

Two large prospective studies of mortality among men who use snuff or chewing tobacco (United States)

S. Jane Henley, Michael J. Thun*, Cari Connell & Eugenia E. Calle

Department of Epidemiology and Surveillance Research, American Cancer Society, Atlanta, GA

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Abstract

Background: Few prospective studies have examined the health risks associated with use of snuff and chewing tobacco.

Methods: We studied the association between the use of spit tobacco (snuff or chewing tobacco) and mortality among men enrolled in Cancer Prevention Study I (CPS-I) in 1959 or Cancer Prevention Study II (CPS-II) in 1982. Analyses were based on men who reported exclusive use of snuff or chewing tobacco (7745 in CPS-I, 3327 in CPS-II) or no previous use of any tobacco product (69,662 in CPS-I, 111,482 in CPS-II) at baseline. Twelve-year follow-up of CPS-I, and 18-year follow-up of CPS-II identified 11,871 and 19,588 deaths, respectively. Cox proportional hazards models were used to control for age and other covariates.

Results: Men who currently used snuff or chewing tobacco at baseline had higher death rates from all causes than men who did not in both CPS-I (hazard ratio [HR] = 1.17, 95% CI = 1.11–1.23) and CPS-II (HR = 1.18, 95% CI = 1.08–1.29). In CPS-I, current use of spit tobacco was statistically significantly associated with death from coronary heart disease (CHD), stroke, and diseases of the respiratory, digestive, and genitourinary systems, but not with death from cancer. In CPS-II, use of these products was significantly associated with death from CHD, stroke, all cancers combined, lung cancer, and cirrhosis. The associations with cardiovascular and other non-malignant endpoints were attenuated, but not eliminated, by controlling for measured covariates. Former use of spit tobacco was not associated with any endpoint in CPS-II. No clear dose response was observed with either the frequency or duration of usage for any endpoint.

Conclusions: These two prospective studies provide limited evidence that current use of chewing tobacco or snuff may increase mortality from heart disease and stroke.

Introduction

More than 7.7 million Americans used spit tobacco in 2003 [1]. Products used in the United States (U.S.) are predominantly oral snuff, a finely ground or shredded tobacco of which a pinch is placed between the cheek and gum, and chewing tobacco, available in loose leaf, plug, or twist forms, and placed as a wad inside the cheek [2]. Men are more likely than women to use these products [3] except in the Southeastern U.S. [4]. Chewing tobacco is used predominantly by older men [2], whereas the use of

moist snuff has been popular among teenage and young adult males since the late 1970s [5].

About 30 epidemiologic studies have examined the morbidity or mortality experience of men who use spit tobacco (reviewed in Critchley and Unal [6]). Most are small, however, and many examine only cancer endpoints. Nearly all [7–11] of the studies that consider cardiovascular endpoints have been conducted in Sweden where the content of tobacco-specific nitrosamines in snuff is said to have been lowered by half between 1983 and 1992 [12]. Only one study examined cardiovascular endpoints in relation to spit tobacco in the U.S.; this was based on only 414 men who exclusively used these products [13].

We examined mortality patterns associated with the use of chewing tobacco and/or snuff in two large

* Address correspondence to: Michael J. Thun, Vice President, Epidemiology and Surveillance Research, American Cancer Society, 1599 Clifton Road, NE, Atlanta, GA 30329. Ph.: 404-329-5747; Fax: 404-327-6450; E-mail: mthun@cancer.org

American Cancer Society (ACS) prospective cohorts, Cancer Prevention Study I (CPS-I) enrolled in 1959, and Cancer Prevention Study II (CPS-II), enrolled in 1982. In CPS-I, 11,871 deaths were identified during 12-years of follow-up among 7745 men who reported exclusive use of chewing tobacco or snuff at enrollment and 69,662 who reported no use of any tobacco product. In CPS-II, 19,588 deaths occurred during 18-year follow-up among 3327 men who reported exclusive use of snuff or chewing tobacco at enrollment, and 111,482 who reported no use of any tobacco product.

Methods

CPS-I and CPS-II used similar methods of enrollment and follow-up [14]. In both cohorts, ACS volunteers invited families of their friends, neighbors, and acquaintances to participate. Enrollment was by household and sought to include all family members, age 30 years and above, in households with at least one person age 35 years or older. Each participant completed a confidential, four-page mailed questionnaire on his or her tobacco habits, alcohol intake, education, and other characteristics. Informed consent to participate in the study was implied by return mailing of the self-administered questionnaire. In CPS-I, over one million US adults (456,487 men and 594,544 women) from 25 states were enlisted by ACS volunteers in 1959 [15, 16]. In CPS-II, nearly 1.2 million U.S. adults (676,306 women and 508,351 men) were enrolled nationwide in the fall of 1982 [16, 17]. The participants in both cohorts reflect the demographic characteristics of the ACS volunteers and are more likely to be more educated, married, middle-class, and white than the general U.S. population [18].

Vital status was determined through personal enquiry by the volunteers for 12 years in CPS-I and the first six years (through September, 1988) in CPS-II. Deaths reported to the volunteers were verified and the causes of death identified from death certificates. CPS-II follow-up since 1988 has continued through automated linkage with the National Death Index [19]; a validation study demonstrated comparability between the two methods of follow-up [19]. CPS-I follow-up through December 1972 identified 23.8% of men as deceased, 64.6% alive, 6.7% lost to follow-up, and 4.9% who had follow-up truncated in 1965 due to inability of the ACS unit to continue the study. CPS-II follow-up through December 2000, identified 34.6% of men as deceased, 65.2% alive, and 0.2% who had follow-up censored on 1 September 1988, due to insufficient data for linkage with the National Death Index. Death certificate infor-

mation was obtained for 97% of known deaths in CPS-I and 98.9% in CPS-II. Underlying cause of death was coded from the death certificate coded according to *The International Classification of Diseases, Seventh Revision (ICD-7)* [20] in CPS-I and *Ninth Revision (ICD-9)* [21] in CPS-II. All aspects of the CPS-II study protocol have been reviewed and approved annually by the Emory University Institutional Review Board.

Information on spit tobacco use was obtained by questionnaire at enrollment but not updated during the follow-up of either cohort. CPS-I men were asked "Do you chew tobacco or use snuff?" and could answer "Never," "Occasionally," or "Regularly." We categorized men who reported occasional or regular use of these products as current users and all others as non-users. The CPS-I questionnaire did not ask specifically about former use; we excluded from the analyses men who volunteered information about former usage. CPS-II men were asked "Have you ever chewed tobacco at least once a week for at least one year?" and "Have you ever used snuff at least once a week for at least year?" For each product, usage was further assessed by asking how many times a week, age at which use began, total years of use, and if the product was used currently. We defined current users of spit tobacco to be men who reported current use of either snuff or chewing tobacco, former users to be those reporting former (but not current) use of either, and nonusers to be men who reported never using either product. All analyses excluded men who reported current or former tobacco smoking of cigarettes, cigars, or pipes. After exclusions, a total of 7745 and 2488 men in CPS-I and CPS-II, respectively were classified as current users and 69,662 and 111,482 were classified as never users. Another 839 CPS-II men were classified as former users. No information was available on the use of chewing tobacco or snuff by women.

Endpoints in the analyses included both broad categories of disease (all causes, all cancers, and diseases of the cardiovascular, respiratory, digestive, genitourinary systems, and external causes) and specific causes of death for conditions associated with cigarette smoking [22, 23] or spit tobacco (6) in other studies. Our analyses excluded men who reported prevalent disease at the time of enrollment. For instance, analyses of cancer mortality excluded persons who reported any prevalent cancer except non-melanoma skin cancer, analysis of coronary heart disease (CHD) mortality excluded men who reported prevalent heart disease or diabetes, analysis of cerebrovascular disease mortality excluded men who reported prevalent stroke, analysis of chronic obstructive pulmonary disease mortality excluded men who reported prevalent chronic

bronchitis or emphysema, and analysis of diabetes mortality excluded men who reported prevalent diabetes. The analysis of all-cause mortality excluded men who reported a history of any of these diseases at enrollment.

We used Cox proportional hazards models to estimate hazard ratios and 95% confidence intervals for mortality associated with spit tobacco use and to adjust for other potential risk factors reported at baseline [24]. All statistical tests were two-sided; hazard ratios were considered statistically significantly elevated if the lower limit of the 95% confidence interval was greater than 1.0 and $p < 0.05$ were considered statistically significant. Indicator variables were used for all independent variables. All models were adjusted for single year of age by stratification. Multivariable Cox

proportional hazards models adjusted for race, education, current alcohol consumption, exercise, aspirin use, body mass index [normal or below (<25), overweight (25–29), and obese (≥ 30)], quartiles of vegetable and fruit consumption, quartiles of dietary fat consumption, and, in CPS-II, type of occupation. Due to differences in wording and coding of the CPS-I and CPS-II questionnaires, we used similar but not identical categories for some covariates (Tables 1 and 2). In CPS-II current spit tobacco use was further characterized by number of times used per week and years of use. We used likelihood ratio testing [25] to assess the linear trend in the hazard ratio with either the duration or frequency of usage for conditions that were associated with current usage. Men who did not use spit tobacco were excluded from the tests for trend.

Table 1. Demographic and other characteristics of CPS-I men who in 1959 reported never use of tobacco products or exclusive use of chewing tobacco or snuff*

Characteristic	Spit Tobacco Use			
	Never		Current	
Total (N = 77,407)	69,662	(90.0)	7745	(10.0)
Median age at enrollment in 1959	53		62	
Race, number (%)				
White	67,882	(97.4)	7343	(94.8)
Nonwhite	1780	(2.6)	402	(5.2)
Education, number (%)				
< high school	25,017	(35.9)	6037	(77.9)
high school graduate	13,009	(18.7)	645	(8.3)
some college	12,240	(17.6)	510	(6.6)
college graduate	18,770	(26.9)	312	(4.0)
Current alcohol consumption, number (%)				
Abstainer	50,993	(73.2)	5429	(70.1)
≤ 1 daily	11,608	(16.7)	1196	(15.4)
> 1 daily	6521	(9.4)	1015	(13.1)
Exercise, number (%)				
None/slight	14,770	(21.2)	1158	(15.0)
Moderate	42,914	(61.6)	4643	(59.9)
Heavy	11,179	(16.0)	1748	(22.6)
Aspirin use, number (%)				
None	11,924	(17.1)	1646	(21.3)
Occasional	48,855	(70.1)	4734	(61.1)
Often	7733	(11.1)	973	(12.6)
BMI, mean	25.8		25.5	
Vegetable/fruit intake, mean	15.5		12.4	
Dietary fat consumption, mean	20.5		22.2	
Reported prevalent disease at enrollment, number (%)				
Cancer (except nonmelanoma skin)	1083	(1.6)	231	(3.0)
Heart disease	3838	(5.5)	724	(9.3)
Diabetes	1582	(2.3)	250	(3.2)
Stroke	842	(1.2)	234	(3.0)
Any of the above	6939	(10.0)	1317	(17.0)

*Percentages may not sum to 100 because of missing values.

Table 2. Demographic and other characteristics* of CPS-II men who in 1982 reported never use of tobacco products or exclusive use of chewing tobacco or snuff*

Characteristic	Spit Tobacco Use					
	Never		Current		Former	
Total (N = 114,809)	111,482	(97.1)	2488	(2.2)	839	(0.7)
Median age at enrollment	56		57		62	
Race, number (%)						
White	104,958	(94)	2316	(93)	768	(92)
Nonwhite	6524	(6)	172	(7)	71	(8)
Education, number (%)						
< high school	11,681	(10)	922	(37)	296	(35)
high school graduate	20,121	(18)	690	(28)	187	(22)
some college	26,092	(23)	448	(18)	175	(21)
college graduate	22,386	(20)	189	(8)	86	(10)
graduate school	29,990	(27)	185	(7)	76	(9)
Current alcohol consumption, number (%)						
Abstainer	27,219	(24)	542	(22)	184	(22)
< 1 daily	22,559	(20)	423	(17)	137	(16)
1 daily	8548	(8)	193	(8)	39	(5)
2-3 daily	8805	(8)	189	(8)	71	(8)
4+ daily	5085	(5)	153	(6)	56	(7)
Exercise, number (%)						
None/slight	24,806	(22)	370	(15)	135	(16)
Moderate	71,304	(64)	1524	(61)	552	(66)
Heavy	14,317	(13)	551	(22)	138	(16)
Aspirin use, number (%)						
None	41,828	(38)	895	(36)	330	(39)
Occasional	34,946	(31)	777	(31)	239	(28)
< 15 days/month	19,218	(17)	385	(15)	115	(14)
15+ days/month	8508	(8)	169	(7)	76	(9)
Currently employed, number (%)	83,654	(75)	1675	(67)	496	(59)
Blue collar occupation, number (%)	27,204	(24)	1198	(48)	381	(45)
BMI, mean	25.8		26.6		26.2	
Vegetable/fruit intake, mean	18.0		15.0		15.5	
Dietary fat consumption, mean	285.7		313.4		286.2	
Reported prevalent disease at enrollment, number (%)						
Cancer (except nonmelanoma skin)	4543	(4)	101	(4)	58	(7)
Heart disease	8292	(7)	215	(9)	89	(11)
Diabetes	5504	(5)	148	(6)	53	(6)
Stroke	1418	(1)	59	(2)	27	(3)
Any of the above	18,269	(16)	470	(19)	202	(24)

*Percentages may not sum to 100 because of missing values.

Results

Demographic and other characteristics of the study population according to spit tobacco use at baseline are presented in Tables 1 and 2. Men who used spit tobacco tended to be older, nonwhite, and less educated and eat fewer fruits and vegetables but more dietary fat than nonusers. In both cohorts, current users were more likely to report heavy physical activity than nonusers. In CPS-II, 48% of the men who currently used spit tobacco were employed in blue-collar occupations, compared to 24% of men who reported no tobacco use, suggesting that the

difference in physical activity may represent occupational rather than leisure time activities. The majority (74%) of the 2488 men in CPS-II who reported current use of spit tobacco used chewing tobacco only; another 14% used snuff only, and 12% used both products.

Table 3 presents hazard ratios adjusted for age and other potentially confounding variables comparing spit tobacco users with never tobacco users in CPS-I. Men who reported current use of spit tobacco had statistically significantly higher death rates than never users from all causes (HR = 1.17; 95% CI = 1.11-1.23), cancers of the digestive system (HR = 1.26; 95% CI =

Table 3. Mortality hazard ratios (HR) and 95% confidence intervals (CI) associated with the use of spit tobacco among men who never used other tobacco products, CPS-I, 1959–1972

Cause of death (ICD-7 code)	Spit tobacco use	No. of Deaths	Age-adjusted HR (95% CI) ^a	Multivariate-adjusted HR (95% CI) ^b
All Causes ^c	Never	9819	1.00 (referent)	1.00 (referent)
	Current	2052	1.24 (1.18–1.30)	1.17 (1.11–1.23)
All Cancers ^d (140–239)	Never	1975	1.00 (referent)	1.00 (referent)
	Current	357	1.10 (0.98–1.23)	1.07 (0.95–1.20)
Oropharynx cancer ^d (140–148)	Never	9	1.00 (referent)	1.00 (referent)
	Current	4	2.38 (0.71–8.01)	2.02 (0.53–7.74)
Digestive system cancer ^d (150–159)	Never	760	1.0 (referent)	1.0 (referent)
	Current	153	1.26 (1.05–1.50)	1.26 (1.05–1.52)
Lung cancer ^d (162–163)	Never	116	1.00 (referent)	1.00 (referent)
	Current	18	1.04 (0.63–1.72)	1.08 (0.64–1.83)
Genitourinary system cancer ^d (177–181)	Never	461	1.00 (referent)	1.00 (referent)
	Current	98	1.07 (0.86–1.34)	0.97 (0.77–1.22)
Other cancers ^d (160–161, 165–170, 190–205)	Never	631	1.00 (referent)	1.00 (referent)
	Current	85	0.91 (0.73–1.15)	0.90 (0.71–1.14)
Cardiovascular Disease ^e (330–468)	Never	6378	1.00 (referent)	1.00 (referent)
	Current	1399	1.25 (1.17–1.32)	1.18 (1.11–1.26)
Coronary heart disease ^f (420)	Never	4035	1.00 (referent)	1.00 (referent)
	Current	799	1.17 (1.09–1.27)	1.12 (1.03–1.21)
Cerebrovascular disease ^g (330–334)	Never	1451	1.00 (referent)	1.00 (referent)
	Current	460	1.56 (1.41–1.74)	1.46 (1.31–1.64)
Other cardiovascular ^e (335–398, 400–419, 421–468)	Never	1214	1.00 (referent)	1.00 (referent)
	Current	255	1.13 (0.98–1.29)	1.05 (0.91–1.22)
Other Causes (001–138, 206–289, 470–E999)	Never	2290	1.00 (referent)	1.00 (referent)
	Current	507	1.31 (1.18–1.44)	1.17 (1.06–1.30)
Diabetes ^h (260)	Never	97	1.00 (referent)	1.00 (referent)
	Current	20	1.08 (0.66–1.75)	0.88 (0.53–1.47)
Respiratory system diseases (470–527)	Never	433	1.00 (referent)	1.00 (referent)
	Current	123	1.39 (1.13–1.70)	1.28 (1.03–1.59)
Influenza, pneumonia (480–493)	Never	299	1.00 (referent)	1.00 (referent)
	Current	79	1.22 (0.94–1.57)	1.16 (0.88–1.51)
Chronic obstructive pulmonary disease (480–493)	Never	65	1.00 (referent)	1.00 (referent)
	Current	25	2.03 (1.27–3.25)	1.86 (1.12–3.06)
Digestive system diseases (530–587)	Never	298	1.00 (referent)	1.00 (referent)
	Current	85	1.70 (1.33–2.17)	1.49 (1.14–1.93)
Colitis and other intestinal diseases (570–578)	Never	124	1.00 (referent)	1.00 (referent)
	Current	35	1.45 (0.99–2.13)	1.42 (0.94–2.12)
Cirrhosis (581)	Never	81	1.00 (referent)	1.00 (referent)
	Current	19	2.00 (1.20–3.34)	1.49 (0.87–2.56)
Genitourinary system diseases (590–637)	Never	222	1.00 (referent)	1.00 (referent)
	Current	64	1.56 (1.18–2.07)	1.34 (1.00–1.80)
Nephritis and other kidney disease (590–603)	Never	174	1.00 (referent)	1.00 (referent)
	Current	51	1.60 (1.16–2.20)	1.37 (0.98–1.92)

Table 3. (Continued)

Cause of death (ICD-7 code)	Spit tobacco use	No. of Deaths	Age-adjusted HR (95% CI) ^a	Multivariate-adjusted HR (95% CI) ^b
External causes (E800–E999)	Never	613	1.00 (referent)	1.00 (referent)
	Current	98	1.17 (0.94–1.46)	1.05 (0.84–1.32)

^a Cox models adjusted for age only.

^b Cox models adjusted for age, race, educational level, body mass index, exercise, alcohol consumption, fat consumption, fruit/vegetable intake, and aspirin use.

^c Analysis for all causes excludes men who reported prevalent cancer, heart disease, diabetes, or stroke in 1959 (due to disease exclusions the number of all cause deaths differs from the summed total of specific causes of death).

^d Analyses for cancers exclude men who reported prevalent cancer in 1959.

^e Analysis for cardiovascular disease excludes men who reported prevalent heart disease, diabetes, or stroke in 1959.

^f Analysis for coronary heart disease excludes men who reported prevalent heart disease or diabetes in 1959.

^g Analysis for stroke excludes men who reported prevalent stroke in 1959.

^h Analysis for diabetes excludes men who reported prevalent diabetes in 1959.

1.05–1.52), CHD (HR = 1.12; 95% CI = 1.03–1.22), cerebrovascular disease (HR = 1.46; 95% CI = 1.31–1.64), chronic obstructive pulmonary disease (HR = 1.86; 95% CI = 1.12–3.06), and genitourinary system diseases (RR = 1.34; 95% CI = 1.00–1.80). Although the mortality rate from cancers of the oropharynx was higher among men who currently used spit tobacco than among non-users (HR = 2.02; 95% CI = 0.53–7.74), this comparison was based on only four deaths in users and was not statistically significant. No association was observed between spit tobacco use and genitourinary system cancers, “other” cardiovascular diseases, or external causes.

Table 4 presents hazard ratios adjusted for age and other potentially confounding variables comparing spit tobacco users with never tobacco users in CPS-II and subcategorizing the users according to their use of chewing tobacco and/or snuff. Current users of any type of spit tobacco had statistically significantly higher death rates than never users from all causes (HR = 1.18; 95% CI = 1.08–1.29), lung cancer (HR = 2.00; 95% CI = 1.23–3.24), CHD (HR = 1.26; 95% CI = 1.08–1.47), cerebrovascular disease (HR = 1.40; 95% CI = 1.10–1.79), and cirrhosis (HR = 3.02; 95% CI = 1.60–5.69). No association was observed between current use of spit tobacco and other endpoints. The magnitude of the association with death from all causes combined, all cardiovascular disease, CHD, and lung cancer was similar in men who had only used chewing tobacco or only snuff. Former use of spit tobacco was not significantly associated with increased risk of death from any disease category.

No discernible trends in multivariable-adjusted relative risks associated with frequency or duration of current spit tobacco use were observed for any endpoint in CPS-II (Table 5).

Discussion

Our principal finding is that men in both cohorts who reported current use of spit tobacco at the time of enrollment had significantly higher death rates from all causes combined and all cardiovascular diseases than men who reported never using any tobacco product. Associations seen with other diseases were less consistent. In CPS-I but not CPS-II, use of spit tobacco was associated with higher death rates from COPD and increased risk of malignant and non-malignant diseases of the digestive system. In CPS-II, but not CPS-I, men who used chewing tobacco or snuff had higher death rates from all cancers combined and lung cancer. No consistent dose-response relationships were seen with any endpoint.

A critical question is whether the association between the use of spit tobacco and increased risk of cardiovascular disease is causal, or merely reflects confounding by extraneous factors such as the lower socioeconomic status of men who use chewing tobacco or snuff. The associations with CHD and stroke in CPS-II were seen only in men who reported current use of spit tobacco at the time of enrollment, not among former users, even though the demographic characteristics of former users were closer to the current than the never users. The associations seen between current use of chewing tobacco or snuff and CHD or stroke were considerably weaker than the association of these endpoints with current cigarette smoking in CPS-I and CPS-II [14]. Furthermore, in contrast with active smoking, no consistent dose response relationships were seen with increasing frequency or duration of spit tobacco use and mortality from any cardiovascular endpoint.

Few studies have examined cardiovascular morbidity or mortality in men who use only chewing tobacco or snuff. Bolinder *et al.* [8] reported a higher death rate

Table 4. Mortality hazard ratios (HR) and 95% confidence intervals (CI) associated with the use of spit tobacco among men who never used any other tobacco product, CPS-II, 1982–2000

Cause of death (ICD-9 code)	Spit tobacco use	No. of Deaths	Age-adjusted HR (95% CI) ^a	Multivariate-adjusted HR (95% CI) ^b
All causes ^c	Never	18,824	1.00 (referent)	1.00 (referent)
	Current	567	1.29 (1.18–1.40)	1.18 (1.08–1.29)
	Chew/never snuff	366	1.26 (1.13–1.40)	1.16 (1.05–1.29)
	Snuff/never chew	70	1.37 (1.08–1.73)	1.25 (0.98–1.58)
	Chew and snuff	82	1.49 (1.20–1.85)	1.36 (1.09–1.69)
	Chew/former snuff	20	1.11 (0.71–1.73)	0.96 (0.61–1.50)
	Snuff/former chew	29	1.12 (0.77–1.63)	1.01 (0.69–1.47)
	Former	197	1.06 (0.92–1.22)	0.98 (0.85–1.13)
All cancers ^d (140–208)	Never	5921	1.00 (referent)	1.00 (referent)
	Current	162	1.24 (1.06–1.45)	1.19 (1.02–1.40)
	Chew/never snuff	113	1.28 (1.06–1.54)	1.23 (1.02–1.49)
	Snuff/never chew	14	0.99 (0.58–1.67)	0.93 (0.55–1.57)
	Chew and snuff	18	1.08 (0.68–1.71)	1.02 (0.64–1.63)
	Chew/former snuff	6	1.38 (0.62–3.06)	1.30 (0.58–2.89)
	Snuff/former chew	11	1.68 (0.93–3.03)	1.58 (0.87–2.87)
	Former	57	1.09 (0.84–1.41)	1.04 (0.80–1.36)
Oropharynx cancer ^d (140–148)	Never	45	1.00 (referent)	1.00 (referent)
	Current	1	1.02 (0.14–7.39)	0.90 (0.12–6.71)
	Former	0		
Digestive system cancer ^d (150–159)	Never	1932	1.00 (referent)	1.00 (referent)
	Current	48	1.11 (0.84–1.48)	1.04 (0.77–1.38)
	Former	19	1.09 (0.69–1.71)	0.99 (0.63–1.57)
Lung cancer ^d (162)	Never	378	1.00 (referent)	1.00 (referent)
	Current	18	2.18 (1.35–3.50)	2.00 (1.23–3.24)
	Chew/never snuff	12	2.12 (1.19–3.78)	1.97 (1.10–3.54)
	Snuff/never chew	2	2.37 (0.59–9.53)	2.08 (0.51–8.46)
	Snuff/former chew	4	10.2 (3.78–27.7)	9.78 (3.58–26.7)
	Former	4	1.26 (0.47–3.38)	1.17 (0.43–3.14)
Genitourinary system cancer ^d (185–189)	Never	1649	1.00 (referent)	1.00 (referent)
	Current	44	1.20 (0.89–1.61)	1.15 (0.85–1.56)
	Former	16	1.01 (0.61–1.65)	0.97 (0.59–1.59)
Hematopoietic cancers ^d (200–208)	Never	895	1.00 (referent)	1.00 (referent)
	Current	19	0.98 (0.62–1.54)	0.95 (0.60–1.51)
	Former	9	1.18 (0.61–2.28)	1.16 (0.60–2.25)
Other cancers ^d (160–161,163–175, 190–199)	Never	1022	1.00 (referent)	1.00 (referent)
	Current	32	1.48 (1.04–2.10)	1.49 (1.04–2.14)
	Former	9	1.16 (0.60–2.23)	1.19 (0.61–2.30)
Cardiovascular disease ^e (390–459)	Never	8315	1.00 (referent)	1.00 (referent)
	Current	278	1.39 (1.23–1.56)	1.23 (1.09–1.39)
	Chew/never snuff	186	1.41 (1.22–1.64)	1.26 (1.09–1.46)
	Snuff/never chew	36	1.57 (1.13–2.18)	1.38 (0.99–1.92)
	Chew and snuff	37	1.42 (1.03–1.97)	1.26 (0.91–1.75)
	Chew/former snuff	9	1.06 (0.55–2.06)	0.87 (0.45–1.70)
	Snuff/former chew	10	0.77 (0.39–1.49)	0.64 (0.33–1.24)
	Former	96	1.03 (0.84–1.26)	0.92 (0.75–1.13)
Coronary heart disease ^f (410–414)	Never	4920	1.00 (referent)	1.00 (referent)
	Current	172	1.44 (1.24–1.68)	1.26 (1.08–1.47)
	Chew/never snuff	111	1.41 (1.17–1.71)	1.25 (1.03–1.51)
	Snuff/never chew	24	1.84 (1.23–2.76)	1.59 (1.06–2.39)
	Chew and snuff	23	1.50 (0.99–2.26)	1.31 (0.87–1.98)
	Chew/former snuff	6	1.24 (0.55–2.80)	1.02 (0.45–2.30)

Table 4. (Continued)

Cause of death (ICD-9 code)	Spit tobacco use	No. of Deaths	Age-adjusted HR (95% CI) ^a	Multivariate-adjusted HR (95% CI) ^b
Cerebrovascular disease ^e (430–438)	Snuff/former chew	8	0.98 (0.46–2.09)	0.80 (0.37–1.70)
	Former	44	0.80 (0.59–1.08)	0.70 (0.52–0.95)
	Never	1858	1.00 (referent)	1.00 (referent)
	Current	71	1.54 (1.22–1.96)	1.40 (1.10–1.79)
	Chew/never snuff	45	1.51 (1.12–2.03)	1.38 (1.02–1.86)
	Snuff/never chew	4	0.70 (0.26–1.87)	0.62 (0.23–1.67)
	Chew and snuff	17	2.83 (1.75–4.57)	2.57 (1.59–4.17)
	Chew/former snuff	3	1.52 (0.49–4.76)	1.24 (0.39–3.91)
	Snuff/former chew	2	0.80 (0.20–3.23)	0.68 (0.17–2.75)
Other cardiovascular ^c (390–405,415–429, 450–459)	Former	29	1.32 (0.91–1.92)	1.21 (0.83–1.76)
	Never	2122	1.00 (referent)	1.00 (referent)
	Current	58	1.17 (0.90–1.53)	1.07 (0.82–1.39)
	Former	31	1.31 (0.91–1.88)	1.20 (0.83–1.72)
Other causes (001–139, 210–389, 460–E999)	Never	8712	1.00 (referent)	1.00 (referent)
	Current	262	1.23 (1.09–1.40)	1.11 (0.97–1.25)
	Chew/never snuff	166	1.18 (1.01–1.38)	1.07 (0.92–1.25)
	Snuff/never chew	29	1.22 (0.85–1.76)	1.07 (0.74–1.54)
	Chew and snuff	41	1.47 (1.08–1.99)	1.29 (0.95–1.76)
	Chew/former snuff	10	1.22 (0.65–2.28)	1.00 (0.53–1.87)
	Snuff/former chew	16	1.35 (0.82–2.21)	1.20 (0.73–1.97)
	Former	120	1.21 (1.01–1.45)	1.10 (0.92–1.33)
Diabetes ^h (250)	Never	250	1.00 (referent)	1.00 (referent)
	Current	8	1.45 (0.71–2.94)	1.12 (0.55–2.29)
	Former	6	2.72 (1.21–6.13)	2.16 (0.95–4.91)
Respiratory system diseases (460–519)	Never	1685	1.00 (referent)	1.00 (referent)
	Current	56	1.27 (0.97–1.66)	1.11 (0.84–1.45)
	Former	28	1.23 (0.84–1.80)	1.10 (0.75–1.62)
Influenza, pneumonia (480–487)	Never	930	1.00 (referent)	1.00 (referent)
	Current	24	0.93 (0.62–1.41)	0.85 (0.56–1.29)
	Former	18	1.27 (0.78–2.06)	1.18 (0.73–1.92)
Chronic obstructive pulmonary disease (490–492, 496)	Never	269	1.00 (referent)	1.00 (referent)
	Current	12	1.81 (1.01–3.23)	1.28 (0.71–2.32)
	Former	8	2.40 (1.18–4.87)	1.88 (0.92–3.84)
Digestive system diseases (520–579)	Never	689	1.00 (referent)	1.00 (referent)
	Current	25	1.57 (1.05–2.34)	1.38 (0.92–2.07)
	Former	9	1.21 (0.63–2.34)	1.05 (0.54–2.03)
Colitis and other intestinal diseases (520–530,535–570,572–579)	Never	467	1.00 (referent)	1.00 (referent)
	Current	14	1.28 (0.75–2.19)	1.12 (0.65–1.92)
	Former	9	1.71 (0.88–3.33)	1.54 (0.79–3.01)
Cirrhosis (571)	Never	157	1.00 (referent)	1.00 (referent)
	Current	11	3.38 (1.83–6.23)	3.02 (1.60–5.69)
	Former	0		
Genitourinary system diseases (580–629)	Never	501	1.00 (referent)	1.00 (referent)
	Current	17	1.30 (0.80–2.13)	1.02 (0.62–1.69)
	Former	5	0.77 (0.32–1.86)	0.62 (0.26–1.51)
Nephritis and other kidney disease (580–589)	Never	299	1.00 (referent)	1.00 (referent)
	Current	10	1.32 (0.70–2.50)	1.01 (0.53–1.93)
	Former	3	0.75 (0.24–2.36)	0.59 (0.19–1.86)

Table 4. (Continued)

Cause of death (ICD-9 code)	Spit tobacco use	No. of Deaths	Age-adjusted HR (95% CI) ^a	Multivariate-adjusted HR (95% CI) ^b
External causes (E800–E999)	Never	1318	1.00 (referent)	1.00 (referent)
	Current	45	1.43 (1.06–1.93)	1.26 (0.93–1.70)
	Former	15	1.15 (0.69–1.92)	1.04 (0.62–1.74)

^a Cox models adjusted for age only.

^b Cox models adjusted for age, race, educational level, body mass index, exercise, alcohol consumption, employment status and type, fat consumption, fruit/vegetable intake, and aspirin use.

^c Analysis for all causes excludes men who reported prevalent cancer, heart disease, diabetes, or stroke in 1982 (due to disease exclusions the number of all cause deaths differs from the summed total of specific causes of death).

^d Analyses for cancers exclude men who reported prevalent cancer in 1982.

^e Analysis for cardiovascular disease excludes men who reported prevalent heart disease, diabetes, or stroke in 1982.

^f Analysis for coronary heart disease excludes men who reported prevalent heart disease or diabetes in 1982.

^g Analysis for stroke excludes men who reported prevalent stroke in 1982.

^h Analysis for diabetes excludes men who reported prevalent diabetes in 1982.

from all cardiovascular conditions combined in a cohort of male construction workers who used predominantly moist snuff (*snus*) in Sweden compared to men who used no tobacco products (RR = 1.4, 95% CI = 1.2–1.6). Workers in this study were exposed to products prior to 1985, after which the nitrosamine content of Swedish *snus* was substantially reduced through changes in the manufacturing process [8]. In contrast, three population-based case control studies conducted more recently in northern Sweden found no association between the use of moist snuff and acute myocardial infarction [7, 9] or stroke [10]. The only other population-based case-control study [13], nested within the first National Health and Nutrition Examination Study (NHANES-I) follow-up in the U.S., found marginally higher death rates from all causes (RR = 1.1, 95% CI = 0.9–1.3) and all cardiovascular conditions (RR = 1.1, 95% CI = 0.8–1.5) in men who used spit tobacco compared to those who did not (although men in the comparison group may have smoked pipes or cigars). This analysis was based on only 414 men who used spit tobacco and had limited statistical power to detect an association of this magnitude. Several studies have compared cross-sectional measures of intermediate cardiovascular endpoints in smokers, persons who use smokeless tobacco, and those who use no tobacco products [reviewed in [10]]. In general, subjects in these studies who use spit tobacco have more closely resembled non-smokers than smokers with respect to lipids and markers of inflammation, hemoconcentration, and atherosclerosis.

No consistent associations between the use of spit tobacco and mortality rates from all cancers combined or specific cancers were seen in either ACS cohort. The death rate from cancers of the oral cavity and pharynx was not significantly associated with current use of spit tobacco in

CPS-I (HR = 2.02, 95% CI = 0.53–7.74) or CPS-II (HR = 0.90, 95% CI = 0.12–6.71), although both studies had limited statistical power to examine this endpoint. Current use of spit tobacco was associated with increased risk of stomach [HR = 1.55 (1.07–2.26)] and colon cancer (HR = 1.34, 0.98–1.83) in CPS-I, but not in CPS-II. Conversely, men who report exclusive use of spit tobacco had higher death rates from lung cancer (HR = 2.00, 95% CI = 1.23–3.24) and “other cancers” (HR = 1.49, 95% CI = 1.04–2.14) in CPS-II but not CPS-I. Some or all of these associations may reflect chance, the inclusion of current or former smokers among those who reported exclusive use of spit tobacco, or confounding by other unidentified factors. The higher death rate from cirrhosis among men who currently use spit tobacco in CPS-II (RR = 3.02, 95% CI = 1.60–5.69) suggests the potential for residual confounding by alcohol consumption.

The use of snuff and various forms of chewing tobacco have been strongly associated with cancers of the oral cavity and pharynx in studies conducted in the Southeastern U.S. [26, 27], India [28–35], and the Sudan [36], although less consistently in Scandinavia [37, 38]. Comprehensive but dated reviews by the U.S. Surgeon General [2] and the International Agency for Research on Cancer [39] have concluded that there is sufficient evidence that the use of snuff is carcinogenic in humans.

Strengths of our studies are their size, prospective design, and ability to examine multiple endpoints. CPS-I is considerably larger than other epidemiologic studies of smokeless tobacco products. Conversely, the limitations of CPS-I and CPS-II are that the information on use of spit tobacco was collected only at baseline and not updated during follow-up, and that the reliance on death certificate information, rather than cancer incidence, is problematic for studying cancers of the oral

Table 5. Mortality hazard ratios (HR)^a and 95% confidence intervals (CI) comparing men who never used any tobacco product with men who currently use spit tobacco by characteristic, CPS-II Men, 1982–2000

Spit tobacco use characteristic (N) ^b	All causes ^c		All cancers ^d		All cardiovascular diseases ^e		Other causes	
	deaths	HR (95% CI)	deaths	HR (95% CI)	deaths	HR (95% CI)	deaths	HR (95% CI)
Never tobacco users	18824	1.00 (referent)	5921	1.00 (referent)	8315	1.00 (referent)	8712	1.00 (referent)
<i>Frequency</i>								
< 7 times/week (511)	99	1.22 (1.00–1.49)	30	1.25 (0.88–1.80)	49	1.37 (1.03–1.82)	42	1.09 (0.80–1.48)
7 times/week (1188)	279	1.14 (1.01–1.28)	75	1.10 (0.87–1.39)	140	1.19 (1.00–1.41)	132	1.09 (0.91–1.29)
> 7 times/week (452)	81	1.20 (0.96–1.49)	28	1.13 (0.76–1.68)	36	1.10 (0.79–1.53)	48	1.25 (0.94–1.66)
<i>p</i> -value for trend ^h		0.9657		0.9992		0.6961		0.3669
<i>Duration</i>								
1–10 years (600)	73	1.08 (0.86–1.36)	25	1.16 (0.79–1.73)	32	1.15 (0.81–1.63)	34	1.11 (0.79–1.56)
11–30 years (676)	94	1.22 (1.00–1.49)	33	1.24 (0.88–1.75)	40	1.24 (0.91–1.70)	38	1.09 (0.79–1.50)
30+ years (905)	309	1.20 (1.07–1.35)	78	1.14 (0.91–1.43)	160	1.24 (1.05–1.45)	153	1.15 (0.98–1.35)
<i>p</i> -value for trend ^h		0.2864		0.8422		0.7429		0.5249
Spit tobacco use characteristic (N) ^b	Lung cancer ^c		Coronary heart disease ^f		Cerebrovascular disease ^g		Chronic obstructive pulmonary disease	
	deaths	HR (95% CI)	deaths	HR (95% CI)	deaths	HR (95% CI)	deaths	HR (95% CI)
Never tobacco users	378	1.00 (referent)	4920	1.00 (referent)	1858	1.00 (referent)	269	1.00 (referent)
<i>Frequency</i>								
< 7 times/week (511)	3	1.95 (0.62–6.09)	28	1.34 (0.92–1.95)	14	1.75 (1.03–2.97)	3	2.45 (0.77–7.74)
7 times/week (1188)	9	2.01 (1.03–3.93)	87	1.23 (0.99–1.53)	40	1.51 (1.09–2.07)	5	1.02 (0.41–2.49)
> 7 times/week (452)	3	2.00 (0.64–6.27)	23	1.13 (0.75–1.70)	10	1.31 (0.70–2.44)	2	1.41 (0.35–5.74)
<i>p</i> -value for trend ^h		0.8917		0.6838		0.3726		0.8510
<i>Duration</i>								
1–10 years (600)	2	1.39 (0.34–5.60)	18	1.08 (0.68–1.73)	7	1.20 (0.57–2.53)	1	1.10 (0.15–7.88)
11–30 years (676)	3	1.64 (0.53–5.15)	27	1.36 (0.93–1.99)	7	1.04 (0.49–2.18)	2	1.81 (0.45–7.34)
30+ years (905)	13	2.96 (1.67–5.24)	93	1.20 (0.97–1.48)	52	1.74 (1.31–2.31)	7	1.17 (0.54–2.53)
<i>p</i> -value for trend ^h		0.5487		0.4142		0.3522		0.8364

^a Cox models adjusted for age, race, educational level, body mass index, exercise, alcohol consumption, employment status and type, fat consumption, fruit/vegetable intake, and aspirin use.

^b Number in category is based on current users before exclusions for prevalent disease; categories may not sum to total because of missing values.

^c Analysis for all causes excludes men who reported prevalent cancer, heart disease, diabetes, or stroke in 1982.

^d Analyses for cancers exclude men who reported prevalent cancer in 1982.

^e Analysis for cardiovascular disease excludes men who reported prevalent heart disease, diabetes, or stroke in 1982.

^f Analysis for coronary heart disease excludes men who reported prevalent heart disease or diabetes in 1982.

^g Analysis for stroke excludes men who reported prevalent stroke in 1982.

^h *p*-value for trend is based on current spit tobacco users only (does not include referent).

cavity and pharynx, for which five-year survival has exceeded 50% since the mid-1970s [40].

Although the hazards associated with the use of spit tobacco in this and other studies [6] are considerably smaller than the risks associated with cigarette smoking [22, 23], we do not agree with the proposal by some researchers [41, 42] and tobacco manufacturers [43] that spit tobacco should be marketed as a less hazardous alternative to smoking. We believe that the appropriate comparison is not between spit tobacco and products that are smoked, but between spit tobacco and nicotine replacement therapy. We know of no convincing evidence that smokeless products are more effective or less

hazardous than nicotine replacement drugs in assisting smokers to quit. Nor has it been established that promoting spit tobacco as an alternative to smoking will reduce, rather than increase the number of people dependent on tobacco, smoked or other.

In summary, these two large prospective studies find higher death rates from cardiovascular and certain other conditions among men who report exclusive use of spit tobacco than in men who use no tobacco product. We believe that it is inappropriate to recommend the use of spit tobacco as an alternative to tobacco smoking unless there is persuasive evidence that these products are less hazardous and at least as effective as nicotine replacement therapy.

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