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Original Contribution

Risk of Incident Cardiovascular Disease Among Users of Smokeless Tobacco in the Atherosclerosis Risk in Communities (ARIC) Study

Hiroshi Yatsuya* and Aaron R. Folsom for the ARIC Investigators

* Correspondence to Dr. Hiroshi Yatsuya, Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, 1300 South 2nd Street, Suite 300, Minneapolis, MN 55454 (e-mail: yatsuya@gmail.com).

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Use of smokeless tobacco in the United States has been relatively constant in recent years, as tobacco companies continue aggressive marketing campaigns. The health effects of smokeless tobacco use need further documentation. Thus, the authors examined whether current use of smokeless tobacco was associated with increased incidence of cardiovascular disease (CVD) in 14,498 men and women aged 45–64 years at baseline (1987–1989) in the Atherosclerosis Risk in Communities (ARIC) Study. There were 2,572 incident CVD events (myocardial infarction, coronary revascularization, coronary death, or stroke) during a median of 16.7 years of follow-up (maximum = 19.1 years). Current use of smokeless tobacco at baseline was associated with 1.27-fold greater CVD incidence (95% confidence interval: 1.06, 1.52) than was nonuse, independently of demographic, socioeconomic, and lifestyle and other tobacco-related variables. Past use of smokeless tobacco was not associated with CVD incidence. In conclusion, current use of smokeless tobacco was associated with increased risk of CVD incidence in ARIC cigarette nonsmokers. Current users of smokeless tobacco should be informed of its harm and advised to quit the practice. Current cigarette smokers should also be given sufficient information on safe, therapeutic methods of quitting which do not include switching to smokeless tobacco.

cardiovascular diseases; epidemiologic studies; prospective studies; tobacco, smokeless; United States

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.

The prevalence of use of smokeless tobacco, especially snuff, in the United States has risen slightly in recent decades (3.1% in 1998, 3.3% in 2003, and 3.5% in 2008) (1, 2) in parallel with aggressive marketing campaigns (3, 4). In 2008, 9.3% of white males, 0.3% of white females, 2.0% of black males, and 1.2% of black females in the United States reported using smokeless tobacco (5). Several cohort studies have shown that current use of smokeless tobacco (chewing tobacco and snuff) in never-smoking men is associated with increased cardiovascular disease (CVD) mortality (6–8), but other prospective studies failed to find such an association (9–12). Two meta-analyses of existing studies derived different conclusions: One found a positive association between smokeless tobacco and CVD (13) and the other found no association, especially regarding Swedish snuff (14). However, the latter meta-analysis did not include 2 recent studies of Swedish construction workers that demonstrated a positive association between smokeless tobacco use and fatal CVD (7, 8). Furthermore, despite data on CVD mortality, the association of smokeless tobacco with CVD incidence remains largely unknown. While the health effects of smokeless tobacco are inconclusive, some people have advocated the substitution of smokeless tobacco, particularly snuff, for cigarette smoking to help reduce smoking rates, under the claim of a smaller risk to health (15).

Thus, it is important to examine the association between smokeless tobacco use and CVD incidence, not mortality, since mortality does not necessarily represent the burden of a disease due to an exposure. It also seems important to

consider possible confounding by other tobacco products, as well as secondhand smoke exposure, for which no previous studies adjusted.

For this analysis, we hypothesized that current use of smokeless tobacco would be associated with increased incidence of CVD.

MATERIALS AND METHODS

Study population

The Atherosclerosis Risk in Communities (ARIC) Study included a cohort of 15,792 persons between the ages of 45 and 64 years at recruitment in 1987–1989. Population samples were selected by probability sampling methods from 4 US communities: Forsyth County, North Carolina (n = 4,035); Jackson, Mississippi (blacks only; n = 3,728); the northwestern suburbs of Minneapolis, Minnesota (n = 4,009); and Washington County, Maryland (n = 4,020). From all black (enrolled in Jackson and Forsyth County) and white ARIC visit 1 participants (n = 15,689), subjects with the following characteristics were excluded from the present analysis: 1) missing values on cigarette smoking status and use of other tobacco products (snuff, chewing tobacco, pipes, and cigars) at baseline (n = 56); 2) missing values on educational level, cigarette smoking status, usual ethanol consumption, or physical activity (n = 169); and 3) a self-reported history of coronary heart disease or stroke at visit 1 (n = 966). This left us with 14,498 persons for analysis.

Institutional review boards at each clinical site approved the study protocol, and written informed consent was obtained from all participants.

Ascertainment of CVD incidence

CVD incidence was ascertained through 2005. Incident CVD consisted of incident coronary heart disease and stroke. A coronary heart disease event was defined as a validated definite or probable hospitalized myocardial infarction, a definite coronary heart disease death, an unrecognized myocardial infarction defined by ARIC electrocardiography reading, or coronary revascularization (16, 17). A stroke event was defined as a validated definite or probable hospitalized ischemic or hemorrhagic stroke confirmed by imaging (18).

Use of smokeless tobacco and other smoking-related variables

Current and past use of chewing tobacco and snuff, assessed at baseline, is collectively called "smokeless tobacco use" here. Current and past use of cigars and pipes and exposure to secondhand smoke (hours/week) were also reported at baseline. For current and past cigarette smokers, cigarette-years of smoking was calculated as the number of cigarettes smoked per day multiplied by the number of years of smoking.

Baseline assessment

Questionnaires were used to assess baseline educational level, total annual household income, alcohol drinking, leisure-time sports participation, use of antihypertensive or diabetic medication, and history of physician-diagnosed diabetes, coronary heart disease, or stroke. The sports index was derived from questionnaire items on numbers of hours per week spent in up to 4 sports and the number of months per year in which the participant engaged in each sport (19). By assuming a sport intensity level (light, moderate, or heavy), we calculated a sports score ranging from 1 (lowest) to 5 (highest). Three blood pressure measurements were taken with a random-zero sphygmomanometer; the last 2 measurements were averaged. Waist circumference was measured at the umbilical level. Blood was drawn after an 8-hour fasting period with minimal trauma from an antecubital vein. Glucose, total and high density lipoprotein cholesterol, and triglycerides were measured centrally by standard methods. Prevalent diabetes was defined as a history of or treatment for diabetes, a fasting glucose level of 126 mg/dL or greater, or a casual blood glucose level of 200 mg/dL or greater.

Statistical analysis

Hazard ratios for CVD among current or past users of smokeless tobacco (with never users as the reference group) and their 95% confidence intervals were calculated using a Cox proportional hazards regression analysis. In multivariate model 1, we adjusted for baseline levels of age (continuous), sex, race-center, educational level (less than high school, high school or vocational school, college, or graduate or professional school), total annual household income ($\leq$\$15,999, \$16,000–\$34,999, $\geq$\$35,000, or no response), usual alcohol consumption (g/week; continuous), sports index score (1, 2–<2.5, 2.5–<3, or $\geq$3), cigarette smoking status (never, past, or current smoker), and cigarette-years of smoking (continuous). In model 2, we adjusted for the variables in model 1 plus baseline pipe use (current, past, or never user), cigar use (current, past, or never user), and secondhand smoke exposure (hours/week; continuous). In model 3, we additionally adjusted for baseline systolic blood pressure (mm Hg; continuous), use of antihypertensive medication (yes, no), diabetes (yes, no), waist circumference (cm; continuous), total and high density lipoprotein cholesterol (IU/L; continuous), and triglycerides (IU/L; continuous). We also fitted a Cox model with time-varying data on smokeless tobacco use through visit 3. Furthermore, we performed a stratified analysis by cigarette smoking status at visit 1.

We assessed the assumption of hazards proportionality by examining the parallelness of the ln (−ln) survival curves for groups defined by current/past use of smokeless tobacco, and by including an interaction term for the interaction between smokeless tobacco use and time (continuous or dichotomized at the median: 10 years) in the Cox model.

RESULTS

At baseline (1987–1989) in the ARIC Study, the overall prevalence of current smokeless tobacco use among cigarette nonsmokers was 3.1% (n = 456). The prevalence was higher in black and white men (5.9% and 5.3%, respectively) and black women (4.0%) and lower in white women (0.4%).

Table 1. Age-, Sex-, and Race-Center-adjusted Baseline Characteristics of Participants According to Use of Smokeless Tobacco (Chewing Tobacco or Snuff), Atherosclerosis Risk in Communities Study, 1987–1989

	Use of Smokeless Tobacco			*P* Value[a]
	Never User (*n* = 13,307)	Past User (*n* = 735)	Current User (*n* = 456)	
Age, years[b]	53.9	55.1	55.1	<0.0001
Male sex, %[b]	39.9	81.2	73.9	<0.0001
Black race/ethnicity, %[b]	25.4	36.5	39.3	<0.0001
Less than high school education, %	22.4	37.7	46.4	<0.0001
Total annual household income ≤$15,999, %	24.5	34.6	38.5	<0.0001
Current cigarette smoker, %	28.5	34.2	23.1	<0.0001
Past cigarette smoker, %	28.6	43.9	36.2	<0.0001
Cigarette-years of smoking (ever smokers only)	517	548	540	0.18
Usual ethanol intake, g/week	41.7	42.3	40.9	0.97
Leisure-time sports index[c] score ≥3, %	26.9	28.8	26.5	0.52
Current pipe smoker, %	1.4	3.1	3.4	<0.0001
Current cigar smoker, %	1.5	3.8	4.0	<0.0001
Secondhand smoke exposure, hours/week	6.8	7.4	7.8	0.32
Use of antihypertensive medication, %	29.9	33.3	37.4	<0.001
Diabetes mellitus, %	11.6	14.3	19.2	<0.0001
Waist circumference, cm	97.0	98.7	101.0	<0.0001
Systolic blood pressure, mm Hg	121.8	121.2	122.5	0.43
Total cholesterol level, IU/L	5.53	5.48	5.52	0.43
High density lipoprotein cholesterol level, IU/L	1.36	1.33	1.33	0.11
Triglyceride level, IU/L	1.42	1.46	1.47	0.33

[a] *P* values were calculated by means of a general linear model.
[b] Crude.
[c] The sports index was derived from questionnaire items on numbers of hours per week spent in up to 4 sports and the number of months per year in which the participant engaged in each sport (19). By assuming a sport intensity level (light, moderate, or heavy), a sports score ranging from 1 (lowest) to 5 (highest) was calculated.

Compared with never users, both current and past users of smokeless tobacco were older, were more likely to be male and black, and had lower education and income levels (Table 1). Current and past users of smokeless tobacco were more likely to smoke pipes and cigars. Prevalences of antihypertensive medication use and diabetes mellitus were higher and waist circumferences were greater in current and past users of smokeless tobacco.

During a median of 16.7 years of follow-up (maximum = 19.1 years), 2,572 incident CVD events were identified. Subjects who were currently using smokeless tobacco had a higher CVD incidence rate than past and never users (21.4/1,000 person-years vs. 16.7/1,000 person-years and 11.3/1,000 person-years, respectively) (Table 2). The CVD rate associated with current use of smokeless tobacco was higher than that for current cigarette smoking (21.4/1,000 person-years vs. 16.4/1,000 person years). After adjustment for potentially confounding factors, including cigarette smoking status and use of other tobacco products, current smokeless tobacco use was still significantly positively associated with CVD incidence (hazard ratio (HR) = 1.27, 95% confidence interval (CI): 1.06, 1.52). After adjustment for CVD risk factors (model 3), some of which may be mediators, a significant association between current smokeless tobacco use and CVD incidence remained (HR = 1.21, 95% CI: 1.00, 1.45) (data not shown in table). Past smokeless tobacco use was not associated with CVD incidence. Although CVD incidence rates in current smokeless tobacco users were higher than those in nonusers among both cigarette nonsmokers and current smokers, the association was statistically significant and independent of confounding factors only in cigarette nonsmokers (Table 3).

Separately calculated associations for never and past cigarette smokers were virtually identical (data not shown). Likewise, current use of smokeless tobacco tended to be positively associated with both coronary heart disease and stroke, but with wide 95% confidence intervals due to smaller numbers when data were analyzed separately (data

Table 2. Incidence Rates and Hazard Ratios for Cardiovascular Disease[a] According to Use of Smokeless Tobacco (Chewing Tobacco or Snuff) and Cigarette Smoking, Atherosclerosis Risk in Communities Study, 1987–2005

	Total No.	No. of Cases	Incidence Rate[b]	Crude		Model 1[c]		Model 2[d]	
				HR	95% CI	HR	95% CI	HR	95% CI
Use of smokeless tobacco									
Never user	13,307	2,270	11.3	1	Referent	1	Referent	1	Referent
Past user	735	171	16.7	1.50	1.28, 1.75	0.90	0.77, 1.06	0.88	0.75, 1.04
Current user	456	131	21.4	1.95	1.63, 2.32	1.29	1.08, 1.55	1.27	1.06, 1.52
Cigarette smoking									
Never smoker	6,201	875	9.0	1	Referent	1	Referent	1	Referent
Past smoker	4,553	849	12.5	1.40	1.28, 1.54	1.01	0.90, 1.12	0.99	0.89, 1.11
Current smoker	3,744	848	16.4	1.87	1.70, 2.06	1.47	1.30, 1.66	1.46	1.29, 1.66

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Cardiovascular disease was defined as hospitalized myocardial infarction, fatal coronary heart disease, electrocardiogram-confirmed myocardial infarction, cardiac procedure, or stroke.

[b] Per 1,000 person-years.

[c] In model 1, hazard ratios were adjusted for age, sex, race-center, educational level, total annual household income, usual alcohol consumption, physical activity, cigarette smoking status (never, past, or current smoker), pack-years of smoking, and use of smokeless tobacco.

[d] Model 2 included all of the variables in model 1 plus past and current use of pipes and cigars and secondhand smoke exposure (hours/week).

not shown). We also performed several additional analyses. Use of a time-varying variable for smokeless tobacco use, with adjustment for model 2 covariates, did not essentially change the finding (for current smokeless tobacco use, HR = 1.36, 95% CI: 1.09, 1.71). Analysis excluding current cigar or pipe users at visit 1 or visit 2, as well as any current cigarette smoking reported at visits 1–4, yielded similar results (for current smokeless tobacco use in model 2, HR = 1.32, 95% CI: 1.04, 1.67). Finally, since the prevalence of smokeless tobacco use in white women was especially low (0.4%), we conducted analysis excluding white women; the results did not materially change (for current smokeless tobacco use in model 2, HR = 1.34, 95% CI: 1.07, 1.69).

DISCUSSION

Our analysis was based on a long-term, community-based US prospective study of both men and women and blacks and whites with validated information on CVD incidence. We found that current smokeless tobacco use at baseline was associated with approximately 27% greater CVD incidence than was nonuse, independently of potential confounding by

Table 3. Incidence Rates and Hazard Ratios for Cardiovascular Disease[a] According to Use of Smokeless Tobacco (Chewing Tobacco or Snuff), by Cigarette Smoking Status, Atherosclerosis Risk in Communities Study, 1987–2005

	Use of Smokeless Tobacco		
	Never User	Past User	Current User
Cigarette nonsmokers			
No. of cases/total no.	1,510/9,906	112/494	102/354
Incidence rate[b]	9.8	16.0	21.0
Hazard ratio[c] (95% CI)	1 (referent)	0.90 (0.73, 1.11)	1.31 (1.06, 1.61)
Current cigarette smokers			
No. of cases/total no.	760/3,401	59/241	29/102
Incidence rate	16.1	18.3	22.9
Hazard ratio (95% CI)	1 (referent)	0.86 (0.65, 1.13)	1.09 (0.74, 1.60)

Abbreviation: CI, confidence interval.

[a] Cardiovascular disease was defined as hospitalized myocardial infarction, fatal coronary heart disease, electrocardiogram-confirmed myocardial infarction, cardiac procedure, or stroke.

[b] Per 1,000 person-years.

[c] Hazard ratios were adjusted for age, sex, race-center, educational level, total annual household income, usual alcohol consumption, physical activity, never or past cigarette smoking (in cigarette nonsmokers), pack-years of smoking, past and current use of pipes and cigars, and secondhand smoke exposure (hours/week).

demographic, socioeconomic, and lifestyle and CVD risk factors.

The present finding is consistent with 4 previous analyses of CVD mortality involving 2 US cohorts (6) and 1 Swedish cohort (7, 8). In the United States, current use of smokeless tobacco (chewing tobacco or snuff) was associated with increased CVD mortality among subjects who had never used other tobacco products in both Cancer Prevention Study I (HR = 1.18, 95% CI: 1.11, 1.26) and Cancer Prevention Study II (HR = 1.23, 95% CI: 1.09, 1.39) (6). In a cohort of construction workers in Sweden who had never smoked cigarettes, current use of snuff was significantly positively associated with fatal myocardial infarction (HR = 1.32, 95% CI: 1.08, 1.61) (7) and fatal ischemic stroke (HR = 1.72, 95% CI: 1.06, 2.78) (8). As in these studies, we also conducted analyses excluding current cigarette smokers in an attempt to remove strong confounding by cigarette smoking, and we found similar associations (6–8).

Our study extended these observations of CVD mortality to the association of smokeless tobacco use with CVD incidence and to the population including past cigarette smokers as well as current cigarette smokers. To our knowledge, this is also the first cohort study to have adjusted for use of other tobacco products. These facts strongly suggest that an independent association exists between current use of smokeless tobacco and CVD incidence.

Current evidence on smokeless tobacco and CVD seems consistent. The most recent meta-analysis demonstrated the excess CVD mortality risk of smokeless tobacco use to be 13% for fatal myocardial infarction (95% CI: 6%, 21%) and 40% for fatal stroke (95% CI: 28%, 54%) (13). Our study showed a 27% excess risk of incident CVD. Even a relative risk of this magnitude poses considerable harm to the health of the nearly 5% of US adults who use smokeless tobacco. The estimated relative risk is comparable to that reported for secondhand smoke (20).

Smokeless tobacco has been reported to contain more than 2,000 chemical compounds, and the major addicting substance is nicotine (21). Mechanisms by which smokeless tobacco might cause CVD have been reviewed (21) and include acute elevation of blood pressure (22), chronic hypertension (23), and acute activation of the sympathetic nervous system (24). Our findings were independent of antihypertensive medication use, sitting blood pressure, diabetes, and plasma lipid levels, implying the existence of other mediating factors. Additional adjustment for heart rate did not materially alter the findings (data not shown). It is conceivable that an acute response to smokeless tobacco use may be responsible for the association. Case-crossover studies (25) inquiring about the use of smokeless tobacco at the time of or prior to the onset of CVD events may be valuable.

Limitations of the present study warrant consideration. First, we did not assess the quantity or duration of smokeless tobacco use, which prevented examination of dose-response. Second, misclassification of smokeless tobacco use is possible. However, since we obtained the exposure information prior to the assessment of CVD events, misclassification would probably have attenuated the observed association. It is also possible that current cigarette smoking was misclassified, since we did not take an objective measurement of cigarette smoking. However, the questionnaire-based interview used different questions for each tobacco practice, making unintentional misclassification unlikely. Nevertheless, future studies collecting data on tobacco biomarkers among smokeless tobacco users may be valuable for confirming the present findings and for elucidating mechanisms underlying the association. Third, the number of subjects who reported using smokeless tobacco was relatively small; therefore, the precision of the hazard ratios was limited for subgroup analyses. In addition, our analysis was based on a sample of middle-aged participants recruited in 1987–1989. Patterns and types of smokeless tobacco use may have changed. Contemporary studies, including those designed to address the health effects of dual use of smokeless tobacco and cigarettes or health effects in younger adults, are warranted. Finally, most of the black participants were from 1 field center and the whites were from 3 other centers, which limits the generalizability of our findings to other cultural or socioeconomic contexts.

In conclusion, current use of smokeless tobacco was associated with increased risk of CVD incidence among nonsmokers in the ARIC Study. Current users of smokeless tobacco should be informed of its harm and advised to quit the habit. Current cigarette smokers should also be given sufficient information on safe, therapeutic methods of quitting which do not include switching to smokeless tobacco.

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Author affiliations: Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota (Hiroshi Yatsuya, Aaron R. Folsom); and Department of Public Health, Graduate School of Medicine, Nagoya University, Nagoya, Japan (Hiroshi Yatsuya).

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