ORIGINAL RESEARCH

Cigarette Smoking and Subclinical Peripheral Arterial Disease in Blacks of the Jackson Heart Study

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***Background*—**Prevalence of peripheral artery disease (PAD) is significantly higher among blacks as compared with non-Hispanic whites, but the role of cigarette smoking in PAD is understudied in blacks. We aimed to evaluate the relationship between cigarette smoking and PAD in blacks in the (JHS) Jackson Heart Study.

***Methods and Results*—**JHS participants (n=5306) were classified by self-reported baseline smoking status into current, past (smoked at least 400 cigarettes/life), or never smokers. We examined multivariable logistic and robust linear regression models to estimate the associations between baseline smoking status, smoking intensity, and measures of subclinical PAD (ankle-brachial index [visit 1] and aortic calcium by computed tomography [visit 2]) to yield odds ratios and β-coefficients (estimated adjusted difference) to compare each smoking status with never smokers (reference group). There were 3579 (68%) never smokers, 986 (19%) past smokers, and 693 (13%) current smokers self-identified at baseline. After adjustment for covariates, current smokers had increased risk of ankle-brachial index <1 (odds ratio, 2.2, 95% CI, 1.5–3.3) and increased risk of abdominal aortic (odds ratio, 8.4, 95% CI, 5.8–12.0) and aortoiliac calcium (odds ratio, 9.6, 95% CI, 6.7–13.7). When stratifying by smoking intensity, those smoking more than 20 cigarettes daily (1 pack) had higher likelihood of subclinical PAD by all of these measures compared with lower-intensity use, suggesting a dose-dependent relationship.

***Conclusions*—**In a large black cohort, cigarette smoking was associated with measures of subclinical PAD in a dose-dependent manner. These findings highlight the association between smoking and PAD in blacks and support further research exploring the impact of interventions on smoking cessation to reduce PAD in this population. **(*J Am Heart Assoc*. 2019;8:e010674. DOI: 10.1161/JAHA.118.010674.)**

Key Words: black • peripheral artery disease • smoking

Peripheral arterial disease (PAD) is associated with increased cardiovascular morbidity and mortality.[1] Cigarette smoking is a powerful predictor for the development of PAD with a magnitude of association even greater than that reported for coronary heart disease.[2] PAD is nearly 3 times more prevalent in blacks as compared with non-Hispanic whites.[1] However, ethnic-specific cohort data indicate that blacks have less atherosclerosis in the thoracic and abdominal aorta,[3,4] suggesting the potential for differential PAD phenotypes. There are limited data directly assessing the association of cigarette smoking on PAD in blacks.[5]

Better understanding the association of smoking and PAD in blacks is important for several reasons. Increasing knowledge on the impact of cigarette smoking and PAD may improve public health campaigns raising awareness of adverse effects associated with tobacco. This is particularly important in the black community, which is more aggressively targeted by the tobacco industry.[6] Although the burden of

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Clinical Perspective

What Is New?

- The role of cigarette smoking in peripheral artery disease among blacks has not been well studied.
- In the JHS (Jackson Heart Study), a large black cohort, cigarette smoking was associated with measures of peripheral artery disease in a dose-dependent manner.

What Are the Clinical Implications?

- These findings support the evaluation of smoking-cessation efforts to reduce the impact of peripheral artery disease in this population.

PAD is significantly higher among blacks, the specific impact of smoking has not been well delineated beyond other risk factors, including hypertension, diabetes mellitus, and obesity. Public policy and clinical interventions to improve PAD outcomes in this population must rely on robust epidemiological research supporting such interventions. The objective of our study was to evaluate the relationship between cigarette smoking and smoking intensity with measures of subclinical PAD in the JHS (Jackson Heart Study), a large black cohort.

Methods

The data, analytical methods, and study materials are available to other researchers for purposes of reproducing the results or replicating the procedure by following the JHS publications procedures and data use agreements.

Study Population

The JHS is a large, prospective cohort study of cardiovascular disease in blacks and includes 5306 participants aged 21 to 84 years at baseline. Participants were recruited from the tricounty area surrounding Jackson, Mississippi, and were evaluated at baseline from 2000 to 2004. Data from visit 2 (2005–2008), including computed tomography (CT) measures of aortic and aortoiliac calcium, were also utilized. We included participants who completed Exam 1 and participated in the substudy undergoing the CT protocol in Exam 2. The study was approved by the institutional review boards of the University of Mississippi Medical Center, Tougaloo College, and Jackson State University. Each participant provided written informed consent.

The baseline examination (V1) included a home interview, self-administered questionnaires, and a clinic visit that included blood and urine collection. Each participant was asked to fast overnight before the clinic visit at which blood pressure (BP) and anthropometric measurements were obtained. Blood and urine samples were collected according to the National Committee for Clinical Laboratory standards, as reported previously.[7]

Study Variables

Cigarette smoking status was obtained via questionnaire at V1. Participants who smoked >400 cigarettes in their lifetime were defined as ever smokers. Participants who gave a positive response to the question, "Do you now smoke cigarettes?" were classified as current smokers. Those who responded negatively to these questions were classified as never smokers. Participants who were classified as ever smokers who no longer smoked at the time of the examination were classified as past smokers. Further information related to number of cigarettes smoked daily was collected. To determine smoking burden (pack-years), the number of cigarettes smoked daily was multiplied by number of years smoked. Age, sex, and anthropometric data, such as body mass index, were recorded at the baseline examination. Hypertension was defined as BP $\geq$140/90 mm Hg or use of BP-lowering medication, and diabetes mellitus was defined as fasting glucose $\geq$126 mg/dL or hemoglobin A1c $\geq$6.5%, or use of diabetes mellitus medications within 2 weeks before the clinic visit.[7] In addition, total cholesterol was measured from plasma with the use of a cholesterol oxidase method (Roche Diagnostics, Indianapolis, IN) on a Roche COBAS FARA centrifugal analyzer.

Ankle-brachial index (ABI) was measured at V1. To determine ABI, ankle and brachial systolic BP were measured by trained technicians using a sphygmomanometer along with an Ultrasonic Doppler Flow Detector (Model 811-B; Parks Medical Electronic-Inc, Aloha, OR). Technicians followed a standard protocol, using a contour wrapping technique with the midpoint of the bladder over the posterior tibial artery; the lower end of the bladder $\approx$3 cm above the medial malleolus. Bilateral systolic BP measurements were taken with ultrasound measurement of the posterior tibial artery while the participant was in the supine position. The dorsalis pedis artery was used for measurement if the posterior tibial pulse could not be found by palpation or by Doppler pen probe. Measurements of the brachial systolic BP, usually in the right brachial, were taken twice. The first brachial measurement was made before leg measurements, and the second measurement was made after the leg measurements were completed. Two ABIs (1 for the right leg and 1 for the left leg) were calculated as the average of the 2 ankle systolic BP measurements divided by the average of the 2 brachial readings. The lower of the 2 ABIs were considered the participants' ABI for the current study.[8]

Abdominal aortic calcification was measured at visit 2 among 2398 participants. The research CT protocol included the heart and lower abdomen using a 16-channel multidetector CT system equipped with cardiac gating (Lightspeed 16 Pro; GE Healthcare, Milwaukee, WI). An effective dose was calculated for the abdominal scan used in the FHS-SCAN (Framingham Heart Study/Subclinical Atherosclerosis Network) and MESA (Multi-Ethnic Study of Atherosclerosis) studies of 2.7 mSv for both women and men is noted because neither sex's gonads are directly irradiated. Scanning took place at the JHS CT Data Acquisition Center located at the Jackson Medical Mall (Jackson, MS). Quality-control and image analysis were performed at a core reading center (Wake Forest University School of Medicine, Winston Salem, NC). The protocol included scout images, 1 ECG-gated series of the entire heart, and a series through the lower abdomen from L3 to S1. Abdominal aortic calcification was quantified utilizing Agatston scoring, modified to account for slice thickness. Calcified artery plaque was computed by multiplying each lesion by a weighted attenuation score on a TeraRecon Aquarius Workstation (TeraRecon, San Mateo, CA); scoring was in Hounsfeld units. Presence of abdominal aortic calcification was defined as Agatston score >0; reproducibility in scoring was 0.99.

Based on previous published data, subclinical PAD is defined as ABI <1 or >1.4 and no history of clinical PAD symptoms (claudication, peripheral artery surgery, or amputation attributed to PAD).[9,10] Subclincal PAD is also defined as the presence of abdominal aortic calcification, which has been associated with significantly higher risk of all-cause mortality.[11]

Statistical Analysis

Data are presented as mean with SDs for continuous variables and frequencies and proportions for categorical variables. Relationships between smoking status (current, former, or never), intensity among current smokers (cigarettes per day), and burden among ever smokers (pack-years) with measures of subclinical PAD (ABI and abdominal aortic calcification) were assessed using robust linear and logistic regression analyses. Based on past research and knowledge of clinically significant factors associated with cardiovascular disease, models were adjusted for age, sex, body mass index, hypertension, diabetes mellitus status, total cholesterol, triglycerides, self-reported prevalent cardiovascular disease, physical activity, alcohol consumption in the past 12 months, and level of education. These adjusted associations were expressed as odds ratios (ORs) and β-coefficients (estimated adjusted differences) to compare each smoking status with never smokers (reference group). All statistical analyses were performed with STATA software (version 14; StataCorp LP,

Table 1. Baseline Characteristics and Measures of Subclinical Peripheral Arterial Disease

Smoking Status	Never (n=3579)	Past (n=986)	Current (n=693)
Age, y	54.3±13.2	60.6±11.0	52.9±11.3
Sex, male (%)	1084 (30.3)	485 (49.2)	350 (50.5)
Body mass index, kg/m^2	32.2±7.3	31.4±6.6	30.0±7.4
Prevalent cardiovascular disease (%)	288 (8.0)	171 (17.3)	107 (15.4)
Hypertension, %	1945 (54.3)	667 (67.6)	360 (52.1)
Diabetes mellitus, %	736 (20.9)	278 (28.3)	126 (18.4)
Total cholesterol, mg/dL	199±39	201±42	197±42
Education less than high school (%)	2967 (83.1)	701 (71.2)	509 (73.9)
Ideal physical activity, %*	701 (19.6)	201 (20.4)	101 (14.6)
Alcohol consumption, %†	1449 (40.7)	465 (47.3)	481 (70.1)
Ankle-brachial index	1.2±0.2	1.2±0.2	1.2±0.2
Ankle-brachial index <1 (%)	141 (4.5)	74 (8.6)	54 (9.1)
Infrarenal abdominal aorta Agatston score >0 (%)	927 (46.3)	410 (74.3)	238 (78.0)
Infrarenal abdominal aorta Agatston score >75th percentile (%)	349 (17.4)	227 (41.1)	138 (45.2)
Aortoiliac Agatston score >0 (%)	1157 (57.8)	456 (82.6)	263 (86.2)
Aortoiliac Agatston score >75th percentile (%)	339 (16.9)	231 (41.8)	144 (47.2)

Continuous values are presented as mean±SD; other values are numbers (percentages) or median [interquartile range].
*≥150 min/week moderate intensity or ≥75 min/week vigorous intensity or combination based on American Heart Association physical activity classification.
†Self-reported as any alcohol consumption within the previous 12 months.

Table 2. Associations Between Cigarette Smoking and Measures of Subclinical Peripheral Arterial Disease

Model	Smoking Status at Baseline			Smoking Intensity		
	Never Smokers	Past Smokers	Current Smokers	Current (1–19 Cigarettes per Day)	Current (≥20 Cigarettes per Day)	Pack-Year Smoking Exposure
Ankle-brachial index, ratio, Beta coefficient	0 (ref)	−0.01 (−0.03 to 0.001)	−0.04 (−0.06 to 0.03)*	−0.04 (−0.06 to 0.019)*	−0.05 (−0.08 to 0.02)†	−0.01 (−0.02 to 0.008)†
Ankle-brachial index <1, odds ratio	1 (ref)	1.5 (1.1 to 2.2)†	2.2 (1.5 to 3.3)*	1.6 (0.96 to 2.6)	3.5 (2.0 to 6.0)*	1.2 (1.1, 1.4)†
Aortic calcium at visit 2, odds ratios (N=2398)						
Infrarenal abdominal aorta Agatston score >0 (%)	1 (ref)	2.3 (1.8 to 3.0)*	7.2 (5.0 to 10.4)*	5.8 (3.8 to 8.8)*	14.99 (7.5 to 29.9)*	1.2 (1.1, 1.2)*
Infrarenal abdominal aorta Agatston score >75th percentile (%)	1 (ref)	2.9 (2.3 to 3.8)*	8.4 (5.8 to 12.0)*	8.6 (5.6 to 13.2)*	10.5 (6.0 to 18.7)*	1.3 (1.2, 1.4)*
Aortoiliac Agatston score >0 (%)	1 (ref)	2.1 (1.6 to 2.8)*	7.1 (4.7 to 10.7)*	6.1 (3.8 to 9.7)*	13.8 (6.1 to 31.1)*	1.1 (1.1, 1.2)*
Aortoiliac Agatston score >75th percentile (%)	1 (ref)	3.1 (2.3 to 4.0)*	9.6 (6.7 to 13.7)*	9.3 (6.1 to 14.3)*	12.8 (7.2 to 22.5)*	1.3 (1.2, 1.4)*

All values are expressed as β coefficients (otherwise), with 95% CIs, unless labeled as odds ratios. Each robust linear and logistic regression model is adjusted for age, sex, body mass index, hypertension, diabetes mellitus status, total cholesterol, triglycerides, prevalent cardiovascular disease, physical activity, and alcohol consumption in the past 12 months and level of education.

*$P<0.001$.

†$P<0.05$.

College Station, TX). A 2-sided $P<0.05$ was considered significant.

Results

Baseline characteristics and measures of subclinical PAD are presented by smoking status in Table 1. In our analysis including 5258 participants (99% of overall cohort) without missing covariates, 3579 (68%) participants were never smokers, 986 (19%) were past smokers, and 693 (13%) were current smokers. Participants who were past or current smokers were more likely to be men and have prevalent cardiovascular disease. On average, all groups had high mean body mass indices (≥30 kg/m^2), low levels of physical activity, and less than a high school education. Current smokers were more likely to consume alcohol. Past smokers were more likely to be older and have associated hypertension and diabetes mellitus. As compared with never smokers, past smokers and current smokers had lower ABI and higher infrarenal and aortoiliac Agatston scores.

After adjustment for covariates, past smokers were significantly more likely to have ABI <1, infrarenal abdominal aorta Agatston score >75th percentile, and aortoiliac Agatston score >75th percentile. As compared with never smokers, current smokers and past smokers had significantly higher mean subclinical PAD measurements, with a greater degree of association among current smokers. Among current smokers, the highest degree of association with subclinical PAD was observed among those smoking ≥20 cigarettes (1 pack) per day and those with higher total pack-year smoking history. Associations between cigarette smoking and measures of subclinical PAD are presented in Table 2.

Discussion

In our community-based black cohort, 13% of participants were current smokers and 19% were past smokers. After risk adjustment, current smokers had 2.2 times the likelihood of subclinical lower-extremity PAD and >8 times the likelihood of a high aortic calcium burden. Among current smokers, there was a dose-dependent response whereby those smoking ≥20 cigarettes per day and higher pack-year smoking exposure demonstrated considerably higher odds of subclinical PAD compared with those smoking 1 to 19 cigarettes per day.

A major finding of this study was the high degree of association between cigarette smoking, smoking intensity, and measures of subclinical PAD in the JHS cohort. In past reports, prevalence of PAD was significantly higher among blacks as compared with other racial groups, which parallels higher rates of hypertension, diabetes mellitus, and obesity.[12] Cigarette smoking is a well-established risk factor for PAD, but the impact of smoking on PAD has been less thoroughly

investigated in blacks. Previous studies were limited to cohorts with smaller numbers of blacks, generally utilizing only ABI and adjusting for smoking as one of many covariates.[13,14] The current study is among the largest analyses in blacks utilizing multiple measures of subclinical PAD, all stratified by smoking status and intensity.

The results of our analysis support clinical efforts and policy initiatives aimed at tobacco control. As compared with never smokers, current smokers and past smokers had higher odds of subclinical PAD, although the odds were comparably lower among past smokers than current smokers. Our findings highlight both the importance of smoking cessation as well as prevention of smoking initiation. These data are particularly important given historical differences in tobacco marketing based on race, given that blacks are more aggressively targeted by cigarette advertising.[6] PAD and its associated morbidity, including claudication, exercise intolerance, decreased quality of life, infection, and amputation, should be included in antismoking campaigns targeting the black community. These additional messaging points are complementary to the often-cited health effects of smoking on heart disease, stroke, and cancer. Furthermore, our data support further research evaluating the efficacy of tobacco control policy intervention, such as cigarette pricing increase, which have been shown to be highly effective at reducing smoking prevalence rates.[15]

In our analysis, there was a particularly strong association between smoking and abdominal aorta and aortoiliac calcium burden. These findings support the large body of clinical and epidemiological data identifying smoking as a dominant risk factor for abdominal aortic calcification.[16,17] Predilection for abdominal aortic pathology in smokers remains to be fully elucidated, but current evidence suggests multiple environmental, genetic, and epigenetic factors.[18] Chronic inflammatory infiltration and smooth muscle changes are thought to contribute.[19] Past work from the MESA Study demonstrated that blacks, compared with whites, have less calcification of the thoracic and abdominal aorta after accounting for cardiovascular disease risk factors.[3,4] Previous findings from the JHS demonstrated an independent association with smoking and progressive decline in renal function.[20] In the current analysis, the high burden of infrarenal aortic calcium among smokers may suggest concomitant renovascular atherosclerosis, potentially mechanistically linking smoking and progressive renal function decline. This hypothesis and the relationships between smoking, PAD, and chronic kidney disease warrant further investigation.

The current study has several limitations that warrant consideration. Our analysis is cross-sectional in design as smoking status and ABI measurement were obtained at V1. There is a 5.5-year mean delay between baseline determination of smoking status at V1 and the CT evaluation at visit 2. Despite strong associations between smoking status and measures of PAD, direction of causality cannot be inferred and we cannot exclude residual confounding.[8] The JHS was conducted in a single community of blacks. We are limited in our ability to generalize to individuals of African ancestry from other regions or countries, and to compare with other races/ethnicities. Cigarette smoking assessment was obtained by self-report; cotinine levels and type of cigarette smoked were not available for analysis. Recall bias may also contribute to inaccuracies in smoking classification. However, validity of self-reported smoking is consistently high in population-based studies.[21] The self-reported use of other tobacco products in the JHS was low (0.6% dip/snuff, 0.3% pipe smokers, and 1.1% cigars), but we cannot exclude effects related to unreported tobacco use. JHS does not capture data related to second- and third-hand smoke; therefore, potential differences in these factors are not accounted for between groups. Also, the participants with available data at baseline who underwent CT measures represented a convenient sample of the cohort at baseline (n=2398/5306) and may have resulted in selection of a group in which the magnitude of the associations of smoking with PAD differed from what might have been observed if CT measures were available in the entire cohort.

In conclusion, in a large black cohort, we observed a strong and dose-dependent association between cigarette smoking and measures of subclinical PAD. There is a particularly strong association between smoking and abdominal aorta and aortoiliac calcification. These data provide further evidence of the deleterious health effects of smoking in blacks and support further research exploring the impact of interventions on smoking cessation to reduce PAD in this population.

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Disclosures

None.

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