = 0 at baseline, instead of >0 in the original definition of Berry [16, 17]. Although AAC progression was not well defined in previous studies, we used a strategy similar to the definition of CAC progression. As AAC is approximately a factor of 10 times higher than the CAC, we defined AAC progression as follows, for those with AAC = 0 at baseline, defined as AAC ≥100 at follow-up; for those with 0< AAC <1000 at baseline, defined as annualized change of ≥100 Agatston units at follow-up; for those with AAC ≥1000 at baseline, defined as annualized percentage change of ≥10% at follow-up.

Ascertainment of covariates

A self-administered questionnaire was used to obtain sociodemographic information such as age, sex, exercise and alcohol consumption, occupation status, education years and other health histories. The average of two blood pressure measurements in the right arm of the seated participant after the

participant emptied their bladder for urinalysis and sat quietly for 5 minutes, using an automated sphygmomanometer with an appropriately-sized cuff was used. We defined hypertension, as use of antihypertensive or systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg. Height and weight were measured without shoes. Body mass index (BMI) was defined as weight (kg) divided by square of height (m). Serum total cholesterol (TC), triglycerides (TG) and plasma glucose from a 12-h fasting blood sample were measured using enzymatic assays, and high-density lipoprotein cholesterol (HDL-c) was determined using a direct method. Low-density lipoprotein cholesterol (LDL-c) was estimated using Friedewald's formula for participants with TG < 400 mg/dL: LDL-c (mg/dL) = TC (mg/dL) − HDL-c (mg/dL) − TG (mg/dL)/5 [18]. For those with TG≥400mg/dL, we treated their LDL-c as missing. Dyslipidemia was defined as TG ≥150 mg/dL or HDL-c <40 mg/dL or use of medication [19]. Hemoglobin A1c (HbA1c) was measured by latex agglutination immunoassay according to the Japan Diabetes Society protocol (JDS). Then the value of HbA1c was converted from HbA1c (JDS) to HbA1c by the National Glycohemoglobin Standardization Program (NGSP) using the following formula: NGSP (%) = 1.02 x JDS (%) + 0.25% [20]. Diabetes mellitus was defined as use of medication or fasting plasma glucose ≥126 mg/dL or HbA1c (NGSP) ≥6.5%.

Statistical analyses

Characteristics of the study participants and participants without follow-up were presented as mean ± standard deviation (SD) or median (25th, 75th) for continuous variables, and as percentages for categorical variables as appropriate. Differences in characteristics were evaluated using 1-way ANOVA or Kruskal–Wallis tests for continuous variables; and $\chi 2$ or Fisher exact tests for categorical variables across categories of smoking status.

Using binary logistic regression, we first obtained odds ratios (ORs) of progression of CAC and AAC according to smoking habits (never, former, current) at baseline. In second analysis, we divided current smokers into tertiles according to pack-years of smoking, and former smokers into tertiles according

to duration of cessation. Tertiles were used for pack-years and duration of cessation because of (1) no well-established cut-off points for these non-normally distributed measures; and (2) a sufficient sample size for each group. We obtained ORs of progression of CAC or that of AAC for each subgroup to examine dose-responses in reference to never smokers. We used the following three models: crude, age-adjusted and multivariable adjusted model which adjusted for age, dyslipidemia (yes/no), hypertension (yes/no), diabetes mellitus (yes/no), body max index, exercise (yes/no), and alcohol intake (g/week). All covariates were based on the information at baseline and were available for all participants. Interaction analyses between smoking status and covariates for risk of CAC or AAC progression were included (data not shown). We repeated the analyses of CAC progression using original definition of Berry [16]. All statistical studies were conducted with the SAS software version 9.4 (SAS Institute, Cary, North Carolina). A 2-tailed p value of $p \leq 0.05$ was considered significant.

RESULTS

Characteristics of the study participants

In our study, follow-up rate was 78%. The baseline characteristics of the study population according to smoking habits at baseline (n = 781) are displayed in Table 1. The average age was 64 years with mean follow-up of 5.0 years. Never smokers comprised 146 (18.7%), former smokers 393 (50.3%), and current smokers 242 (31.0%) of the study participants at baseline. Current smokers were younger and more likely to be company employees. They consumed more alcohol, had a lower blood pressure and high frequency of diabetes mellitus than former and never smokers. Former smokers were older, and had high levels of blood pressure, TC, LDL-c. Age, SBP, HDL-c, TG, education years, C-reactive protein, number of cigarettes per day, pack-years of smoking, percentage of anti-hypertensive medication and dyslipidemia medication were significantly different between smoking status categories.

Current smoking associated with atherosclerosis progression

Table 2 shows ORs of CAC and AAC progression according to smoking status at baseline. In multivariable analyses controlling for age, and other CVD risk factors, current smoker had 73% higher odds of CAC progression and 147% higher odds of AAC progression, compared with never smoker. All ORs tended to be attenuated after adjusting for covariates. In dose-response analyses, we observed a graded positive relationship of cumulative smoking exposure by pack-years with CAC progression (multivariable adjusted ORs: 1.23, 1.72, and 2.42 from the lowest to the highest tertile of pack-years) but not with AAC progression (Figure 1, Supplementary Table 1 and 2). There were no interactions between smoking and other covariates.

Smoking cessation

As shown in Table 2, in a multivariable adjusted model, former smokers had higher odds of either CAC or AAC progression but the relationships were not statistically significant. Among former smokers, recent quitters (<10.7 years) had 133% higher odds of AAC compared with never smoker (Figure 1, Supplementary Table 2). Otherwise, former smokers with longer duration of cessation (≥10.7 years) did not have higher odds of AAC compared with never smokers. We noted a similar pattern of results for CAC progression but the odds for recent quitters were elevated only in crude and age-adjusted models (Figure 1, Supplementary Table 1).

For progression of CAC, we also performed analyses with original definition of Berry, but the results were similar (Supplementary Table 3).

DISCUSSION

Smoking and atherosclerosis progression

This study is one of the first longitudinal evidences in a general population free of CVD showing a dose-dependent relationship between tobacco use and cessation on atherosclerosis progression in coronary arteries and the aorta. Our study shows several important findings. First, continued cigarette smokers, despite their age, had overall progression of CAC and AAC about 2 times as high as that among otherwise similar persons who had never smoked. Moreover, the increase magnitude of effect in heavy smoking highlights a biological gradient of smoking in the causal relationship with atherosclerosis. Finally, our study adds to prior literature by demonstrating that smoking cessation, irrespective of the number of previous pack-years, could reduce the progression of atherosclerosis, but a residual effect on AAC appears to be present for at least 10 years after cessation.

Our results support previous findings from epidemiological studies on the relationship of smoking and atherosclerosis [21, 22]. All of those studies examined progression of subclinical atherosclerosis at two anatomically distinct sites: CAC, and carotid intima-media thickness, but not AAC. The first longitudinal study reporting effect of continued or past smoking on CAC progression was based on a Danish trial [22]. Although, these sub-analyses did not consider cessation time of former smokers at baseline, the conclusion on the dose-response effects of smoking continuation in long-term smokers with regard to subclinical CVD was concordant. Our findings are also in line with a previous cross-sectional study based on this population [5], and others reporting the significant association of cigarette smoking with prevalence of CAC and AAC [6-11].

In pathophysiological perspective, artery calcification is categorized into two types: atherosclerotic and medial artery calcification. The mechanisms by which smoking induces artery calcification were reported to be related to atherosclerosis occurring in the intima. Enhanced secretion of inflammatory cytokines and elevated lipid content within atherosclerotic lesions leads to osteogenic differentiation of vascular smooth muscle cells [23]. CAC and AAC as surrogate markers of atherosclerosis were

found to be independent predictors of CVD events and all-cause mortality in individuals with no previous history of CVD [24-26]. Moreover, progression of CAC has been reported to be associated with future CVD events [27]. To manage lifetime risks of CVD events, sensitive biomarkers for stratification and prediction of treatment response are needed. The dose relationship of smoking relative to smoking cessation with presence and progression of CAC or AAC demonstrate the potential utility of these biomarkers in early detection and management of CVD risk.

Conversely, smoking cessation has been shown to return levels of inflammatory cytokines to levels comparable to those of non-smokers [28], and to reverse all-cause mortality including CVD risk [3, 4]. Previous studies on either general or high risk male populations have described the variation from 3 to 10 years in speed of risk-reduction after cessation [29-33]. Given stratified analyses of quitting time, our study results suggest that it takes more than ten years after smoking cessation for an individual's level of sub-clinical atherosclerosis to return to a level comparable to that of never smokers. Even though attempting smoking cessation is associated with an early reduction in risk of hard outcome, our study emphasizes on long-term maintenance of smoking cessation in order to avoid the residual effects. Despite the recent declining trend of cigarette smoking in developed Western nations, smoking rates in developing Asian countries still remain high [34]. This might be due to the lack of efforts on public awareness on health consequences of cigarette smoking in those countries. Using subclinical outcomes, our findings, as well as those from other recent studies on CVD incidence and mortality [3], highlight the importance of early and continued smoking cessation. In the present study, the association of smoking with CAC and AAC progression attenuated after full adjustment in all models, which suggests that other factors such as diabetes mellitus, and alcohol consumption also have strong associations with CAC and AAC progression.

Limitations and Strengths

There are some important limitations in this study. First, the current study was conducted only in men, hence the results may not be applicable to women. Second, information of smoking parameters and

adjusting covariates were only based on self-reports at baseline. It should be noted that the association in this study was estimated by calculating OR, which are surrogate for relative risk and should not be misunderstood as such. We also cannot dismiss the possibility that the relatively small sample size in our study is the cause for not finding significant interactions with covariates. Additionally, artery calcification at the baseline was assessed by either EBCT or MDCT, while all participants were scanned by MDCT in follow-up. The technique differences in image acquisition between EBCT and MDCT may lead to interscan variability [35]. Finally, we were unable to examine non-calcified plaque in the current study, thus limiting our ability to detect early atherosclerosis [36]. The strengths of our study include a randomly-selected sample to minimize bias and well-standardized measurements of relevant parameters including CAC, AAC and other laboratory data.

CONCLUSIONS

Compared to never smokers, current smokers (especially those with greater pack-years at baseline) had greater risk of progression of atherosclerosis in a community-based sample of men. Importantly, the residual adverse effect on coronary artery and aorta appears to be present for at least ten years after smoking cessation. The findings highlight the importance of avoiding or minimizing smoking exposure for the prevention of subclinical cardiovascular disease.

CONFLICT OF INTEREST

We do not have conflicts of interest to disclose.

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Table 1. Baseline characteristics of 781 male participants aged 40–79 years (SESSA, Shiga, Japan, 2006–2008 at baseline and 2010–2014 at follow-up)

Baseline characteristic	Study participants according to smoking status at baseline				
	Total (n = 781)	Never (n = 146)	Former (n = 393)	Current (n = 242)	*P* value
Age, years	63.8 ± 9.5	64.3 ± 9.8	65.4 ± 9.0	60.8 ± 9.5	<0.01
Body mass index, kg/m^2	23.5 ± 2.9	23.8 ± 2.7	23.5 ± 2.9	23.5 ± 3.1	0.49
Systolic blood pressure, mmHg	135.7 ± 18.4	135.3 ± 17.6	137.5 ± 18.8	133.2 ± 17.9	0.02
Diastolic blood pressure, mmHg	79.9 ± 11.0	80.0 ± 9.8	80.5 ± 11.6	78.7 ± 10.7	0.15
Diabetes mellitus, %	18.6	16.4	17.6	21.5	0.33
Total cholesterol, mg/dL	210.3 ± 32.9	209.3 (33.4)	211.3 ± 31.3	209.2 ± 35.2	0.69
HDL cholesterol, mg/dL	59.1 ± 17.0	59.9 (15.8)	60.8 ± 17.9	55.8 ± 15.7	<0.01
LDL cholesterol, mg/dL	126.4 ± 30.9	126.6 (30.5)	126.9 ± 28.7	125.3 ± 34.6	0.81
Triglycerides, mg/dL	106.0 (77.0, 150.0)	97.0 (69.0, 141.0)	101.0 (74.0, 142.0)	127.5 (86.0,167.0)	<0.01
Medication for hypertension, %	28.2	26.0	33.8	20.1	<0.01
Medication for dyslipidemia, %	13.2	17.8	13.5	9.9	0.09
Alcohol intake, g/week	98.0 (7.0, 258.6)	29.3 (0.0, 151.9)	99.1 (12.5, 256.4)	149.2 (12.3, 322.6)	<0.01
Exercise, %	45.6	45.2	54.7	31.0	<0.01
Occupation status, %					0.20
Self-employed, agriculture	13.4	11.6	12.8	15.4	
Company employees	44.4	42.5	41.8	49.8	
Unemployed	32.7	34.3	35.7	27.0	
Others	9.5	11.6	9.7	7.9	
Education years, year	12.8 ± 2.4	13.2 ± 2.4	12.5 ± 2.5	12.5 ± 2.3	0.03
C-reactive protein, mg/L	0.4 (0.2, 0.9)	0.4 (0.2, 0.6)	0.4 (0.2, 0.9)	0.5 (0.2, 1.0)	<0.01
Number of cigarettes per day	NA	NA	20.0 (15.0, 30,0)	20.0 (15.0, 25,0)	<0.01
Pack-years of smoking	NA	NA	25.0 (12.0, 42.0)	38.7 (23.7, 50.9)	<0.01

Values are expressed as mean ± standard deviation, median (25th, 75th), or percentage. Body mass index was defined as weight (kg) divided by square of height (m). Differences in characteristics were evaluated using the analysis of variance, $\chi 2$ test, or Kruskal–Wallis test.

HDL, high-density lipoprotein ; LDL, low-density lipoprotein ; CAC, coronary artery calcification; AAC, Aorta Artery calcification. Diabetes mellitus was defined as either fasting glucose ≥126 mg/dL or HbA1c (NGSP) ≥6.5%, or medication use.

Table 2 Odds ratios of having CAC and AAC progression by smoking status at baseline in 781 men aged 40-79 years (SESSA, Shiga, Japan, 2006–2008 at baseline and 2010–2014 at follow-up)

Smoking status at baseline	No. of participants	No. of CAC progression (%)	Odd ratios of having CAC progression (95% CI)			No. of AAC progression (%)	Odd ratios of having AAC progression (95% CI)		
			Crude	Age adjusted	Multivariable adjusted		Crude	Age adjusted	Multivariable adjusted
Never	146	49 (33.6)	1 (Ref)	1 (Ref)	1 (Ref)	21 (14.4)	1 (Ref)	1 (Ref)	1 (Ref)
Former smoker	393	157 (40.0)	1.32 (0.89−1.96)	1.28 (0.85−1.91)	1.22 (0.80−1.84)	97 (24.7)	1.95 (1.16−3.27) [a]	1.90 (1.12−3.20) [a]	1.64 (0.95−2.81)
Current smoker	242	107 (44.2)	1.57 (1.02−2.41) [a]	1.82 (1.17−2.82) [a]	1.73 (1.09−2.73) [a]	64 (26.5)	2.14 (1.24−3.69) [b]	2.67 (1.52−4.68) [b]	2.47 (1.38−4.44) [b]

Multivariable adjusted model was adjusted for age, dyslipidemia (yes/no), hypertension (yes/no), diabetes mellitus (yes/no), body max index, exercise (yes/no), and alcohol intake (g/week).

CAC, coronary artery calcification; AAC, Aorta Artery calcification; CI, confidence interval.

Progression of coronary artery calcification was defined as follows, for those with CACS = 0 at baseline, defined as CAC ≥10 at follow-up; for those with 0< CAC <100 at baseline, defined as annualized change of ≥10 Agatston units at follow-up; for those with CAC ≥100 at baseline, defined as annualized percentage change of ≥ 10% at follow-up.

Progression of aorta calcification was defined as follows, for those with AAC =0 at baseline, defined as AAC ≥100 at follow-up; for those with 0< AAC <1000 at baseline, defined as annualized change of ≥ 100 Agatston units at follow-up; for those with AAC ≥1000 at baseline, defined as annualized percentage change of ≥10% at follow-up.

P value a <0.05; b <0.01

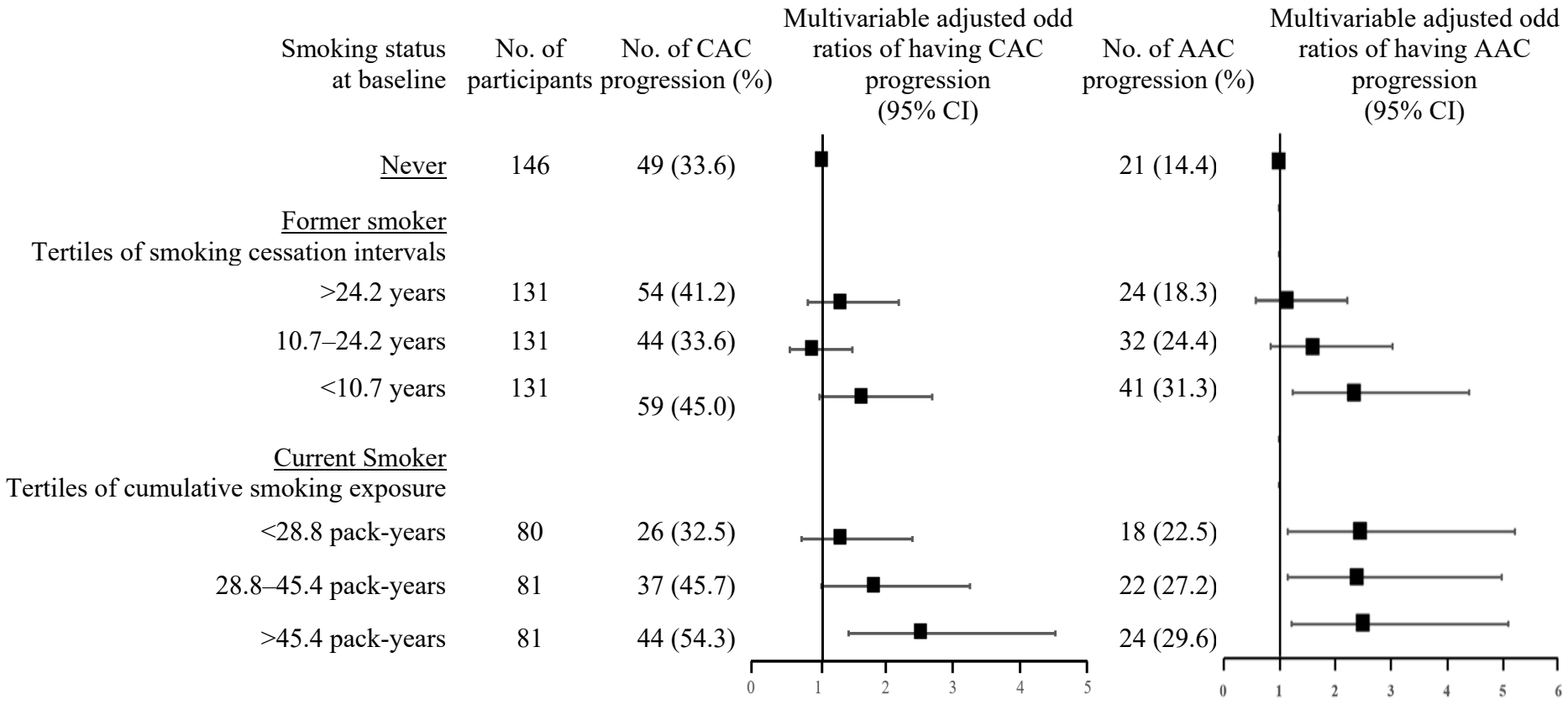

Figure 1. Odds Ratios of having CAC and AAC progression by Smoking Status at baseline, Cumulative Smoking Exposure by Pack-years and Smoking Cessation Intervals in 781 Men Aged 40-79 Years (SESSA, Shiga, Japan, 2006-2008 at baseline and 2010-2014 at follow-up)

CAC, coronary artery calcification; AAC, Aorta Artery calcification; CI, confidence interval. Multivariable model adjusted for age, dyslipidemia (yes/no), hypertension (yes/no), diabetes mellitus (yes/no), body max index, exercise (yes/no), and alcohol intake (g/week).

Supplementary Table 1. Odds ratios of having CAC progression by smoking status at baseline, cumulative smoking exposure by pack-years and smoking cessation Intervals

Smoking status at baseline	No. of participant	No. of CAC progression (%)	Odd ratios (95% CI)		
			Crude	Age adjusted	Multivariable adjusted
Never	146	49 (33.6)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Former smoker					
Tertiles of smoking cessation intervals					
>24.2 years	131	54 (41.2)	1.39 (0.85−2.26)	1.25 (0.76−2.04)	1.26 (0.76−2.10)
10.7 – 24.2 years	131	44 (33.6)	1.00 (0.61−1.65)	0.97 (0.59−1.61)	0.87 (0.52−1.47)
<10.7 years	131	59 (45.0)	1.62 (1.00−2.64)	1.70 (1.04−2.79) [a]	1.63 (0.98−2.72)
Current smoker					
Tertiles of cumulative smoking exposure					
<28.8 pack-years	80	26 (32.5)	0.95 (0.53−1.70)	1.18 (0.65−2.14)	1.23 (0.67−2.28)
28.8 – 45.4 pack-years	81	37 (45.7)	1.67 (0.96−2.90)	1.96 (1.11−3.45) [a]	1.72 (0.95−3.13)
≥45.4 pack-years	81	44 (54.3)	2.35 (1.35−4.11) [b]	2.50 (1.42−4.39) [b]	2.42 (1.34−4.38) [a]

CAC, coronary artery calcification; CI, confidence interval.

Multivariable model adjusted for age, dyslipidemia (yes/no), hypertension (yes/no), diabetes mellitus (yes/no), body max index, exercise (yes/no), and alcohol intake (g/week).

P value a <0.05; b <0.01

Supplementary Table 2. Odds ratios of having AAC progression by smoking status at baseline, cumulative smoking exposure by pack-years and smoking cessation intervals

Smoking status at baseline	No. of participant	No. of AAC progression (%)	Odd ratios (95% CI)		
			Crude	Age adjusted	Multivariable adjusted
Never	147	21 (14.4)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Former smoker					
Tertiles of smoking cessation intervals					
>24.2 years	122	24 (18.3)	1.34 (0.70−2.53)	1.16 (0.61−2.22)	1.14 (0.58−2.22)
10.7 – 24.2 years	133	32 (24.4)	1.92 (1.05−3.54) [a]	1.88 (1.01−3.51) [a]	1.60 (0.84−3.03)
<10.7 years	132	41 (31.3)	2.71 (1.50−4.90) [b]	2.98 (1.63−5.46) [b]	2.33 (1.24−4.38) [b]
Current smoker					
Tertiles of cumulative smoking exposure					
<28.8 pack-years	80	18 (22.5)	1.73 (0.86−3.48)	2.42 (1.17−5.00) [a]	2.51 (1.18−5.32) [a]
28.8 – 45.4 pack-years	81	22 (27.2)	2.22 (1.13−4.35) [a]	2.93 (1.46−5.87) [b]	2.45 (1.18−5.06) [a]
≥45.4 pack-years	81	24 (29.6)	2.51 (1.29−4.87) [b]	2.80 (1.42−5.52) [b]	2.55 (1.25−5.20) [a]

AAC, Aorta Artery calcification; CI, confidence interval.

Multivariable model adjusted for age, dyslipidemia (yes/no), hypertension (yes/no), diabetes mellitus (yes/no), body max index, exercise (yes/no), and alcohol intake (g/week).

P value a <0.05; b <0.01

Supplementary Table 3. Odds ratios of having CAC progression by original definition of Berry by smoking status at baseline, cumulative smoking exposure by pack-years and smoking cessation intervals

Smoking status at baseline	No. of participant	No. of CAC progression (%)	Odd ratios (95% CI)		
			Crude	Age adjusted	Multivariable adjusted
Never	146	49 (33.6)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Former smoker					
Tertiles of smoking cessation intervals					
>24.2 years	131	54 (41.2)	1.21 (0.76−1.95)	1.09 (0.68−1.77)	1.19 (0.69−1.85)
10.7 – 24.2 years	131	44 (33.6)	0.81 (0.50−1.31)	0.78 (0.48−1.27)	0.73 (0.44−1.20)
<10.7 years	131	59 (45.0)	1.42 (0.88−2.28)	1.47 (0.91−2.38)	1.40 (0.86−2.31)
Current smoker					
Tertiles of cumulative smoking exposure					
<28.8 pack-years	80	26 (32.5)	0.88 (0.51−1.54)	1.07 (0.60−1.89)	1.10 (0.61−1.98)
28.8 – 45.4 pack-years	81	37 (45.7)	1.29 (0.75−2.23)	1.48 (0.85−2.59)	1.32 (0.74−2.35)
≥45.4 pack-years	81	44 (54.3)	2.03 (1.17−3.52) [b]	2.13 (1.22−3.71) [b]	2.01 (1.13−3.58) [a]

CAC, coronary artery calcification; CI, confidence interval.

Multivariable model adjusted for age, dyslipidemia (yes/no), hypertension (yes/no), diabetes mellitus (yes/no), body max index, exercise (yes/no), and alcohol intake (g/week).

P value a <0.05; b <0.01

Original definition of Berry: Progression of coronary artery calcification was defined as follows, for those with CACS = 0 at baseline, defined as CAC >0 at follow-up; for those with 0< CAC <100 at baseline, defined as annualized change of ≥10 Agatston units at follow-up; for those with CAC ≥100 at baseline, defined as annualized percentage change of ≥ 10% at follow-up.