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Chronic Disease Mortality in a Cohort of Smokeless Tobacco Users

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The purpose of this study was to characterize the relation between smokeless tobacco use and the risk of all-cause and disease-specific mortality. Using data from the First National Health and Nutrition Examination Survey Epidemiologic Followup Study, the authors assessed the 20-year mortality experience of smokeless tobacco users. Subjects aged 45 years or more at baseline (1971–1975) were categorized as either smokeless tobacco users ($n = 1,068$) or non-smokeless tobacco users ($n = 5,737$). Subjects were further stratified by smoking status and gender. Proportional hazard ratios were used to assess associations. After adjustment for confounders, no association between smokeless tobacco use and all-cause (hazard ratio = 1.1, 95% confidence interval (CI): 0.9, 1.3), all cancer (hazard ratio = 1.1, 95% CI: 0.6, 1.9), or all cardiovascular (hazard ratio = 1.1, 95% CI: 0.8, 1.5) mortality was found. There was an increase in all cancer mortality of borderline significance among female smokeless tobacco users (hazard ratio = 1.7, 95% CI: 1.0, 2.8). The lung cancer mortality rate among combined users (smokeless tobacco and cigarettes), based on the rates for exclusive smokeless tobacco users and exclusive smokers, was higher than expected, possibly because of heavier smoking among these subjects. The mortality experience of smokeless tobacco users was not significantly greater than that of non-tobacco users and was appreciably less than that of cigarette smokers. Furthermore, combined use of smokeless tobacco and cigarettes did not increase overall mortality beyond that expected from use of the individual products.

cardiovascular diseases; mortality; neoplasms; tobacco, smokeless

Abbreviations: CI, confidence interval; ICD-9, *International Classification of Diseases*, Ninth Revision; NHANES I, First National Health and Nutrition Examination Survey; NHEFS, NHANES I Epidemiologic Followup Study.

Smokeless tobacco use may be associated with an increase in oral cancer incidence (1) and with elevated rates of other cancers and cardiovascular disease (2–4). However, little research has been done on the relation between smokeless tobacco use and mortality from chronic diseases. We investigated the relation between smokeless tobacco use and mortality from both broad classifications of chronic disease and several specific disease outcomes. Because information on smoking status was available, we also compared the effects of smokeless tobacco use with that of cigarette smoking and investigated the mortality associated with the combined use of these two tobacco products.

There is growing interest in the possible adverse health effects of smokeless tobacco because of the increasing prevalence of smokeless tobacco use among young adult White males (5, 6) and the role of smokeless tobacco as a nicotine replacement for cigarette smoking (7). The prevalence of smokeless tobacco use among adolescents (students in grades 9–12) increased from 2.2 percent in 1970 to 9.3 percent in 1997, with White males having the highest prevalence (20.6 percent) (8, 9). According to the 1989 Teenage Attitudes and Practices Survey, each day more than 2,200 adolescents (ages 12–18 years) first try smokeless tobacco and about 830 (38 percent) become regular users (10).

Smokeless tobacco may be used by some smokers as a method to quit smoking and by others as a substitute for cigarettes in locations where cigarette smoking is not allowed. A recent Swedish study found that smokeless tobacco use can lead to higher smoking quit rates (11). A 1986 US tobacco survey found that approximately 7 percent

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of adults who formerly smoked reported substituting other tobacco products (including snuff and chewing tobacco) for cigarettes in an effort to stop smoking (7). One national survey found that, among current smokeless tobacco users, one third were former smokers (12), suggesting that smokeless tobacco is occasionally used as a substitute for cigarettes. Recently, some researchers have proposed smokeless tobacco as nicotine replacement therapy for inveterate cigarette smokers (13). The use of smokeless tobacco as a safe alternative to cigarette smoking requires a complete understanding of the risks associated with smokeless tobacco use.

Our aims are to assess the potential increased mortality risks associated with ever smokeless tobacco use in a representative sample of the US population and to evaluate the effects of the combined use of smokeless tobacco and cigarette smoking on mortality from chronic diseases.

MATERIALS AND METHODS

Data sources for determination of mortality risk associated with smokeless tobacco use

We used data from the First National Health and Nutrition Examination Survey (NHANES I) and the NHANES I Epidemiologic Followup Study (NHEFS) to determine whether any increased mortality risks were associated with smokeless tobacco use. The prospective nature of the data collection provided a unique opportunity to examine multiple mortality outcomes over an approximate 20-year follow-up period. The wide range of available information on a variety of risk factors allowed us to control for many potential confounders.

The survey design and data collection methods of NHANES I and NHEFS have been described elsewhere (14–19). Briefly, NHANES I was a national probability sample of the noninstitutionalized US population conducted from 1971 to 1975, with oversampling of the elderly, the poor, and women of childbearing age. NHANES I used a multistage sampling design leading to unequal probabilities for selection of sample subjects. The initial survey included in-person interviews covering a wide array of health behaviors, as well as a physical examination. The NHEFS surveys were conducted in 1982–1984, 1986 (limited to subjects ≥55 years of age at baseline), 1987, and 1992 to provide approximately 10, 15, and 20 years of follow-up information.

NHANES I included 14,407 adults ranging from 25 to 74 years of age who underwent a physical examination in 1971–1975. Of these subjects, 13,861 (96 percent) were successfully traced in at least one follow-up survey. By 1992, 4,604 (32 percent) subjects were identified as deceased, with death certificates available for 98 percent of the decedents.

Exposure variable

Only a random sample (n = 3,847) of all subjects in NHANES I were asked about smokeless tobacco use at baseline, but all subjects successfully interviewed during the 1982–1984 NHEFS were asked questions regarding smokeless tobacco use. Data from the 1982–1984 NHEFS were used to infer smokeless tobacco status at baseline when necessary. Subjects reporting current smokeless tobacco use in NHANES I or ever use in the 1982–1984 NHEFS were considered ever smokeless tobacco users (n =1,503) in this study. Subjects reporting neither current use nor ever use in either survey were considered never smokeless tobacco users (n = 10,948). Of the 1,503 ever smokeless tobacco users, there were 505 (33.6 percent) who had never smoked ("exclusive" smokeless tobacco users), 952 (63.3 percent) who had ever smoked ("combined" users), and 46 (3.1 percent) with unknown smoking status.

Confounding variables

The demographic variables considered in this analysis include age at examination, race, sex, region of residence (Northeast, Midwest, South, West), and poverty index ratio. A poverty index ratio equal to 1.0 designates the poverty level, with ratios less than 1.0 below and ratios greater than 1.0 above poverty level. A poverty index ratio was calculated for only a sample of subjects in NHANES I (n = 11,348). Definitions of these variables are provided in the *Plan and Operation of the Health and Nutrition Examination Survey, United States—1971–1973* (14).

Cigarette smoking information was gathered on only a sample of subjects in NHANES I. Pack-years of smoking were calculated by multiplying the reported average number of cigarettes smoked daily by the duration smoked divided by 20 (1 pack = 20 cigarettes). For subjects whose smoking information was not obtained in NHANES I, smoking status and pack-years at baseline were inferred from responses to the 1982–1984 NHEFS, whenever possible. Other tobacco habits such as pipe or cigar use were not considered in the formation of tobacco exposure categories (i.e., a subject who did not use smokeless tobacco or smoke cigarettes but did smoke a pipe would be considered a non-tobacco user).

Nutritional information was obtained via a 24-hour recall dietary questionnaire and was asked of only a sample of the NHANES I subjects at baseline (n = 11,348). Standard food-composition data were used to calculate nutrient intake (20). Other potential confounders for which information was available from either the baseline interview or the physical examination include alcohol consumption, recreational physical activity, body mass index, blood pressure, serum cholesterol, and family history (parents, siblings, or children) of cancer.

Outcome variables

Both underlying and multiple cause-of-death codes, using *International Classification of Diseases*, Ninth Revision (ICD-9), codes obtained from the death certificate, were used to categorize deaths. The underlying cause of death was used to calculate hazard ratios for the broad classifications of disease, whereas multiple cause-of-death codes were used to calculate hazard ratios for specific causes of death. Decedents identified only through proxy interview (n = 107) were not included in this analysis because no ICD-9 code was available from the data set.

TABLE 1. Distribution of subjects according to tobacco use categories for selected baseline characteristics, First National Health and Nutrition Examination Survey Epidemiologic Followup Study, 1971–1992

	No tobacco		Exclusive smokeless tobacco use		Exclusive smoking		Both smokeless tobacco use and smoking	
	No.	%	No.	%	No.	%	No.	%
Subjects	5,192		505		5,523		952	
Age (years) at examination (mean)	47.8		54.0		44.9		47.9	
Subjects ≥45 years of age	2,986*		414*		2,751*		654*	
Males	722	24.2	225	56.0	1,591	55.7	592	92.7
Whites	2,629	92.0	248	66.6	2,448	93.0	551	90.7
Poverty index ratio (mean)	2.4		1.8		2.5		2.0	
Region of residence								
Northeast	678	26.8	42	11.5	660	25.2	91	13.8
Midwest	758	26.7	60	17.7	658	24.6	136	23.4
South	756	21.7	239	50.9	672	23.0	265	38.6
West	794	24.8	73	19.9	761	27.2	162	24.2
Smoking status								
Current					1,682	62.9	329	53.6
Former					1,069	37.1	325	46.4
Pack-years (mean)					35.1		42.3	
Alcohol†								
None	1,451	41.5	218	42.2	616	19.1	193	25.9
Less than 12 times/year	693	25.4	54	18.3	569	20.1	113	16.4
About 13–48 times/year	430	16.3	72	19.5	638	23.5	132	20.2
At least 104–156 times/year	407	16.9	68	20.0	922	37.4	212	37.4
Fruit and vegetable intake								
None or <1 serving/day	201	5.8	88	28.2	240	8.4	83	15.5
1 or 1.5 servings/day	583	24.6	123	28.2	567	27.8	193	35.8
2 or 2.5 servings/day	913	38.9	98	31.3	734	41.5	156	32.2
≥3 servings/day	636	30.7	30	12.4	378	22.4	63	16.6
Recreational physical activity								
Little	1,472	46.7	235	49.5	1,227	43.7	280	41.6
Moderate	1,089	37.7	127	33.6	1,053	38.7	237	39.0
Much	424	15.6	51	16.9	470	17.6	136	19.4
Blood cholesterol (mg/dl) (mean)	237.8		228.7		235.1		226.9	
Systolic blood pressure (mmHg) (mean)	142.3		147.8		136.6		139.2	
Body mass index (kg/m^2) (mean)	26.8		27.5		25.5		25.7	
Vitamin A intake (IU) (mean)	5,699.9		5,203.5		5,620.2		4,376.3	
Vitamin C intake (mg) (mean)	94.4		76.1		88.5		77.3	
Dietary fat intake (g) (mean)	62.4		72.1		77.6		84.6	

* Individual variable totals may not add up to column total because of missing responses.
† In 12 months prior to baseline.

This analysis was limited to White subjects and Black subjects, because of the small number of subjects in the "other" race category (n = 172). Because of the differences in age between exclusive smokeless tobacco users and non-tobacco users (table 1) and the low prevalence of smokeless tobacco use among subjects less than 45 years of age, the mortality analyses were restricted to those subjects 45–75 years of age at baseline (n = 6,805).

Statistical analysis

The distribution of potential confounding variables was calculated for the four tobacco categories (non-tobacco users, exclusive smokeless tobacco users, exclusive smokers, and combined smokeless tobacco users and smokers). The Cox proportional hazards model was used to calculate both the crude and the adjusted hazard ratios. Most

TABLE 2. Hazard ratios for selected causes of death for exclusive smokeless tobacco users relative to non-tobacco users, First National Health and Nutrition Examination Survey Epidemiologic Followup Study, 1971–1992

Disease classification (ICD-9* code)	Males				Females			
	Crude HR*	95% CI*	Adjusted HR†	95% CI	Crude HR	95% CI	Adjusted HR†	95% CI
All causes	1.5	1.1, 1.9	1.0	0.8, 1.3	1.7	1.2, 2.4	1.3	0.9, 1.7
Malignant neoplasms (140–209)	1.1	0.5, 2.4	0.9	0.3, 2.3	1.6	1.0, 2.6	1.7	1.0, 2.8
Endocrine, nutritional, and metabolic diseases and immunity disorders (240–279)	2.7	0.7, 10.9	2.4	0.7, 8.8	2.9	0.6, 13.4	1.4	0.1, 13.5
Diseases of the nervous system and sense organs (320–389)	1.6	0.2, 10.2	1.1	0.2, 5.2	0.3	0.1, 1.3	0.6	0.1, 2.6
Diseases of the circulatory system (390–459)	1.5	1.1, 2.0	1.0	0.7, 1.5	1.8	1.0, 3.1	1.2	0.7, 1.9
Diseases of the respiratory system (460–519)	2.1	0.7, 5.8	0.9	0.3, 2.5	0.7	0.2, 2.5	0.6	0.1, 2.3
Diseases of the digestive system (520–579)	3.1	0.7, 12.7	1.9	0.4, 9.8	0.0‡		0.0§	

* ICD-9, *International Classification of Diseases*, Ninth Revision; HR, hazard ratio; CI, confidence interval.

† Adjusted for age, race, and poverty index ratio.

‡ Crude hazard ratio derived from 0/29, where the numerator represents the number of cases among exclusive smokeless tobacco users, and the denominator represents the number of cases among non-tobacco users.

§ Adjusted hazard ratio derived from 0/24, where the numerator represents the number of cases among exclusive smokeless tobacco users, and the denominator represents the number of cases among non-tobacco users.

analyses were stratified by gender. Follow-up time was calculated from the date of examination to the time the subject died, the time the subject was last known alive, or the endpoint of the study. Subjects lost to follow-up (i.e., not traced in any of the four studies of the NHEFS) were excluded from the analyses ($n = 100$). Subjects with a preexisting condition at baseline were excluded for analyses of that particular condition (e.g., subjects reporting stroke history at baseline were excluded from all analyses of stroke outcomes). To account for the complex survey design and the oversampling of certain populations, SUDAAN software was used to conduct the majority of the analyses. SUDAAN software (Research Triangle Institute, Research Triangle Park, North Carolina) is a software package specifically designed to analyze data from complex surveys that incorporate multistage sampling designs and unequally weighted designs (21).

Standardized mortality ratios were calculated as the measure of effect for oral cancer. Expected numbers were based on mortality rates from the National Center for Health Statistics for 1982, the approximate midpoint of the follow-up period.

RESULTS

There were 1,068 smokeless tobacco users in this cohort 45 years of age or older, 414 (39 percent) of whom were never smokers. Exclusive smokeless tobacco users were older (mean age = 64.9 years), poorer (mean poverty index ratio = 1.8), and more likely to reside in the South than other subjects (table 1). Crude differences between smokeless tobacco users and other subjects also were found in the frequency of alcohol intake (they drink less often than smokers), fruit and vegetable intake (less than smokers and non-tobacco users), and recreational physical exercise (less than smokers and non-tobacco users). Crude blood pressure and body mass index levels were higher among exclusive smokeless tobacco users than for other tobacco categories. Intakes of vitamin A, vitamin C, and dietary fat also differed across the four tobacco use categories.

After adjustment for age, race, gender, and poverty status, exclusive smokeless tobacco users did not experience statistically significant increased mortality from all causes (hazard ratio = 1.1, 95 percent confidence interval (CI): 0.9, 1.3), all cancer (hazard ratio = 1.1, 95 percent CI: 0.6, 1.9), or all cardiovascular outcomes (hazard ratio = 1.1, 95 percent CI: 0.8, 1.5) compared with non-tobacco users. Table 2 describes the relation between exclusive smokeless tobacco use and the causes of death for which there were at least 30 deaths, stratified by gender. Male smokeless tobacco users experienced statistically nonsignificant increases in mortality from endocrine, nutritional, and metabolic diseases and immunity disorders (hazard ratio = 2.4, 95 percent CI: 0.7, 8.8) and from diseases of the digestive system (hazard ratio = 1.9, 95 percent CI: 0.4, 9.8). Female smokeless tobacco users experienced an increase in mortality from all cancers (hazard ratio = 1.7, 95 percent CI: 1.0, 2.8) of borderline significance.

Table 3 presents hazard ratios from several specific chronic diseases. Male exclusive smokeless tobacco users did not experience significant increases in mortality for any type of cancer considered. The increased mortality from lung cancer among female smokeless tobacco users (never or ever smokers), although statistically significant, was based on only three deaths and four deaths, respectively. Smokeless tobacco use was not associated with significant increases in mortality for ischemic heart disease or stroke in either gender.

TABLE 3. Hazard ratios according to smokeless tobacco use relative to non-tobacco use for specific causes of death, First National Health and Nutrition Examination Survey Epidemiologic Followup Study, 1971–1992

Cause of death (ICD-9* code)	Ever smokeless tobacco users: males								Ever smokeless tobacco users: females							
	Never smokers				Ever smokers				Never smokers				Ever smokers			
	Crude HR*	95% CI*	Adjusted HR	95% CI	Crude HR	95% CI	Adjusted HR	95% CI	Crude HR	95% CI	Adjusted HR	95% CI	Crude HR	95% CI	Adjusted HR	95% CI
Lung cancer (162)	0.0†		0.0‡,§		0.5	0.1, 3.8	22.6‡	6.4, 80.3	7.0	1.6, 30.9	9.1‡	1.1, 75.4	8.7	3.3, 22.4	1.2‡	0.2, 8.9
Digestive cancers (150–159)	1.2	0.5, 3.1	0.9¶	0.3, 2.3	0.3	0.1, 1.0	0.7¶	0.3, 1.8	0.8	0.3, 2.4	0.8¶	0.3, 2.7	0.7	0.3, 1.7	0.2¶	0.1, 1.1
IHD* (410–414)	1.4	0.9, 2.1	0.6#	0.3, 1.2	1.1	0.8, 1.6	1.0#	0.6, 1.7	1.7	1.1, 2.8	1.4#	0.8, 2.2	1.1	0.4, 2.7	1.1#	0.4, 3.2
Stroke (430–438)	1.2	0.5, 2.7	0.7**	0.2, 2.0	0.7	0.3, 1.3	0.7**	0.3, 1.5	2.2	1.2, 4.0	1.0**	0.3, 2.9	1.7	0.5, 6.4	1.7**	0.4, 7.0

* ICD-9, *International Classification of Diseases*, Ninth Revision; HR, hazard ratio; CI, confidence interval; IHD, ischemic heart disease.

† Crude hazard ratio derived from 0/9, where the numerator represents the number of cases among exclusive smokeless tobacco users, and the denominator represents the number of cases among non-tobacco users.

‡ Adjusted for age, race, poverty index ratio, region of residence, alcohol, recreational physical exercise, and fruit/vegetable intake.

§ Adjusted hazard ratio derived from 0/6, where the numerator represents the number of cases among exclusive smokeless tobacco users, and the denominator represents the number of cases among non-tobacco users.

¶ Adjusted for age, race, poverty index ratio, alcohol, and dietary fat intake.

Adjusted for age, race, poverty index ratio, alcohol, recreational physical exercise, fruit/vegetable intake, systolic blood pressure, serum cholesterol, and body mass index.

** Adjusted for age, race, poverty index ratio, alcohol, recreational physical exercise, fruit/vegetable intake, and systolic blood pressure.

The analyses investigating the combined effects of smokeless tobacco use and smoking on specific outcomes were restricted to male subjects because of the low prevalence of combined use among females ($n = 62$). As shown in table 4, the lung cancer mortality among combined users was nearly twice that of exclusive smokers (hazard ratios = 22.6 and 13.2, respectively). Combined users did not experience increased mortality for ischemic heart disease, although exclusive smokers had a statistically significant increase in mortality (hazard ratio = 1.6, 95 percent CI: 1.3, 1.9).

There were no oral cancer deaths among exclusive smokeless tobacco users (table 5). In a cohort of this size followed for approximately 20 years, only one death would have been expected. Among ever smokeless tobacco users, two deaths from oral cancer were observed and two deaths were expected. Both oral cancer decedents among smokeless tobacco users were White males. Once again, this is

TABLE 4. Adjusted hazard ratios according to smokeless tobacco use and smoking status relative to non-tobacco users: males, First National Health and Nutrition Examination Survey Epidemiologic Followup Study, 1971–1992

	IHD*		Lung cancer		All cancer	
	HR*,†	95% CI*	HR‡	95% CI	HR§	95% CI
Non-tobacco users	1.0		1.0		1.0	
Exclusive smokeless tobacco users	0.6	0.3, 1.2	0.0¶		1.0	0.3, 2.5
Exclusive smokers	1.5	1.1, 2.1	13.2	4.5, 38.2	1.3	0.8, 2.1
Current	2.0	1.4, 2.8	24.7	8.3, 73.5	1.8	1.1, 3.1
Former	1.2	0.8, 2.0	7.0	2.1, 23.2	1.0	0.5, 1.8
Smokeless tobacco users and smokers	1.0	0.6, 1.7	22.6	6.4, 80.3	1.6	0.9, 2.7
Smokeless tobacco and current	0.8	0.5, 1.5	33.9	8.0, 143.7	2.2	1.2, 3.7
Smokeless tobacco and former	1.1	0.6, 2.1	9.0	2.0, 40.8	0.9	0.4, 1.8

* IHD, ischemic heart disease; HR, hazard ratio; CI, confidence interval.

† Adjusted for age, race, poverty index ratio, alcohol, recreational physical exercise, fruit/vegetable intake, systolic blood pressure, serum cholesterol, and body mass index.

‡ Adjusted for age, race, poverty index ratio, region of residence, alcohol frequency, recreational physical exercise, and fruit/vegetable intake.

§ Adjusted for age, race, poverty index ratio, alcohol, recreational physical exercise, fruit/vegetable intake, dietary fat intake, and family history of cancer.

¶ Adjusted hazard ratio derived from 0/6, where the numerator represents the number of cases among exclusive smokeless tobacco users, and the denominator represents the number of cases among non-tobacco users.

TABLE 5. Observed and expected deaths according to tobacco status: oral cancer, First National Health and Nutrition Examination Survey Epidemiologic Followup Study, 1971–1992

	Observed deaths	Expected deaths*	SMR†,‡	95% CI†
Overall	19	12.2	156	93, 231
Ever smokeless tobacco user	2	1.9	107	10, 308
Exclusive smokeless tobacco user	0	0.8	0	0, 580
Ever smoker	14	5.0	278	150, 439
Exclusive smoker	11	3.8	288	142, 480

* Based on 1982 mortality rates for US adults 45–75 years of age.
† SMR, standardized mortality ratio; CI, confidence interval.
‡ Indirectly adjusted only for age.

what would be expected in a cohort of this size (standardized mortality ratio among White males = 114, 95 percent CI: 11, 327). Comparatively, among all smokers, 14 oral cancer deaths were observed, whereas only five were expected (standardized mortality ratio = 278, 95 percent CI: 150, 439).

DISCUSSION

The crude hazard ratios show increased mortality among smokeless tobacco users, largely because smokeless tobacco users were older than non-tobacco users and smokers. After controlling for age, gender, race, and poverty status, we found that smokeless tobacco users did not experience higher mortality than did non-tobacco users in this cohort. After stratification by gender, no statistically significant increases in mortality were found for males. Among females, a borderline statistically significant increase was found for all cancer mortality.

Few studies have investigated mortality in relation to smokeless tobacco use. Results from the National Mortality Followback Survey showed that smokeless tobacco use was not associated with increased risk for all cancer, oral cancer, or cancer of the digestive organs (22). Zahm et al. (23) found a nonsignificant increase in soft tissue sarcoma among US veterans who had ever chewed tobacco or used snuff (relative risk = 1.4, 95 percent CI: 0.8, 2.6), with no soft tissue sarcoma originating in the head, neck, and face region among smokeless tobacco users. They found no soft tissue sarcoma deaths among those who used smokeless tobacco only. They did find an increase in mortality from buccal cancer among smokeless tobacco users (relative risk = 3.0, 95 percent CI: 2.0, 4.5) (23). In a recent ecologic study, no increased mortality rate for oral/pharyngeal cancer was found in West Virginia, the state with the highest prevalence of smokeless tobacco use, compared with the United States as a whole (24). Although few in number, these studies generally support the results of our analysis.

The scant body of epidemiologic evidence for smokeless tobacco use and cardiovascular disease mortality differs from our results. A study of Swedish construction workers found a small but statistically significant increased risk for all cardiovascular disease mortality (relative risk = 1.4, 95 percent CI: 1.2, 1.6), ischemic heart disease, and stroke (3). However, common risk factors for cardiovascular disease such as blood pressure, exercise, diet, and alcohol were not controlled and may explain the increased risk. Of note in the Swedish study was the absence of an increased risk for all cancer deaths (relative risk = 1.1, 95 percent CI: 0.9, 1.4), similar to our results. Another study from Sweden found a small but statistically nonsignificant increased risk from fatal myocardial infarction (including sudden death) among snuff dippers (odds ratio = 1.5, 95 percent CI: 0.5, 5.0) (4).

Although smokeless tobacco users in the present study experienced no increased risk in cardiovascular disease mortality, smokers experienced a small but statistically significant increased risk for ischemic heart disease. This disparity supports evidence that something other than nicotine is causing the increase in cardiovascular mortality (25).

Although oral cancer is the adverse effect most accepted as a consequence of smokeless tobacco use (1), we found no association between oral cancer mortality and ever smokeless tobacco use. Although the number of observed deaths among exclusive smokeless tobacco users was too small to calculate a hazard ratio, the number of expected deaths in this cohort was less than one. The reasons why smokeless tobacco leads to an increase in oral cancer incidence but not to an increase in oral cancer mortality may be due to advances in cancer detection and treatment or to insufficient follow-up time for deaths to occur among a small number of cases.

The validity of the data should not be a concern, as the hazard ratio for oral cancer mortality among cigarette smokers is similar to the findings of other studies (26). Similarly, the magnitude of association between cigarette smoking and lung cancer (hazard ratio = 13.2, 95 percent CI: 4.5, 38.2 among males) is consistent with that observed in other studies, as is the finding of greater lung cancer mortality among current smokers than former smokers (27).

The complex survey design and oversampling of certain populations required the use of SUDAAN software to analyze the data set. However, results reflecting a small number of outcomes have been found to strongly influence estimates (28). Although we found statistically nonsignificant associations between smokeless tobacco use by males and diseases of the endocrine and digestive systems and

statistically significant increases in all cancer and lung cancer mortality among female smokeless tobacco users, these results could be due to outcomes experienced by a small number of subjects having large sample weights. The association for all cancer among female smokeless tobacco users was influenced by a small number of deaths at two sites (three lung cancer deaths and two uterine cancer deaths among smokeless tobacco users). Future studies, including both male and female subjects, should be conducted to determine whether these associations with smokeless tobacco use are causal.

Although the mortality rate among combined users was higher than that expected from the individual rates, this result is not likely due to a synergistic effect between smokeless tobacco and cigarettes. The combined users smoked more than exclusive smokers did (42.3 and 35.1 mean pack-years, respectively). The higher cigarette smoking dose, not the use of smokeless tobacco, is likely leading to the increased lung cancer mortality among combined users. A possible explanation is that combined users may be strongly addicted to nicotine and using smokeless tobacco in addition to cigarettes rather than as a substitute for them.

The apparent lack of an effect among combined users for ischemic heart disease mortality is counterintuitive. Combined users smoked more than exclusive smokers did, yet their ischemic heart disease mortality was less than that of exclusive smokers. Combined users were more likely to be former smokers than were exclusive smokers, possibly accounting for the decreased risk found here.

Of the two oral cancer deaths among ever smokeless tobacco users (both White males), one was a current smoker and the other was a former smoker. However, these two observed deaths were not more than expected in this cohort, even when limiting the analysis to White males. In this cohort, cigarette smoking was responsible for the increased oral cancer mortality.

One limitation of this analysis is that the exposure category is based only on ever use of smokeless tobacco. Therefore, potential increases in mortality associated with current versus former use could not be determined. Similarly, no dose-response analysis could be done. Because of the lack of information on lifetime use, subjects who used smokeless tobacco once were categorized the same as those who used smokeless tobacco many times.

Rouse (29) found that, among males who had ever tried smokeless tobacco, 60 percent used it in the past year; among females who had tried it, 42 percent used it in the past year. She also found that, among those who reported any lifetime use, 26 percent used it almost daily in the past year (29). Therefore, it may be a reasonable assumption that smokeless tobacco users in our study were not one-time users, with many having used smokeless tobacco regularly. Also, the restriction to subjects 45 years of age or more created a homogeneous exposure group with respect to duration of smokeless tobacco use. The majority of smokeless tobacco users initiate smokeless tobacco use prior to the age of 18 years (30).

Tobacco categories represent self-reported responses, and neither smokeless tobacco status nor smoking status was biologically confirmed. Confounding variables were also self-reported (e.g., alcohol intake, physical activity). However, as this information was collected prospectively, the potential for recall bias is much less than that found in case-control studies.

Although this analysis was restricted to subjects 45–75 years of age at baseline to create more similar comparison groups with respect to unknown and uncontrolled confounders, residual or uncontrolled confounding (e.g., other tobacco habits or factors relating to survival) may contribute to the results found in this study.

Because only a sample of individuals were asked about their tobacco habits in NHANES I, the results from 1971 to 1975 were supplemented by information collected in the 1982–1984 NHEFS. This approach may have resulted in some nondifferential misclassification of tobacco use, as data from 1982–1984 may not be as accurate as those collected in 1971–1975 (because of recall error or the use of proxies for subjects who died between the baseline interview and the initial follow-up). The expected effect would be a bias toward the null hypothesis of no association. However, as smokeless tobacco use is defined as only ever/never, this effect should be minimal.

This analysis represents one of the most comprehensive studies of the relation between smokeless tobacco use and mortality. The 20-year follow-up period allowed ample time to investigate common outcomes among smokeless tobacco users in a representative US population. Available data on a wide variety of risk factors allowed us to minimize the potential for confounding as an explanation for any results.

Overall, we found no increased mortality for subjects who reported ever smokeless tobacco use when compared with subjects who reported no tobacco use. The few increases in mortality that we discovered, although likely due to chance, should be investigated further. Evidence from this study shows that smokeless tobacco use is a safer alternative than continued cigarette smoking. Mortality for exclusive smokeless tobacco users is considerably less than mortality for exclusive smokers for all cancer (especially lung cancer) and for ischemic heart disease. Further studies are needed to determine whether regular smokeless tobacco use is appreciably more harmful than ever use and to determine whether there is increasing risk with increasing amount or duration of use of smokeless tobacco products.

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REFERENCES

1. Winn DM, Blot WJ, Shy CM, et al. Snuff dipping and oral cancer among women in the southern United States. N Engl J Med 1981;304:745–9.
2. Winn DM. Smokeless tobacco and cancer: the epidemiologic evidence. CA Cancer J Clin 1988;38:236–43.
3. Bolinder G, Alfredsson L, Englund A, et al. Smokeless tobacco use and increased cardiovascular mortality among Swedish construction workers. Am J Public Health 1994;84:399–404.
4. Huhtasaari F, Lundberg V, Eliasson M, et al. Smokeless tobacco as a possible risk factor for myocardial infarction: a population-based study in middle-aged men. J Am Coll Cardiol 1999;34:1784–90.
5. Giovino GA, Schooley MW, Zhu BP, et al. Surveillance for selected tobacco-use behaviors—United States, 1900–1994. Mor Mortal Wkly Rep CDC Surveill Summ 1994;43:1–43.
6. Hunter SM, Croft JB, Burke GL, et al. Longitudinal patterns of cigarette smoking and smokeless tobacco use in youth: the Bogalusa Heart Study. Am J Public Health 1986;76:193–5.
7. Fiore M, Novotny TE, Pierce JP, et al. Methods used to quit smoking in the United States: do cessation programs help? JAMA 1990;263:2760–5.
8. Everett SA, Husten CG, Warren CW, et al. Trends in tobacco use among high school students in the United States, 1991–1995. J Sch Health 1998;68:137–40.
9. Tobacco use among high school students—United States, 1997. MMWR Morb Mortal Wkly Rep 1998;47:229–33.
10. Tomar SL, Giovino GA. Incidence and predictors of smokeless tobacco use among US youth. Am J Public Health 1998;88:20–6.
11. Fagerstrom KO, Ramstrom L. Can smokeless tobacco rid us of tobacco smoke? Am J Med 1998;104:501–3.
12. Use of smokeless tobacco among adults—United States, 1991. MMWR Morb Mortal Wkly Rep 1993;42:263–6.
13. Tilashalski K, Rodu B, Cole P. A pilot study of smokeless tobacco in smoking cessation. Am J Med 1998;104:456–8.
14. National Center for Health Statistics. Plan and operation of the Health and Nutrition Examination Survey, United States—1971–1973. Hyattsville, MD: National Center for Health Statistics, 1977. (Vital and health statistics, series 1: programs and collection procedures, no. 10b) (DHEW publication no. (PHS) 79-1310).
15. National Center for Health Statistics. Plan and operation of the HANES I Augmentation Survey of adults 25–74 years, United States, 1974–1975. Hyattsville, MD: National Center for Health Statistics, 1978. (Vital and health statistics, series 1: programs and collection procedures, no. 14) (DHEW publication no. (PHS) 78-1314).
16. National Center for Health Statistics. Plan and operation of the NHANES I Epidemiologic Followup Study, 1982–84. Hyattsville, MD: National Center for Health Statistics, 1987. (Vital and health statistics, series 1: programs and collection procedures, no. 22) (DHHS publication no. (PHS) 87-1324).
17. Finucane FF, Freid VM, Madans JH, et al. Plan and operation of the NHANES I Epidemiologic Followup Study, 1986. Hyattsville, MD: National Center for Health Statistics, 1990. (Vital and health statistics, series 1: programs and collection procedures, no. 25) (DHHS publication no. (PHS) 90-1307).
18. Cox CS, Rothwell ST, Madans JH, et al. Plan and operation of the NHANES I Epidemiologic Followup Study, 1987. Hyattsville, MD: National Center for Health Statistics, 1992. (Vital and health statistics, series 1: programs and collection procedures, no. 27) (DHHS publication no. (PHS) 92-1303).
19. Cox CS, Mussolino ME, Rothwell ST, et al. Plan and operation of the NHANES I Epidemiologic Followup Study, 1992. Hyattsville, MD: National Center for Health Statistics, 1997. (Vital and health statistics, series 1: programs and collection procedures, no. 35) (DHHS publication no. (PHS) 98-1311).
20. National Center for Health Statistics. Caloric and selected nutrient values for persons 1–74 years of age: First Health and Nutrition Examination Survey, United States, 1971–1974. Hyattsville, MD: National Center for Health Statistics, 1979. (Vital and health statistics, series 11: data from the National Health Survey, no. 209) (DHEW publication no. (PHS) 79-1657).
21. Shah BV, Barnwell BG, Bieler GS. SUDAAN software for analysis of correlated data. Release 8.0. Research Triangle Park, NC: Research Triangle Institute, 1995.
22. Sterling TD, Rosenbaum WL, Weinkam JJ. Analysis of the relationship between smokeless tobacco and cancer based on data from the National Mortality Followback Survey. J Clin Epidemiol 1992;45:223–31.
23. Zahm SH, Heineman EF, Vaught JB. Soft tissue sarcoma and tobacco use: data from a prospective cohort study of United States veterans. Cancer Causes Control 1992;3:371–6.
24. Bouquot JE, Meckstroth RL. Oral cancer in a tobacco-chewing US population—no apparent increased incidence or mortality. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;86:697–706.
25. Bolinder G, Noren A, de Faire U, et al. Smokeless tobacco use and atherosclerosis: an ultrasonographic investigation of carotid intima media thickness in healthy middle-aged men. Atherosclerosis 1997;132:95–103.
26. US Department of Health and Human Services. The health benefits of smoking cessation: a report of the Surgeon General. Rockville, MD: US Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1990. (DHHS publication no. (CDC) 90-8416).
27. Cigarette smoking-attributable mortality and years of potential life lost—United States, 1990. MMWR Morb Mortal Wkly Rep 1993;42:645–9.
28. Ingram DD, Makuc DM. Statistical issues in analyzing the NHANES I Epidemiologic Followup Study. Hyattsville, MD: National Center for Health Statistics, 1994. (Vital and health statistics, series 2: data evaluation and methods research, no. 121) (DHHS publication no. (PHS) 94-1395).
29. Rouse BA. smokeless tobacco use: a national study. Natl Cancer Inst Monogr 1989;8:29–33.
30. Riley WT, Kaugars GE, Grisius TM, et al. Adult smokeless tobacco use and age of onset. Addict Behav 1996;21:135–8.