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A longitudinal study of smokeless tobacco use and mortality in the United States

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Cancer Epidemiology

Few studies in the United States have examined longitudinally the mortality risks associated with use of smokeless tobacco (SLT). The sample of our study was composed of participants from the National Longitudinal Mortality Study who completed a single Tobacco Use Supplement to the Current Population Survey between the years 1985 and 2011. Using survival methods, SLT use at the baseline survey was examined as a predictor of all-cause mortality and cause-specific mortalities in models that excluded individuals who had ever smoked cigarettes, cigars or used pipes (final $n = 349,282$). The participants had median and maximum follow-up times of 8.8 and 26.3 years, respectively. Regression analyses indicated that compared to the never tobacco users, the current SLT users did not have elevated mortality risks from all cancers combined, the digestive system cancers and cerebrovascular disease. However, current SLT users had a higher mortality risk for coronary heart disease (CHD) [hazard ratio (HR) (95% CI) = 1.24 (1.05, 1.46)] relative to never tobacco users. In a separate model, the elevated risk for CHD mortality corresponded to the use of moist snuff [HR (95% CI) = 1.30 (1.03, 1.63)]. The associations with CHD mortality could be attributed to long-term nicotine exposure, other SLT constituents (*e.g.*, metals) or the confounding effects of CHD risk factors not accounted for in our study. The study's findings contribute to the ongoing dialogue on tobacco harm reduction and the US FDA's evaluation of Modified Risk Tobacco Product applications submitted by American SLT manufacturers.

Epidemiologic studies of smokeless tobacco (SLT) use and health outcomes in the United States are few in number and challenged by low exposure prevalence[1,2] and temporal changes in product constituents (*e.g.*, toxicants).[3] The investigation of both rare and common outcomes associated with SLT use has necessitated the use of various epidemiologic study designs. In contrast to the longitudinal design, the case–control study design is effective in amassing a sufficient number of diseased individuals for investigating causes of a rare outcome, such as head and neck cancer (HNC).[4] A meta-analysis of 11 US case–control studies indicated a positive association between ever use of snuff and the occurrence of HNC [OR (95% CI) = 1.71 (1.08–2.70)]. In contrast, Wyss *et al.*[4] did not observe a statistically significant association between ever use of chewing tobacco and HNC. Varying levels of tobacco-specific nitrosamines (TSNAs) in moist snuff versus chewing tobacco[3] could possibly account for the discrepant findings observed in the meta-analysis. Chewing tobacco in recent years has experienced a diminishing US market share as evidenced by its decline from 9.0% in 2005 to 4.3% in 2011.[5] In addition to head and neck cancer, ever use of SLT has been linked to two other uncommon cancers, esophageal cancer [RR (95% CI) = 1.6 (1.1–2.3)] and pancreatic cancer [RR (95% CI) = 1.6 (1.1–2.2)], in data pooled from US and Nordic countries.[6]

Longitudinal studies in the US have tested for associations between SLT use and common causes of mortality by linking death certificate data to a single, baseline assessment of tobacco use behaviors.[7–9] Using this approach, Henley *et al.*[8] reported statistically significant associations between current SLT use and various common causes of death, such as coronary heart disease [hazard ratio (HR) (95% CI) = 1.26 (1.08–1.47)] and cerebrovascular disease [HR (95% CI) = 1.40 (1.10–1.79)] in the Cancer Prevention Study II. Similar estimates were reported in a meta-analysis of three US longitudinal studies,[10] two of which corresponded to Cancer Prevention Studies I (CPS-I) and II (CPS-II).[8] A fourth US study linked mortality to tobacco use behaviors from the

Key words: smokeless tobacco, longitudinal study, mortality, survival methods

Abbreviations: CHD: coronary heart disease;; FDA: Food and Drug Administration; MRTP: modified risk tobacco product; NLMS: National Longitudinal Mortality Study; SLT: Smokeless Tobacco; TUS-CPS: Tobacco Use Supplement to the Current Population Survey

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What's new?
This epidemiologic investigation represents one of the few longitudinal studies that tracked the mortality status of US residents according to their use of smokeless tobacco. While users of smokeless tobacco have an elevated risk of dying from coronary heart disease, they do not have elevated mortality risks from all cancers (combined) and the digestive system cancers. These findings contribute to the ongoing dialogue on tobacco harm reduction in the United States.

1987–2005 National Health Interview Surveys.[9] Two of the four longitudinal studies were funded by tobacco companies,[7,9] highlighting the need for an investigation unfettered by industry interests. In fulfilling this need, we utilized a longitudinal study design in estimating mortality risks in a large sample of never smokers ($n = 349,282$) who participated in a Tobacco Use Supplement to the Current Population Survey.

Material and Methods

Study participants

Participants were selected from the National Longitudinal Mortality Study (NLMS), a study funded by the US Census Bureau, the National Center for Health Statistics and the National Institutes of Health.[11,12] The NLMS has tracked the mortality status of approximately 3.8 million individuals who are categorized into one of 39 cohorts, defined according to the month and year (1973–2011) of administration of the Current Population Survey and the Annual Social and Economic Supplement. Participants of NLMS were randomly selected by household via complex probability sampling of noninstitutionalized US residents. The current study consisted of a subset of individuals from 18 of the 39 NLMS cohorts. These participants were administered a single Tobacco Use Supplement to the Current Population Survey (TUS-CPS) in one of the following years: 1985, 1992–1993, 1995–1996, 1998–1999, 2000, 2001–2002, 2003, 2006–2007 and 2010–2011.

The cohorts in NLMS were only tracked with respect to mortality in the United States. Consequently, measurements of demographics and tobacco use behaviors were assessed exclusively at the baseline survey. The survey did not query participants about existing morbidities and, thus, could not be used in excluding those with such conditions. In the current study, individuals who had ever smoked 100 cigarettes (or more) or had ever used cigars or pipes were excluded from all analyses. The final sample ($n = 349,282$) was limited to current SLT users, former SLT users and never tobacco users to eliminate the confounding effects of cigarette smoking and other tobacco use.[8,13]

Outcome measures

Cause-specific mortalities were linked to NLMS records through the National Death Index (NDI). The mortalities were defined according to the National Center for Health Statistics standardized list of 113 causes of death.[12] As coded in the NLMS, the causes of death were based on a compilation of codes from Version 9 and Version 10 of the International Classification of Diseases (ICD). From the 113 causes of death, five outcomes were selected on the basis of their associations with SLT in published epidemiologic studies (including morbidity studies).[4,6,10] They were mortality from cancer of the oral cavity or pharynx; mortality from pancreatic cancer; mortality from esophageal cancer; mortality from cerebrovascular disease; and mortality from coronary heart disease (CHD), the latter of which included acute myocardial infarction, atherosclerotic cardiovascular disease and other acute/chronic ischemic heart disease. Three additional outcomes, which have not been consistently associated with SLT, were selected for comparison with the estimates from other US longitudinal studies.[7,8] They were all-cause mortality; mortality attributed to all malignant neoplasms and mortality attributed to malignant neoplasms of the digestive system organs (esophagus, pancreas, stomach, small intestine, gallbladder, colon, rectum, anus and liver).

Independent variables

The primary predictor of the five common outcomes in our study (mortality from all causes, all cancers, coronary heart disease, cerebrovascular disease and digestive system cancers)was a nominal variable consisting of three groups of participants: (*i*) never tobacco users, (*ii*) former SLT users who used snuff or chewing tobacco prior to the baseline survey and (*iii*) current SLT users who reported use of snuff or chewing tobacco at the baseline survey. The NLMS staff constructed binary variables for current use of snuff and chewing tobacco from questions that slightly varied across surveys (*e.g.*, "Does use?", "Does currently use?").[12] The primary predictor of mortality from the three uncommon outcomes in our study (pancreatic cancer, esophageal cancer and cancer of the oral cavity or pharynx) consisted of only two groups: (*i*) never tobacco users and (*ii*) ever users of snuff or chewing tobacco. Current and former SLT users were combined into a single group of ever SLT users due to the rarity of the three cancer outcomes. Inconsistent assessment of detailed tobacco measures (*e.g.*, number of days of SLT used in past month) precluded examination of the dose–response relationship between SLT use and mortality.

In an additional set of analyses, a four-level nominal variable for type of SLT was examined as a predictor of mortality. The four categories consisted of never tobacco users, users of snuff only, users of chewing tobacco only and users of both snuff and chewing tobacco. The nominal variable was examined separately among two groups of participants consisting of: (*i*) never tobacco users and ever SLT users ($n = 349,282$) and (*ii*) never tobacco users and current SLT users ($n = 345,541$).

Table 1. Demographic characteristics of participants from the 1985–2011 TUS-CPS who did not smoke cigarettes, cigars or used pipes

		SLT[1] Status at Baseline Survey (row %)			
Demographic variable	Col. (%)	Never user	Former SLT user	Current SLT user	$\chi^2_{(df)}$
Sample size		340,622	3,741	4,919	
Cohort					
1985–1996	32.6	97.4	0.5	2.1	
1998–2003	32.6	97.5	1.3	1.2	
2006–2011	34.8	98.1	1.1	0.8	$1{,}180^{£}_{(4)}$
Age group					
<35 years of age	38.6	97.2	1.1	1.7	
35–49 years of age	26.6	97.4	1.3	1.3	
≥50 years of age	34.8	98.4	0.6	1.0	$508^{£}_{(4)}$
Gender					
Male	39.8	95.2	1.9	2.9	
Female	60.2	99.3	0.4	0.3	$6{,}659^{£}_{(2)}$
Race/Ethnicity					
Non-Hispanic white	71.7	97.3	1.1	1.6	
Non-Hispanic black	12.4	98.1	0.6	1.3	
Other race/ethnicity	15.9	99.2	0.5	0.3	$832^{£}_{(4)}$
Education[2]					
Didn't complete H.S.	20.5	97.4	0.7	1.9	
Completed H.S.	29.2	97.3	0.9	1.8	
≥Some college	50.3	98.0	1.1	0.9	$714^{£}_{(4)}$
Family income					
<$20,000	28.4	97.6	0.7	1.7	
≥$20,000	71.6	97.7	1.1	1.2	$190^{£}_{(2)}$
Type of SLT (ever use)					
Snuff only	42.8	NA[3]	37.1	62.9	
Chew only	50.4	NA	47.1	52.9	
Snuff and chew	6.8	NA	37.8	62.2	$84^{£}_{(2)}$

[1]Smokeless tobacco.
[2]Recoded variable represents highest grade completed.
[3]Not applicable (limited to ever users of SLT). $^{£}p < 0.00001$.

The former SLT users were not differentiated from the current users in the first group and excluded from the second group due to the large number of possible combinations of current and former users of snuff and chewing tobacco. Type of SLT use, both ever and current, was examined as a predictor for the three most common outcomes (mortality from all causes, all cancers and coronary heart disease). The demographic variables, which were treated as covariates in regression models, were gender, age, race/ethnicity, education and family income at the time of the baseline survey (refer Table 1 for categories). Alcohol consumption was not queried in the TUS-CPS, and, therefore, not adjusted for in any of the analyses.

Statistical analysis

Continuous-time survival methods were employed in testing for associations between SLT use and the mortality outcomes. For descriptive analyses, the log-rank test was used in comparing the survival curves of current SLT users, former SLT users and never tobacco users. Time to event was defined as the period in years between administration of the baseline survey and death. The censored individuals had either died from a cause of death not examined in our study, or survived until the last recorded assessment of the NLMS, December 31, 2011. Respondents who relocated to another country were not tracked, and, thus, would have been misclassified as censored had they died from the outcome of interest.

Cox proportional hazards regression was used for modeling time to event with adjustment for covariates. The model was specified by the equation $\log\ h(t) = \log\ h_o(t) + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_q X_q$, where t represents time to event; h_o is the baseline hazard; X_1–X_2 are indicator variables representing former and current SLT users; X_3 is age in years; X_4 is

gender; X_5–X_6 are indicator variables for non-Hispanic Blacks and other racial/ethnic groups, respectively; X_7–X_8 are indicator variables for high school completion and college attendance, respectively; and X_9 is having a family income of less than $20,000. The other set of models included three indicator variables representing type of SLT used (snuff, chew, snuff and chew), as well as the other covariates mentioned previously.

The regression models utilized the Breslow approximation for handling ties as implemented in Proc PHREG in SAS v9.4.[14] The 18 cohorts of the TUS-CPS covered a multitude of sampling designs, which precluded development of replicate weights for proper variance estimation. Sampling weights, however, were incorporated in all models and reweighted to account for differences in cohort size. Using a SAS macro provided by the US Census Bureau, the combined data was reweighted to represent the noninstitutionalized US population. Analyses were conducted between February 2016 and August 2016 at the US Census Bureau's Regional Data Center on the campus of the University of California, Irvine.

Statistical power

The power to detect the significant effect of SLT use on each of the eight outcomes was estimated on the basis of the Cox proportional hazards model, as implemented in the software package STATA v12.[15] The models incorporated sample size of the study ($n = 349{,}282$); event probabilities for each of the eight outcomes; standard deviations for current SLT use (sd = 0.118) and ever SLT use (sd = 0.155) for the five common and three uncommon outcomes, respectively; and effect estimates (*i.e.*, HRs) ranging from 1.05 to 3.0. For all-cause mortality, the sample yielded 0.80 power and 0.96 power to detect significant HRs of 1.15 and 1.20, respectively. For CHD mortality and mortality attributed to all cancers combined, the sample yielded 0.86 and 0.87 power, respectively, to detect a significant HR of 1.40. In contrast to the common outcomes, statistical power was insufficient to detect a significant effect of ever SLT use on esophageal cancer and cancer of the oral cavity or pharynx. Even for a strong effect (*i.e.*, HR = 3.0), power did not exceed 0.40 for either of the two outcomes.

Results

Descriptive statistics

The majority of participants were alive (91.7%) at the conclusion of the study (December 31, 2011), and, thus, treated as censored observations. The median and maximum follow-up times for all participants ($n = 349{,}282$) were 8.8 years and 26.3 years, respectively. As indicated in Table 1, the sample was predominantly female (60.2%) due to the exclusion of participants who had ever smoked cigarettes, cigars or used pipes. Yet, males were the predominant users of SLT compared to females (4.8% vs. 0.7%, respectively), a discrepancy warranting sex-stratified analyses. Ever use of SLT also differed by the other demographic variables in Table 1. The demographic groups with the highest percentage of ever users were the non-Hispanic whites, those under the age of 35 years, and those with a high school degree or less. There were noticeable differences between the current and former SLT users. For example, 62.9% of ever snuff users were current users, while only 52.9% of ever chew users were current users.

Mortality by SLT use

An examination of mortality rates by SLT use (Table 2) revealed that for the common causes of death, current SLT users had the highest death rates followed by the never users and former users. Log-rank tests of survival indicated significant differences for only two of the eight outcomes, all-cause mortality ($\chi^2_{(2\ df)} = 15.0$; $p < 0.001$) and CHD mortality ($\chi^2_{(2\ df)} = 23.7$; $p < 0.0001$). Accounting for multiple comparisons, the pairwise comparisons of the three SLT groups (current, former, never) revealed statistically significant differences between current SLT users and never users for all-cause mortality ($\chi^2_{(1\ df)}=6.4$; $p = 0.03$) and CHD mortality ($\chi^2_{(1\ df)}=12.7$; $p = 0.001$). Also, significant differences were observed between former and current users for all-cause mortality ($\chi^2_{(1\ df)}=15.0$; $p < 0.001$) and CHD mortality ($\chi^2_{(1\ df)}=23.1$; $p < 0.0001$). In contrast, no difference was observed between the former and never users for either of the two outcomes.

Cox regression models

The unadjusted HRs in Table 2 indicate that current SLT users have significantly greater risks compared to never users for all-cause mortality and CHD mortality. These findings are consistent with results from the log-rank tests. However, upon adjustment for covariates, a null association was observed between current SLT use and all-cause mortality. A closer examination revealed that the addition of age, sex and race/ethnicity to the model yielded an estimate for current SLT use that was diminished in magnitude, but still statistically significant [HR (95% CI) = 1.11 (1.03, 1.21)]. Once education and family income were added to the model, the coefficient for current SLT use was no longer statistically significant [HR (95% CI) = 1.01 (0.93, 1.10)].

In contrast to all-cause mortality, the association between current SLT use and CHD mortality remained statistically significant upon addition of all covariates (refer to Table 2). The adjusted estimate indicates that current SLT users have a 24% increased risk of dying from CHD relative to the never tobacco users. Upon restricting the sample to males ($n = 137{,}789$), current SLT users' increased risk of dying from CHD was statistically significant and comparable in magnitude [HR (95% CI) = 1.31 (1.06, 1.63)] to the estimate from the full sample. No association was observed for any of the other outcomes for males. In a separate model of females only ($n = 211{,}493$), former but not current SLT users had significantly greater risks than never tobacco users for all-cause mortality [HR (95% CI) = 1.49 (1.21, 1.83)] and cerebrovascular disease mortality [HR (95% CI) = 2.69 (1.55, 4.68)], but not CHD or any of the cancer outcomes.

Table 2. Associations between baseline smokeless tobacco use and cause-specific mortalities in unadjusted and adjusted proportional hazards models ($n = 349,282$)

Mortality	Status of SLT[1] user	No. of deaths	Deaths/ 1,000 p-yrs.[2]	Unadjusted HR (95% CI)	Adjusted[3] HR (95% CI)
All causes	Never user[4]	28,387	7.758	Referent	
	Former user[5]	196	6.841	0.89 (0.78, 1.03)	1.14 (0.99, 1.31)
	Current user[6]	580	9.477	1.21 (1.12, 1.31)[£]	1.01 (0.93, 1.10)
All cancers	Never user	5,895	1.594	Referent	
	Former user	39	1.285	0.80 (0.58, 1.11)	1.01 (0.73, 1.39)
	Current user	96	1.677	1.05 (0.87, 1.27)	.99 (0.82, 1.21)
Coronary heart disease	Never user	5,770	1.564	Referent	
	Former user	33	1.149	0.74 (0.52, 1.03)	0.93 (0.66, 1.30)
	Current user	147	2.467	1.57 (1.34, 1.84)[£]	1.24 (1.05, 1.46)[€]
Cerebrovascular disease	Never user	2,237	0.633	Referent	
	Former user	13	0.550	0.88 (0.54, 1.43)	1.33 (0.81, 2.18)
	Current user	40	0.653	1.02 (0.75, 1.39)	0.92 (0.67, 1.27)
Digestive system cancers[7]	Never user	1,633	0.433	Referent	
	Former user	11	0.332	0.77 (0.41, 1.44)	0.87 (0.46, 1.64)
	Current user	32	0.555	1.28 (0.92, 1.78)	0.99 (0.70, 1.41)
Pancreatic cancer	Never user	419	0.114	Referent	
	Ever user	8	0.083	0.73 (0.36, 1.47)	0.70 (0.34, 1.43)
Esophageal cancer	Never user	95	0.027	Referent	
	Ever user	NR[8]	0.019	0.71 (0.16, 3.04)	0.46 (0.11, 2.00)
Oral cavity cancer[9]	Never user	38	0.010	Referent	
	Ever user	NR[8]	0.011	1.09 (0.13, 8.95)	0.83 (0.10, 7.03)

[1]Smokeless tobacco.
[2]Unadjusted mortality rate (deaths/1,000 person-years).
[3]Hazard ratio adjusted for age, gender, race/ethnicity, education and family income.
[4]Reference group consists of participants who never used tobacco ($n = 340,622$).
[5]($n = 3,741$).
[6]($n = 4,919$).
[7]Includes pancreatic and esophageal cancer.
[8]Not reported due to US Census Bureau policy (<5 deaths).
[9]Cancer of the oral cavity or pharynx. *$p < 0.05$. [€]$p < 0.01$. [£]$p < 0.001$

The mortality risks by SLT type are summarized in Table 3. Neither the ever use of a single product nor the ever use of both products (snuff and chewing tobacco) was associated with any of the three common causes of death. Yet, the current use of snuff (but not chewing tobacco) was associated with CHD mortality [HR (95% CI) = 1.30 (1.03, 1.63)]. The current use of both SLT products was predictive of all-cause mortality and CHD mortality in adjusted models. Current use of both snuff and chewing tobacco was also predictive of CHD mortality in a model restricted to males [HR (95% CI) = 3.07 (1.39, 6.78)].

Discussion

The statistically significant association between current SLT use and mortality from coronary heart disease was the primary finding of our study. Further analyses revealed that the association occurred among males and current users of moist snuff. The SLT users' elevated risk for CHD mortality in our study is generally consistent with the findings from other US longitudinal studies as summarized in reviews.[10,16,17] Significant associations between current SLT use and CHD mortality were observed in both CPS-I and CPS-II.[8] The adjusted HR for CHD mortality from CPS-II was remarkably similar in magnitude [HR (95% CI) = 1.26 (1.08, 1.47)] to our own estimate [HR (95% CI) = 1.24 (1.05, 1.46)]. The risk for cardiovascular mortality, however, was not significantly greater among exclusive SLT users compared to the nontobacco users who participated in the NHANES I Follow-up Study [HR (95% CI) = 1.1 (0.8, 1.5)].[7] But, the NHANES Study had a considerably smaller sample size ($n = 5,697$) compared to the other US longitudinal studies, including CPS-I, CPS-II and the current study.

Adjustment for education and family income was one attempt to control for potential confounding effects on the association between SLT use and CHD mortality. But, the absence of known CHD risk factors in the TUS-CPS was an

Table 3. Associations between type of smokeless tobacco (snuff/chewing tobacco) and common causes of mortality by ever and current use

		Unadjusted rate[2]		Adjusted hazard ratio[3] (95% CI)	
Mortality	Use of SLT[1]	No. of deaths	Deaths/ 1,000 p-yr.	Ever SLT use ($n = 349,282$)	Current SLT use[4] ($n = 345,541$)
All causes	Never user[5]	28,387	7.758	Referent	
	Snuff only[6]	355	10.781	1.10 (0.99, 1.22)	1.01 (0.90, 1.14)
	Chew only[7]	371	7.210	0.98 (0.88, 1.09)	0.97 (0.86, 1.10)
	Snuff and chew[8]	50	8.736	1.05 (0.81, 1.37)	1.49 (1.05, 2.13)*
All cancers	Never user	5,895	1.594	Referent	
	Snuff only	49	1.533	0.88 (0.67, 1.15)	0.83 (0.61, 1.14)
	Chew only	76	1.573	1.11 (0.89, 1.39)	1.08 (0.83, 1.41)
	Snuff and chew	10	1.529	0.92 (0.49, 1.75)	1.83 (0.87, 3.82)
Coronary heart disease	Never user	5,770	1.564	Referent	
	Snuff only	86	2.493	1.22 (0.99, 1.52)	1.30 (1.03, 1.63)*
	Chew only	86	1.782	1.12 (0.91, 1.38)	1.11 (0.88, 1.42)
	Snuff and chew	8	1.877	1.18 (0.66, 2.09)	2.35 (1.24, 4.46)€

[1]Smokeless tobacco.
[2]Corresponds to ever SLT use (deaths/1,000 person-years).
[3]Hazard ratio adjusted for age, gender, race/ethnicity, education and family income.
[4]Excludes former SLT users.
[5]Reference group consists of never tobacco users ($n = 340,622$).
[6]($n = 3,596$).
[7]($n = 4,499$).
[8]($n = 565$). *$p < 0.05$. €$p < 0.01$.

important limitation of our study, which raises the possibility of a noncausal association. It is conceivable that our estimate [HR (95% CI) = 1.24 (1.05, 1.46)] was inflated relative to the estimate pooled from three US longitudinal studies [RR (95% CI) = 1.11 (1.04, 1.19)][10] due to the residual confounding of lack of exercise and fruit/vegetable intake (which were accounted for in the three studies). If our estimate was inflated from residual confounding, but still reflective of a causal association, then long-term nicotine exposure may have contributed to a fatal CHD event.[18] As reviewed by Benowitz and Burbank,[19] there are several mechanisms through which nicotine exposure could cause cardiovascular disease, such as inflammatory responses and dyslipidemia. Alternatively, other SLT constituents (*e.g.*, metals, salts) may have contributed to the elevated risk for CHD mortality. In contrast to CHD, we did not observe a significant effect of current SLT use on mortality from cerebrovascular disease (*i.e.*, stroke). However, greater risk for stroke mortality was observed among females who formerly used SLT (vs. never tobacco users), which could reflect a poor health condition or diagnosis prior to SLT cessation.[2]

The advantages of conducting a longitudinal study over a case–control study for the uncommon outcomes were offset by the few participants who died from cancer of the oral cavity or pharynx, esophageal cancer and to a lesser extent pancreatic cancer. Increasing the number of cases (per exposure group), via the combining of current and former SLT users into a single group of ever SLT users, had negligible effects on the estimates. The few deaths attributed to the uncommon cancers, which were not unexpected, contributed to low statistical power and high standard errors for the HRs. The few deaths from the uncommon cancers also occurred in the other US longitudinal studies.[7,8] In the NHANES Study, Accortt *et al.*[7] observed only two deaths from oropharyngeal cancer among ever SLT users, and, thus, utilized expected deaths from population-level mortality rates in deriving a nonsignificant standardized mortality ratio (95% CI) of 107 (10, 308). Similarly, Henley *et al.*[8] only observed four deaths from oropharyngeal cancer among current SLT users in CPS-I and only a single death in CPS-II. Relative to CPS-I and CPS-II, our study benefited from a larger sample of never tobacco users; however, we had fewer current SLT users compared to CPS-I (4,919 vs. 7,745, respectively). The low prevalence of current SLT use in the US and rarity of mortality from oropharyngeal cancer highlight the challenges and need for amassing enormous samples for future longitudinal studies.

The grouping of cause-specific mortalities into broader categories of mortality (*i.e.*, mortality due to all causes, all cancers and digestive system cancers) was one means of addressing the limited statistical power in assessing effects of SLT use on the uncommon outcomes. Unlike CPS-I, we did not observe a statistically significant effect of current SLT use on mortality from the digestive system cancers. Yet, similar to CPS-I, we observed a null association between current SLT use and mortality from all cancers combined. Null associations with this outcome were also observed in the NHANES I Epidemiologic Follow-up Study[7] and the1987–2005 National Health Interview Surveys (NHIS).[9]

Our investigation benefited from a large nationally-representative sample of participants whose mortality was accurately tracked over a 26-year period (8.8 years. median). Despite this strength, there were notable limitations that could have affected the validity of the findings. First, the assessment of a single, baseline measure of SLT use did not reflect participants' likely change in tobacco use over time. Such change could have been the uptake or discontinuation of SLT use, or possibly the transition from chewing tobacco to moist snuff. The discrepancy between the higher prevalence of ever using chewing tobacco (vs. snuff) and low market share (*e.g.*, 4.3% in 2011[5]) could be attributed to a decline in preference for chewing tobacco over time, or the misclassification of self-reported SLT type. A second limitation was the absence of measures in the TUS-CPS for diet, alcohol use and other behavioral factors that could have confounded the associations with cause-specific mortalities, notably coronary heart disease. Third, the NLMS did not track the mortality status of individuals who were living abroad. Fourth, the NLMS did not have information on diagnoses, and, therefore, limited our analyses to fatal outcomes. Similarly, the baseline TUS-CPS did not query participants about any preexisting conditions (*i.e.*, causes of mortality in our study), which may have affected the tobacco use behaviors at the baseline survey. While it is likely that individuals discontinued their SLT use following a disease diagnosis, it is unlikely that they would have initiated use. Thus, our estimates may have underestimated rather than overestimated the effect of SLT use on the cause-specific mortalities.

This investigation complements the few US longitudinal studies on mortality risks associated with SLT use. The findings contribute to the dialogue on tobacco harm reduction and the FDA's evaluation of applications seeking to modify SLT warning labels. A recent example of the latter is Swedish Match's efforts to replace three warning labels with a label stating that use of snus has lower health risks compared to cigarettes.[20] While our results do not pertain to Swedish snus, the results could conceivably be used in the FDA's review of a Modified Risk Tobacco Product application submitted by an American SLT manufacturer. Our findings could also be used by the FDA in evaluating whether the addition of a warning label for coronary heart disease is warranted. The 24% increased risk for CHD mortality among current SLT users is very similar in magnitude to the CHD risk from exposure to secondhand smoke.[21] But, our association could have been confounded by other CHD risk factors, which should be adjusted for in observational studies. Given the low statistical power for the uncommon outcomes, our findings do not shed light on whether American SLT products increase a user's risk for oral cancer. However, statistical power was sufficient for detecting modest effects of SLT on mortality from all cancers and the digestive system cancers, neither of which was observed in our study.

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