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Second-Hand Tobacco Smoke in Never Smokers Is a Significant Risk Factor for Coronary Artery Calcification

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OBJECTIVES The aim of this study was to assess the relationship of the extent of subclinical atherosclerosis measured by coronary artery calcification (CAC) to the extent of second-hand tobacco smoke (SHTS) exposure in asymptomatic people who never smoked.

BACKGROUND An association between SHTS and CAC was recently reported in a single study, but the quantitative aspects of the relationship are not known.

METHODS A cohort of 3,098 never smokers 40 to 80 years of age, enrolled in the Flight Attendant Medical Research Institute International Early Lung Cancer Action Program screening program, completed a SHTS questionnaire, and had a low-dose nongated computed tomography scan. The questionnaire provided a quantitative score for total SHTS exposure, as well as separately as a child and as an adult at home and at work; 4 categories of exposure to SHTS were identified (minimal, low, moderate, and high exposure). CAC was graded using a previously validated ordinal scale score that ranged from 0 to 12. Logistic regression analysis of the prevalence and ordered logistic regression analysis of the extent of CAC were performed to assess the independent contribution of SHTS adjusted for age, sex, diabetes, hypercholesterolemia, hypertension, and renal disease. Linear and quadratic regression analyses of CAC and SHTS were performed.

RESULTS The prevalence of CAC was 24% ($n = 754$) and was significantly higher in those with more than minimal SHTS exposure compared with those with minimal SHTS exposure (21% vs. 19%, $p < 0.0001$). The adjusted odds ratios for CAC prevalence were 1.54 (95% confidence interval: 1.17 to 2.20) for low SHTS exposure, 1.60 (95% confidence interval: 1.21 to 2.10) for moderate exposure, and 1.93 (95% confidence interval: 1.49 to 2.51) for high exposure. The association of the extent of SHTS with the extent of CAC was confirmed by the adjusted odds ratio ($p < 0.0001$).

CONCLUSIONS The presence and extent of CAC were associated with extent of SHTS exposure even when adjusted for other risk factors for CAC, suggesting that SHTS exposure causes CAC. (J Am Coll Cardiol Img 2013;xx:xxx) © 2013 by the American College of Cardiology Foundation

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The link between second-hand tobacco smoke exposure (SHTS) and clinical coronary artery disease (CAD) has been extensively investigated. Hirayama (1,2) reported the association of CAD with SHTS exposure in his cohort studies of 91,540 never-smoking women in Japan in 1984. In 1985, Garland et al. (3) also showed the association in 695 lifetime never smokers in California. Subsequently, additional cohort and case-control studies addressing the association of SHTS and CAD were performed (4,5), including studies that convincingly demonstrated that the increased risk due to SHTS persisted even when other risk factors for CAD were considered (6–8). Based on this accumulated evidence, the Surgeon General's 2006 report (5) concluded that the data supported a causal association between SHTS and CAD mortality and morbidity.

An association between SHTS with subclinical atherosclerosis as evidenced by coronary artery calcification (CAC) was first demonstrated in a recent report (9). It showed that CAC scores were significantly higher in SHTS-exposed than in nonexposed individuals, even after adjustment for other cardiovascular risk factors. CAC measurement using computed tomography (CT) (10–16) is increasingly being used for CAD risk stratification and has been shown to be superior to risk-based algorithms (13). It has received class IIa status in the 2010 American College of Cardiology Foundation/American Heart Association Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults for evaluation of intermediate risk people (16).

ABBREVIATIONS AND ACRONYMS

CAC = coronary artery calcification

CAD = coronary artery disease

CI = confidence interval

CT = computed tomography

OR = odds ratio

SHTS = second-hand tobacco smoke

In this report, we address the prevalence and extent of subclinical atherosclerosis manifesting by CAC with the extent of SHTS on low-dose nongated CT in a large cohort of asymptomatic people who had never smoked. Although most CAC studies have used gated scans, we have previously demonstrated that low-dose nongated CT scans obtained when screening for lung cancer provided prognostic CAD information similar to that of gated acquisitions in a cohort of smokers (17).

METHODS

Cohort. We identified all men and women who had enrolled in the Flight Attendant Medical Research Institute International Early Lung Cancer Action Program CT screening program from 2005 to 2012 who had no history of and were asymptomatic for CAD. This program was established to assess the association of SHTS exposure with pulmonary and cardiovascular diseases by prospectively enrolling never smokers and assessing the extent of CAC on demonstrated low-dose CT scans. All 3,098 participants were never smokers, defined by the accepted convention as having smoked <100 cigarettes in their lifetime. Consent was obtained from all participants according to Health Insurance Portability and Accountability Act–compliant protocols, approved by the institutional review boards of the collaborating institutions. Once consent was obtained, all participants completed a background form. It asked the participant whether he or she had a known diagnosis of diabetes, hypertension, hypercholesterolemia, or renal disease. For this study, we selected all participants who were 40 to 80 years of age; 49% of the participants were white, 49% were Asian (2% were other), and 82% had completed high school.

Low-dose baseline CT scan. A low-dose nongated, noncontrast CT scan was performed on each individual at ≤120 kVp and ≤60 mA and collimation of ≤1.25 mm. Images were obtained from the lung apices to the bases in a single breath-hold at maximum inspiration. The CT readings used in this study were performed at the co-ordinating center on high-resolution monitors. CAC assessment was done using standard mediastinal settings (width, 350 Hounsfield units; level, 50 Hounsfield units). The presence of CAC in the main, left anterior descending, circumflex, and right coronary arteries were categorized as absent, mild, moderate, or severe and scored as 0, 1, 2, or 3, respectively (17,18). CAC was classified as mild calcification if less than one-third of the length of the entire artery containing calcification (CAC = 1), moderate if one-third to two-thirds (CAC = 2), and severe if more than two-thirds of the artery showed calcification (CAC = 3). Each participant received a total CAC score that was the sum of the CAC score for each of the coronary arteries, ranging from 0 to 12. The CAC scores were divided into 3 categories of increasing severity: 0, 1 to 3, and 4 to 12 (17).

SHTS exposure score. All participants completed a background questionnaire about SHTS exposure before age 18 as a child and after age 18 as an adult at home and at work (Table 1). The answers determined the permission status, duration of SHTS exposure (years), daily intensity of the SHTS exposure (packs per day) for each of these life exposures (as a child and as an adult at home and at

Table 1. Second-Hand Tobacco Smoke Questions

A. Second-hand smoke exposure: childhood
1. Did anyone in your house smoke in the home when you were under 18? No/Yes
If yes, was smoking allowed inside the house? Not permitted, restricted, allowed anywhere.
2. Did your mother/primary caregiver smoke when you were younger than 7 years of age? No/Yes
3. Did your mother/primary caregiver smoke when you were 7 to 18 years of age? No/Yes
4. Did anyone else besides your mother/primary caregiver smoke in the home when you were younger than 18 years of age? No/Yes
B. Second-hand smoke exposure: adult at home
5. Do you currently live with a smoker? No/Yes
6. After 18 years of age, did you live with someone for >1 year who smoked in your presence? No/Yes
If yes, at what ages did you live with someone who smoked around you and how much did they smoke? (Give details for the last 4, starting with most recent first.)
Age range, amount, smoking not permitted, restricted, allowed anywhere.
C. Second-hand smoke exposure: adult at work
7. After 18 years of age, did you work for >1 year at a worksite where smoking was allowed? No/Yes
If yes, give details on the last 4 places, starting with the most recent first.
Age range, job, smoking not permitted, restricted, allowed anywhere.

work). The permission status was 1.0 if smoking was allowed anywhere, 0.5 if smoking was restricted, or 0.0 if smoking was not permitted. The exposure duration was the sum of the years that the participant was exposed to SHTS. The daily exposure intensity was determined as a child and as an adult at work and at home: as a child, 1.0 pack per day if household members smoked; as an adult at work, 1.5 packs per day if others smoked at work; as an adult at home if household members smoked, it was 1.5 if more than 25 cigarettes per day, 1.0 if 15 to 24 cigarettes per day, 0.35 if <15 cigarettes per day, 0.70 if number of cigarettes smoked was unknown. Total SHTS exposure score was the product of permission status × exposure duration × daily exposure intensity for each life exposure (as a child and as an adult at home and at work).

The total SHTS exposure score was the sum of these SHTS life exposure scores divided by 204, the maximum possible SHTS score for an 80-year-old enrollee. The total SHTS exposure score ranged from 0.0 to 0.70. The exposure was classified as minimal if the total SHTS exposure score was <0.005 (n = 821), and these never smokers provided the comparison group for the remaining 2,277 never smokers with higher SHTS scores. The 2,277 never smokers were equally divided into tertiles: low (0.005 ≤ SHTS <0.093, n = 759), moderate (0.093 ≤ SHTS <0.18, n = 759), and high (SHTS ≥ 0.18, n = 759) (Fig. 1). The average scores for minimal, low, moderate, and extensive SHTS exposure were 0.0047, 0.053, 0.13, and 0.29, respectively.

Statistical analysis. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina). For graphs, we used PASW Statistics 18 (formerly SPSS) (Chicago, Illinois). Frequencies and descriptive statistics were obtained for all the variables. Univariate analysis of the prevalence of any CAC, SHTS exposure score, and other variables was performed using Kruskal-Wallis, chi-square, and Fisher exact tests. Logistic regression analysis was used to address the relationship of the prevalence of CAC to SHTS exposure categories while adjusting for other risk factors of CAC: age, sex, diabetes, hypercholesterolemia, hypertension, and renal disease, as reported on the background questionnaire. The extent of CAC was analyzed for the 3 categories of CAC (0, 1 to 3, 4 to 12) using ordered logistic regression analysis adjusting for the other risk factors of CAC.

RESULTS

The prevalence of CAC (CAC > 0) was higher for those with higher than minimal SHTS exposure than those with minimal SHTS exposure (26.4% vs. 18.5%, p < 0.0001) (Table 2). This was also the case for the CAC categories 1 to 3 and 4 to 12. Participants with more than minimal SHTS exposure were older (55 vs. 53 years of age), more frequently women (64.5% vs. 46.2%), and more frequently had diabetes, hypercholesterolemia, and hypertension than those with minimal SHTS exposure.

The prevalence of CAC for men and women by decades of age is given in Table 3. For every decade, the prevalence of CAC was significantly higher for those with more than minimal SHTS exposure compared with those with minimal exposure, for both men (p < 0.0001) and women (p = 0.04).

The prevalence of any CAC increased significantly (p < 0.0001) with increasing SHTS exposure categories of minimal (18.5%), low (22.1%), moderate (22.1%), and high (35.1%).

Multivariate logistic regression analysis of the contributors to the prevalence of CAC revealed odds ratios (ORs) of 1.5 (95% confidence interval [CI]: 1.2 to 2.0; p = 0.002) for low SHTS

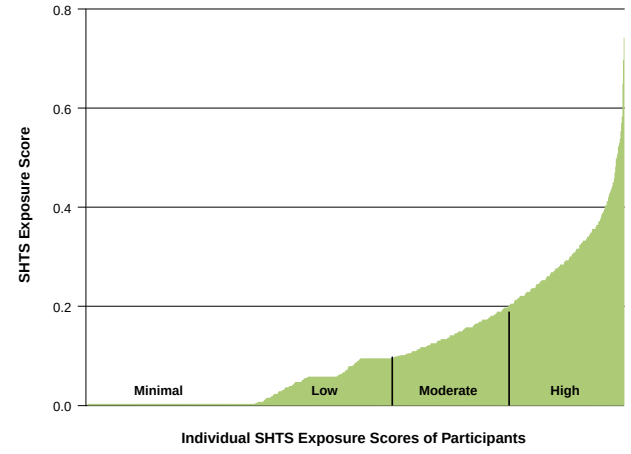

Figure 1. SHTS Exposure Scores for 3,098 Never Smokers

Second-hand tobacco smoke (SHTS) exposure score distribution for the never smokers according to their exposure category (minimal, low, moderate, high).

exposure, 1.6 (95% CI: 1.2 to 2.1; p = 0.0008) for moderate exposure, and 1.9 (95% CI: 1.5 to 2.5; p < 0.0001) for high SHTS exposure. Table 4 gives the ORs for the SHTS exposure categories (low, moderate, high) when adjusted for the other risk factors for CAC (age, diabetes, hypercholesterolemia, hypertension, and renal disease). The adjusted OR was 1.5 (95% CI: 1.2 to 2.0; p = 0.002), 1.6 (95% CI: 1.2 to 2.1; p = 0.0008), and 1.9 (95% CI: 1.5 to 2.5; p < 0.000) for low, moderate, and high SHTS exposure, respectively, thus demonstrating that SHTS exposure was an independent predictor of the prevalence of CAC. To determine whether the SHTS exposure categories were independent predictors of the extent of CAC (0, 1 to 3, 4 to 12), ordered logistic regression analysis was performed adjusting for the other risk factors of CAC as before, and the results were consistent with the results from the multivariate logistic regression analysis. The prevalence of any CAC increased monotonically with SHTS score.

The total SHTS score was a significant independent predictor of the prevalence of CAC (p < 0.0001) after adjusting for the other risk factors of age, diabetes, hypercholesterolemia, hypertension, and renal disease in the logistic regression analysis. Replacing the total SHTS score by the childhood SHTS exposure score, it was a significant independent predictor of CAC (p = 0.03). Similarly, SHTS exposure as an adult at home exposure alone was a significant independent predictor of CAC (p = 0.02), as was the adult at work exposure (p = 0.0007).

DISCUSSION

This study is the first to document the significant quantitative relationship in never smokers between SHTS exposure and the prevalence and extent of subclinical atherosclerosis manifested by CAC. It also showed that when considering SHTS exposure in childhood, as an adult at home, and as an adult at work separately, each was an independent predictor of the prevalence of CAC. Moreover, it establishes that with increasing SHTS exposure, there is an increase in the extent of CAC and that a significant dose relationship existed. In this study, the ORs for SHTS are as high as or higher than decade of age, diabetes, hypertension, hypercholesterolemia, and renal disease, all well-established risk factors for CAD. The present study reinforces previous studies showing the increased risk of CAD from SHTS and particularly with increasing SHTS exposure.

There was no evaluation of the association of CAC and SHTS exposure until the Heinz Nixdorf Recall Study, a prospective population-based cohort of asymptomatic participants undergoing gated CT scans for CAC (9). Their study reported an OR of 1.38 for the presence of CAC in 379 never smokers with SHTS exposure compared with 1,387 never smokers with no SHTS exposure adjusted for age, sex, and other major cardiovascular risk factors. SHTS exposure was categorized as present/absent

Table 2. Distribution of Age, Sex, CAC, Diabetes, Hypercholesterolemia, Hypertension, and Renal Disease in 3,098 Asymptomatic Never Smokers by SHTS Exposure Category

	SHTS Exposure Category		
	Minimal (n = 821)	More Than Minimal (n = 2,277)	p Value
CAC			
Any	18.5 (152)	26.4 (602)	<0.0001
0	81.5 (669)	73.6 (1,675)	<0.0001
1–3	13.9 (114)	21.1 (480)	
4–12	4.6 (38)	5.4 (122)	
Sex			
Male	53.8 (442)	35.5 (809)	<0.0001
Female	46.2 (379)	64.5 (1,468)	
Median age, yrs	53	55	<0.0001
Diabetes	3.5 (29)	5.4 (122)	0.04
Hypercholesterolemia	16.1 (132)	29.2 (666)	<0.0001
Hypertension	15.8 (130)	23.3 (530)	<0.0001
Renal disease	1.7 (14)	1.4 (32)	0.54

Values are % (n).
CAC = coronary artery calcification; SHTS = second-hand tobacco smoke.

Table 3. Prevalence of CAC, Separately by SHTS Exposure Category, Men and Women, and Decades of Age

	Extent of SHTS Exposure			
	Men		Women	
	Minimal SHTS (n = 442)	More Than Minimal SHTS (n = 809)	Minimal SHTS (n = 379)	More Than Minimal SHTS (n = 1,468)
Age, yrs				
40–49	6.5 (11/170)	18.16 (51/281)	2.2 (3/138)	8.1 (31/383)
50–59	25.0 (37/148)	35.5 (108/304)	16.7 (23/138)	15.5 (87/562)
60–69	27.2 (22/81)	56.5 (95/168)	30.0 (21/70)	31.4 (130/414)
70–80	46.5 (20/43)	69.6 (39/56)	45.5 (15/33)	56.0 (61/109)

Values are % coronary artery calcification (n).
Abbreviations as in Table 2.

at work, at home, or other places as an adult in their study. In our study, a detailed, prospectively administered SHTS exposure questionnaire permitted evaluation of the quantitative relationship between the extent of SHTS and the extent of CAC and suggested that the association might be stronger than previously estimated.

SHTS exposure is an underappreciated major global health issue. A large global study showed that 40% of children, 33% of male never smokers, and 35% of female never smokers in 2004 were exposed to SHTS (19). The estimated worldwide mortality was 605,000 deaths, ~1% of the world's mortality: 379,000 from CAD, 165,000 from lower respiratory infections, 36,900 from asthma, and 24,000 from lung cancer. Among the deaths, women accounted for 47%, men for 26%, and children for 28%. The remarkable number attributable to cardiovascular disease mandates more vigorous prevention of exposure and identification and treatment of those with early stages of the disease.

Table 4. Logistic Regression Analysis of the Prevalence of CAC in 3,098 Asymptomatic Never Smokers Using Indicator Variables for Having Low, Moderate, or High SHTS Exposure, Adjusted for Other Determinants

	OR	95% CI	p Value
SHTS categories			
Low	1.5	1.2–2.0	0.002
Moderate	1.6	1.2–2.1	0.0008
Extensive	1.9	1.5–2.5	<0.0001
Other risk factors			
Age per decade	1.1	1.1–1.1	<0.0001
Male	2.5	2.0–3.0	<0.0001
Diabetes	1.9	1.3–2.7	0.0008
High cholesterol	1.6	1.3–1.9	<0.0001
Hypertension	1.4	1.2–1.8	0.001
Renal disease	1.3	0.7–2.6	0.45

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 2.

A number of reports have consistently documented factors contributing to cardiovascular disease that are associated with SHTS exposure (5,20–23). Among these are platelet activation and aggregation, endothelial dysfunction, flow-mediated dilation, arterial stiffness, carotid intima-media thickening, dysfunctional endothelial progenitor cells, increased endothelial microparticles, abolished endothelial progenitor cell chemotaxis, and an increase in the following: white blood cells, C-reactive protein, homocysteine, oxidative stress, insulin resistance, heart and blood pressure, and infarct size. As stated in the Surgeon General's report (5), current exposure to SHTS appears to be more harmful than past exposure and previous studies also suggest a higher risk of CAD from high-intensity exposure. Also, the magnitude of the effect of SHTS on platelet aggregation and endothelial dysfunction has been shown to be nonlinear (5), which may be the explanation for the strong effect of the high SHTS exposure.

Study limitations. Visual CAC scores from nongated CT scans were used rather than conventional Agatston scoring obtained from gated CT scans. However, we had previously shown that the visual CAC score was a powerful predictor of death caused by cardiovascular disease in smokers (17). Moreover, misclassification of CAC because of the visual scoring would not bias the association with SHTS, barring the unlikely possibility that misclassification would differ among the exposure categories. Also, the use of ordinal values for the visual CAC scoring rather than the use of the Agatston score limits quantitative comparison. Another limitation may be the lack of confirmation of the smoking status by the use of cotinine testing. However, this test would only confirm the lack of smoking in the very recent past as opposed to the lifelong status of being a never smoker (5). The

SHTS questionnaire was developed before the start of the study. It focused on the cumulative damage over longer intervals of time to examine the question of differences in the average intensity of exposure compared with the duration of exposure in producing chronic injury. The validity of the intensity measures in the questionnaire for actual biological exposures was previously documented (5). The concern that early life exposures may make a contribution to the chronic injury led us to capture these data to the extent possible, although in this older cohort, recall of early exposure may not be as reliable as the recall as an adult. Possible biases of self-reporting of SHTS were extensively addressed in the 2006 report. It was recognized that SHTS exposure is typically underreported. Such underreporting is particularly found in prospective studies such as ours, and this underreporting bias tends to underestimate the association of SHTS with a disease, in our case, subclinical atherosclerosis, rather than to overestimate the association (23).

CONCLUSIONS

With the increasing body of evidence linking SHTS exposure to CAD, consideration should be given to its official recognition as an important independent risk factor. Standard medical history taking should be broadened to include SHTS exposure. It is critical to recognize that it is an eminently avoidable risk factor, as evidenced by the reduction in acute myocardial infarction after implementation of smoke-free laws (24–28). The ability to document increased cardiovascular risk in never smokers exposed to SHTS from a low-dose screening CT scan offers an opportunity for combined early detection and treatment of lung cancer (29,30), emphysema (31), and cardiovascular disease (17), the 3 major diseases attributable to SHTS exposure. Ongoing progress in the development of gated CT scans at low-dose radiation is the next step in the routine inclusion of CAC assessment while screening for lung cancer.

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Key Words: coronary artery calcification ■ CT screening ■ second-hand smoke exposure.

▶ APPENDIX

For a list of the FAMRI-IELCAP Investigators, please see the online version of this article.