Smokeless Tobacco Use and Increased Cardiovascular Mortality among Swedish Construction Workers

Gunilla Bolinder, MD, Lars Alfredsson, PhD, Anders Englund, MD, and Ulf de Faire, MD, PhD

ABSTRACT

Objectives. Little is known about the risks of cardiovascular disease associated with the use of smokeless tobacco, which produces blood nicotine levels similar to those caused by cigarette smoking.

Methods. Male Swedish construction industry employees (n = 135 036) who attended a health examination were followed by studying cause-specific mortality during a 12-year period. The study population comprised 6297 smokeless tobacco users, 14 983 smokers of fewer than 15 cigarettes per day, 13 518 smokers of 15 or more cigarettes per day, 17 437 ex-smokers, 50 255 "other" tobacco users, and 32 546 nonusers.

Results. The age-adjusted relative risk of dying from cardiovascular disease was 1.4 for smokeless tobacco users and 1.9 for smokers of 15 or more cigarettes per day, compared with nonusers. Among men aged 35 through 54 years at the start of follow-up, the relative risk was 2.1 for smokeless tobacco users and 3.2 for smokers. When data were adjusted for body mass index, blood pressure, and history of heart symptoms, the results were essentially unchanged. Cancer mortality was not raised in smokeless tobacco users.

Conclusions. Both smokeless tobacco users and smokers face a higher risk of dying from cardiovascular disease than nonusers. Although the risk is lower for smokeless tobacco users than for smokers, the excess risk gives cause for preventive actions. (*Am J Public Health* 1994;84:399–404)

Introduction

Although there is well-established evidence for a causal link between cigarette smoking and cardiovascular damage and disease,[1] the reasons behind the development of atherosclerosis in smokers are not fully understood. The nicotine content of cigarette smoke is a suspected contributor to vascular damage, as nicotine has a variety of potentially relevant cardiovascular effects. Nicotine most likely promotes atherosclerotic disease by its actions on lipid metabolism and coagulation,[2–5] by hemodynamic effects,[1,4] and/or by causing endothelial injury.[6]

However, there have been no studies on long-term exposure to pure nicotine in humans, and only limited experience from animal studies.[7] Therefore, users of smokeless tobacco (snuff) present an excellent opportunity for studying the effects of exposure to nicotine without simultaneous exposure to carbon monoxide and other combustion products of tobacco smoke. It has been shown that the use of smokeless tobacco, during which nicotine is absorbed through the buccal mucosa, produces maximum blood levels of nicotine similar to those produced by cigarette smoking and results in a larger overall exposure to nicotine owing to prolonged absorption.[8,9]

In a recent cross-sectional study, it was observed that middle-aged and older smokeless tobacco users had a significantly higher prevalence of hypertension than either nonusers or smokers.[10] The smokeless tobacco users were also affected more than nonusers by cardiovascular symptoms. During a 4-year follow-up period, smokeless tobacco users had a higher risk than nonusers of disability retirement due to cardiovascular diseases. The excess risk was quite similar to the excess risk observed in smokers.

The aim of the present study was to investigate whether long-term exposure to smokeless tobacco is associated with an excess risk of dying from cardiovascular disease in users compared with nonusers and to compare this potential excess risk among smokeless tobacco users with the corresponding excess risk among cigarette smokers.

Materials and Methods

Subjects

The study population comprised 135 036 men who had received medical checkups under the auspices of the Swedish Construction Industry's Organization for Working Environment Safety and Health during the years 1971 through 1974. The cohort included construction workers, electricians, painters, sheet metal workers, and other construction industry employees in the whole of Sweden. The invitation to the voluntary medical examination was sent out by the construction site staff and about 75%

Gunilla Bolinder and Ulf de Faire are with the Department of Medicine, Karolinska Hospital, Stockholm, Sweden. Lars Alfredsson is with the Division of Epidemiology, Institute of Environmental Medicine, Karolinska Institute, Stockholm. Anders Englund is with the Swedish Construction Industry's Organization for Working Environment Safety and Health, Danderyd, Sweden.

Requests for reprints should be sent to Gunilla Bolinder, MD, Department of Medicine, Karolinska Hospital, S-17176 Stockholm, Sweden.

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TABLE 1—Distribution of the Study Population, by Age and Tobacco Habit

Age	Nonusers	Smokeless Tobacco Users	Smokers, <15 cig/d	Smokers, ≥15 cig/d	Ex-Smokers	Total
<35 y	13 120	2891	7 626	6 350	4 369	34 356
35–54 y	13 784	1672	5 225	5 785	8 222	34 688
55–65 y	5 642	1734	2 132	1 383	4 846	15 737
All	32 546	6297	14 983	13 518	17 437	84 781

Note. Those who had mixed tobacco use or who smoked pipes or cigars (50 255 subjects, or 37.2% of the total sample of 135 036) are excluded from table.

responded to it. In 1974 there were 183 865 registered workers in the Swedish construction industry; it is not known to what extent the nonattending workers (≈25%) were not reached by the invitation or were not willing to come. Women (< 0.5% of workers in the construction industry) were excluded from the study.

Procedures

A standardized program was followed for the medical examination. Body weight and height were determined. Blood pressure was measured after 5 minutes of rest in a supine position. A standard mercury manometer on the upper arm was used to record the systolic level when phase 1 (Korotkoff) sounds were heard and the diastolic level at phase 5 (disappearance of sounds). Blood pressure was recorded to the nearest 2 mm Hg. Heart rate was recorded as beats per minute, simultaneously with the blood pressure measurement.

Tobacco habits by kind of tobacco use (cigarettes, smokeless tobacco, pipe, cigar, or mixed use), amount of smoked tobacco, and duration of the tobacco consumption habit were recorded with the aid of a questionnaire that the subject filled out together with a nurse. The questionnaire also requested information about present or past history of symptoms and diseases as well as current medication.

The members of the study population identified between 1971 and 1974 and who were alive on January 1, 1974, were followed regarding cause-specific mortality during the period 1974 through 1985 with the aid of the National Cause of Death Register,[11] with certification of the underlying cause of death according to the *International Classification of Diseases*, 8th revision (ICD-8). The underlying cause of death is defined as the illness that started the chain of events that directly led to death. The diagnoses specifically studied were ischemic heart disease (ICD 410–414), cerebrovascular disorders (ICD 430–438), all cardiovascular diagnoses (ICD 390–458), and all malignant neoplasms (ICD 140–209).

Analyses

The classification of tobacco habits was aimed at isolating subjects in groups with a single type of exposure to tobacco. Tobacco users were divided into smokeless tobacco users, smokers, ex-smokers, and others. Nonusers were subjects who reported that they had never used tobacco. Smokers were divided into cigarette smokers who smoked fewer than 15 cigarettes per day and those who smoked 15 cigarettes per day or more, both groups being without any other kind of former or present tobacco use. Smokeless tobacco users were subjects who reported only present smokeless tobacco use and no former or present smoking. Ex-smokers were cigarette smokers who had never smoked a pipe, smoked cigars, or used smokeless tobacco and who had quit smoking; they were further divided into those who had not smoked for less than 5 years and those who had not smoked for 5 or more years. "Others" were all subjects with mixed tobacco use or subjects who smoked a pipe or cigars. The duration of the tobacco habit was divided into less than 15 years and 15 or more years. Because smokers of more than 15 cigarettes per day consume about the same amount of nicotine as daily smokeless tobacco users,[9,12] special emphasis should be placed on this group when interpreting the analysis.

In the analysis, blood pressure was divided into four categories: systolic blood pressure ≤ 140, 141–159, 160–179, and ≥180 mm Hg and diastolic blood pressure <85, 85–94, 95–104, and ≥105 mm Hg. Blood pressure and heart rate data were missing for 0.2% of the subjects. The body mass index was calculated as body weight in kilograms divided by height in meters squared. Body mass indexes were divided into four categories: ≤20.0, 20.1–25.0, 25.1–30.0, and >30.0.

Relative risks of death due to specific causes, together with 95% confidence intervals, were estimated for subjects with different tobacco habits in comparison with the nonusers. To adjust for potential confounding factors, the Mantel-Haenszel procedure was used[13] and 95% confidence intervals were estimated according to Greenland et al.[14] Potential confounding factors were considered to be age (5-year brackets), area of domicile, blood pressure, blood pressure medication, previous cardiac symptoms, diabetes, and body mass index.

Analyses of the relationship between different tobacco habits and mortality were performed for the entire cohort, for workers entering the study at ages 35 through 54 years, and for those entering the study at ages 55 through 65 years.

Results

The distribution of the study population by tobacco habit is shown in Table 1; 24.1% of the subjects were nonusers, 4.7% were smokeless tobacco users, 11.1% were smokers of fewer than 15 cigarettes per day, 10.0% were smokers of more than 15 cigarettes per day, and 12.9% were ex-smokers. The 37.2% of the population who smoked pipes or cigars or who had mixed tobacco use (n = 50 255) were excluded from all analyses.

During the follow-up period (1974 through 1985), there were a total of 8293 deaths in the whole study cohort. Fifty-seven percent of the deaths occurred in the analyzed tobacco-use groups: nonusers, 1322; smokeless tobacco users, 440; smokers of fewer than 15 cigarettes per day, 900; smokers of 15 or more cigarettes per day, 923; and ex-smokers, 1126. Cardiovascular disease was the most common cause of death among the construction workers. Ischemic heart disease caused 38% of the deaths in the whole study population, implying a crude cumulative mortality of 2.3% during the 12-year follow-up period.

TABLE 2—Observed Numbers of Deaths and Relative Risks (RRs)[a] for Causes of Death for Different Tobacco Habit Groups Compared with Nonusers

Cause of Death	Nonusers[b] (At-Risk n = 32 546)	Smokeless Tobacco Users (At-Risk n = 6297)		Smokers, <15 cig/d (At-Risk n = 14 983)		Smokers ≥15 cig/d (At-Risk n = 13 518)		Ex-Smokers, 1–5 y (At-Risk n = 6761)		Ex-Smokers, >5 y (At-Risk n = 9800)	
	No.	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)
All cardiovascular disease	641	220	1.4 (1.2, 1.6)	450	1.8 (1.6, 2.0)	381	1.9 (1.7, 2.2)	169	1.4 (1.1, 1.6)	402	1.1 (0.9, 1.2)
All cancer	372	96	1.1 (0.9, 1.4)	216	1.5 (1.3, 1.8)	276	2.5 (2.2, 3.0)	119	1.6 (1.3, 2.0)	249	1.3 (1.1, 1.6)
All causes	1322	440	1.4 (1.3, 1.8)	900	1.7 (1.6, 1.9)	923	2.2 (2.0, 2.4)	350	1.3 (1.2, 1.5)	776	1.1 (1.0, 1.2)

Note. The deaths of 3582 men who were pipe or cigar smokers or had a mixed tobacco use habit are not presented in the table. For 876 ex-smokers (5%), length of time since quitting smoking was unknown; these ex-smokers were not included in this analysis. CI = confidence interval.
[a]Adjusted for age in 5-year intervals and for region of origin.
[b]Nonusers are the referent category (RR = 1.0).

Table 2 shows the age-adjusted relative risks of dying of cardiovascular disease, malignant tumors, and any cause for different tobacco-use groups compared with the nonusers. The excess risk of dying of cardiovascular disease was most pronounced for smokers, with a dose–response relation. In ex-smokers, the excess risk diminished with the time since smoking was stopped. Smokeless tobacco use was also found to be associated with an excess risk of dying of cardiovascular disease, whereas regarding death from cancer, no excess risk was observed. Although the present study did not analyze different cancer diagnoses in detail, it was obvious that smoking had a dose–response relationship to overall cancer risk and that the excess risk diminished gradually with the time since smoking was stopped.

Table 3 shows the results of the analysis of more specific causes of death in workers in two age groups. Higher relative risks were observed in the younger than in the older group for both smokeless tobacco users and smokers, compared with the nonusers. For smokeless tobacco users compared with nonusers, the relative risk of dying of cardiovascular disease was 2.1 (95% confidence interval [CI] = 1.5, 2.9) for those in the younger group and only 1.1 (95% CI = 1.0, 1.4) for those in the older group.

Death from stroke was less common than death from ischemic heart disease, but with regard to tobacco habits, the risk patterns for ischemic heart disease and stroke were the same. The relative risk of stroke among the younger smokeless tobacco users was close to 2, compared with the nonusers, but the number of cases was small and therefore the confidence interval was wide.

Lung cancer was studied specifically to evaluate whether hidden smokers could be found among the declared smokeless tobacco users. Three deaths from lung cancer were found in this group, whose relative risk compared with the nonusers was 0.9 (95% CI = 0.2, 3.0).

When potential confounding due to age, area of domicile, body mass index, blood pressure, diabetes, and history of heart symptoms or blood pressure medication at the time of entering the study was analyzed according to the Mantel-Haenszel procedure, the relative risks of death from cardiovascular diseases remained essentially unchanged. For cancer and overall mortality, no changes in the relative risk estimates were found when confounding factors were considered.

It was not considered meaningful to evaluate the duration of the tobacco habit in relation to cardiovascular mortality because very few subjects in age groups prone to various cardiovascular manifestations (i.e., those older than 45 years) exhibited a duration of tobacco use of less than 15 years, as most tobacco users start the habit at a young age. Eighty-seven percent of the cardiovascular deaths among smokeless tobacco users were associated with a tobacco habit duration of more than 15 years at the time the subjects entered the study. The corresponding figure for smokers of fewer than 15 cigarettes per day was 89%; for smokers of 15 or more cigarettes per day, the figure was 97%.

Figure 1 shows, for subjects who entered the study at ages 35 through 54 years, the relative risk of dying of ischemic heart disease for subjects in different tobacco-use categories compared with the nonusers. For smokeless tobacco users, the risk of death from ischemic heart disease was higher than that of nonusers and ex-smokers but lower than that of cigarette smokers.

Discussion

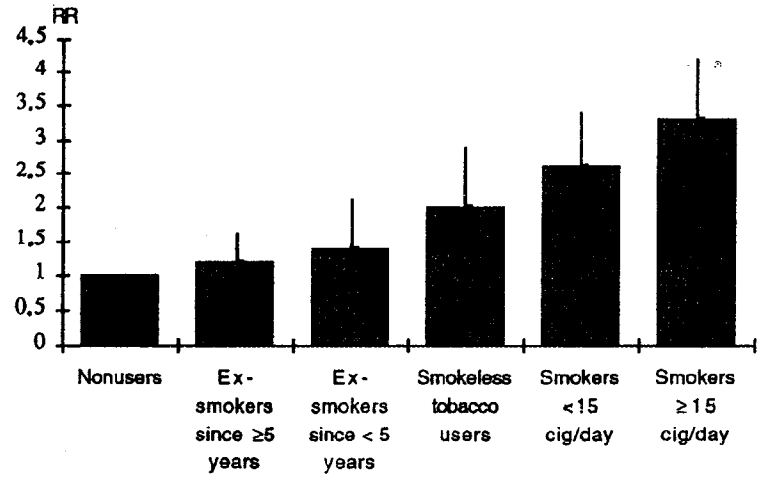
The present study of cardiovascular and cerebrovascular mortality in a cohort comprising more than 6000 smokeless tobacco users is the first observational epidemiological cohort study with the possibility of comparing a large group of smokeless tobacco users with both smokers and subjects not using any kind of tobacco. The results indicate an apparent excess risk of death from cardiovascular and cerebrovascular diseases of about 40% to 100% among smokeless tobacco users, compared with nonusers, when possible confounding factors are taken into account. Smokers face even higher risks of both cardiovascular and cerebrovascular causes of death.

In a recent case–control study from northern Sweden encompassing 35- through 64-year-old men with a first myocardial infarction and population-derived controls, smoking but not the use of smokeless tobacco was associated with an increased risk of myocardial infarction.[15] These results, which are contradictory to ours, could be due to differences in study design and composition of reference groups. Reasonably, the power to detect potential hazard effects from smokeless tobacco use is greater in an observational cohort study

TABLE 3—Cause-Specific Mortality among Swedish Construction Workers during 12-Year Follow-Up after 1971–1974 Health Examination

Cause of Death	Nonusers[a]	Smokeless Tobacco Users		Smokers, <15 cig/d		Smokers ≥15 cig/d		Ex-Smokers, 1–5 y		Ex-Smokers, >5 y	
	No.	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)	No.	RR (95% CI)
Age 35–54 years at entry into study											
	(At-Risk n = 13 784)	(At-Risk n = 1672)		(At-Risk n = 5225)		(At-Risk n = 5785)		(At-Risk n = 2882)		(At-Risk n = 5005)	
Ischemic heart disease	123	35	2.0 (1.4, 2.9)	128	2.6 (2.1, 3.4)	162	3.3 (2.6, 4.2)	37	1.4 (1.0, 2.1)	67	1.2 (0.9, 1.6)
Stroke	16	4	1.9 (0.6, 5.7)	17	2.7 (1.4, 5.4)	19	3.0 (1.5, 5.7)	4	1.2 (0.4, 3.7)	5	0.7 (0.2, 1.9)
All cardiovascular disease	154	44	2.1 (1.5, 2.9)	164	2.7 (2.2, 3.4)	199	3.2 (2.6, 3.9)	46	1.4 (1.0, 2.0)	83	1.1 (0.9, 1.5)
All cancer	128	22	1.2 (0.8, 1.9)	62	1.2 (0.9, 1.7)	116	2.2 (1.8, 2.9)	42	1.6 (1.1, 2.2)	62	1.1 (0.8, 1.5)
Lung cancer	5	1	1.2 (0.2, 9.1)	16	8.1 (3.2, 20.4)	43	21.4 (8.5, 54.1)	7	6.7 (2.3, 19.7)	3	1.2 (0.3, 4.5)
All causes	410	105	1.9 (1.6, 2.4)	317	2.0 (1.7, 2.3)	437	2.6 (2.3, 3.0)	114	1.3 (1.1, 1.6)	189	1.0 (0.9, 1.2)
Age 55–65 years at entry into study											
	(At-Risk n = 5642)	(At-Risk n = 1734)		(At-Risk n = 2132)		(At-Risk n = 1383)		(At-Risk n = 1076)		(At-Risk n = 3660)	
Ischemic heart disease	359	137	1.2 (1.0, 1.5)	225	1.7 (1.4, 1.9)	122	1.4 (1.2, 1.8)	89	1.3 (1.1, 1.6)	248	1.1 (0.9, 1.2)
Stroke	70	26	1.2 (0.7, 1.8)	19	0.7 (0.4, 1.2)	25	1.6 (1.0, 2.5)	20	1.5 (0.9, 2.5)	35	0.8 (0.5, 1.2)
All cardiovascular disease	480	174	1.1 (1.0, 1.4)	272	1.5 (1.3, 1.7)	167	1.5 (1.3, 1.7)	120	1.3 (1.1, 1.6)	317	1.0 (0.9, 1.2)
All cancer	223	69	1.0 (0.8, 1.3)	145	1.7 (1.4, 2.1)	148	2.9 (2.3, 3.5)	69	1.6 (1.3, 2.1)	183	1.3 (1.1, 1.5)
Lung cancer	8	2	0.8 (0.1, 3.9)	36	11.9 (5.5, 25.6)	57	30.6 (14.6, 64.1)	14	9.4 (3.9, 22.3)	12	2.3 (1.0, 5.7)
All deaths	820	301	1.2 (1.0, 1.3)	496	1.6 (1.5, 1.8)	377	2.0 (1.8, 2.2)	212	1.4 (1.2, 1.6)	576	1.1 (1.0, 1.2)

Note. For some ex-smokers (335 [4.1%] of those aged 35–54 years at entry and 110 [2.3%] of those aged 55–65 years at entry), length of time since quitting smoking was unknown; these ex-smokers were not included in this analysis. No. = number of deaths in the group; RR = relative risk, adjusted for age (5-year intervals) and for region of origin, for tobacco users compared with nonusers; CI = confidence interval.
[a]Nonusers are the referent category (RR = 1.0).



Note. Only subjects who were 35–54 years of age at entry into the study are included.

FIGURE 1—Adjusted relative risk (RR), together with 95% confidence interval, of dying due to ischemic heart disease among subjects in different tobacco habit groups as compared with nonusers.

with 3159 deaths due to ischemic heart disease (of which 172 were smokeless tobacco users) than in a smaller case–control study with 585 incident cases of myocardial infarction (of which 59 were smokeless tobacco users). In addition, our nonusers had never used any tobacco, whereas the nonusers in the case–control study included both former smokers and former smokeless tobacco users. The use of such "nonusers" might have contributed to a dilution of a possible excess risk for myocardial infarction in smokeless tobacco users.

Possible bias due to misclassification of both exposure and disease should be considered in our study. Assuming that smokers have a higher risk of dying from cardiovascular disease than smokeless tobacco users, a misclassification of smokers in the smokeless tobacco users group would lead to an overestimation of the relative risk associated with smokeless tobacco (i.e., the observed relative risk would be too high). How-

ever, if the proportion of misclassified smokers in the group classified as using smokeless tobacco was considerable, an elevated risk of dying from lung cancer would have been expected. Only three deaths from lung cancer were found among those classified as smokeless tobacco users. The corresponding relative risk of dying from lung cancer, compared with nonusers, was 0.9 (95% CI = 0.2, 3.0). In addition, different kinds of smokers or smokeless tobacco users wrongly classified as nonusers would result in an underestimation of the correlation between smokeless tobacco use and mortality due to cardiovascular disease. On combining different sources of bias due to misclassification of exposure, one finds that an underestimation of the relative risk of death from cardiovascular disease associated with smokeless tobacco use is more likely than an overestimation.

No follow-up recording of subjects' tobacco habits after entry into the study has been made. The most common change in tobacco habits in adults is to quit using tobacco. If our subjects had quit using tobacco, the relative risk estimates might have been diluted compared with what would be expected if no change took place during the follow-up period. If smokeless tobacco users had a tendency to start smoking, the estimated relative risks for smokeless tobacco users would be exaggerated. Nearly all smokeless tobacco users had used smokeless tobacco for more than 15 years without smoking, so it is reasonable to assume that the possible influence of such changes has been small.

The completeness of the Swedish National Cause of Death Register is almost 100%, as all deaths are required to be registered.[16] The validity of the underlying causes of death stated in death certificates has been evaluated and found to be high regarding cardiovascular diseases, stroke, and cancer.[17] Possible misclassifications are not likely to be dependent on the type of tobacco habit and therefore should not affect the relative risk estimates.[18]

The relationship between smokeless tobacco use and mortality due to specific causes was scrutinized regarding potential confounding from age, area of domicile, body mass index, blood pressure, diabetes, and history of heart symptoms or blood pressure medication at the time of entering the study. Cardiovascular risk markers such as total cholesterol were not routinely measured at the time of the medical examinations of this cohort, and therefore it was not possible to adjust for hypercholesterolemia as a confounding factor in the analysis. Cholesterol and high-density lipoprotein cholesterol did not differ between smokeless tobacco users and nonusers in two studies of relatively young users of smokeless tobacco,[19,20] but significantly higher levels of plasma cholesterol were found in smokeless tobacco users in one study in which older users were also examined.[21] The body mass index of smokeless tobacco users is generally higher than that of nonusers and considerably higher than that of smokers,[10] possibly implying differences in lipoprotein levels. However, the body mass index regarded as a confounder in the analysis did not change the relative risk estimates for the association between smokeless tobacco use and mortality due to cardiovascular disease.

It was not possible to consider potential confounding due to alcohol use, as no information on alcohol use was included in the medical examination data for this cohort. There is a positive correlation between hypertension and alcohol consumption.[22] Other studies have shown that smokeless tobacco users consume more alcohol than nonusers.[19,20] Similarly, tobacco users tend to exhibit other risk behaviors more often than nonusers.[22] Considering the relative homogeneity of the study population—all of whom were construction industry employees—and the relative risk associated with smokeless tobacco use among subjects aged 35 through 54 years at entry into the study, as well as the relative risk associated with heavy alcohol consumption,[23] it is unlikely that differences in alcohol consumption (between smokeless tobacco users and nonusers) would explain the findings entirely. Moreover, the studies on the relationship between alcohol consumption and cardiovascular disease have been ambiguous.[24] There have been, however, no observations indicating a difference in alcohol consumption between smokeless tobacco users and cigarette smokers, and therefore the possible confounding effect of alcohol use can be suspected to be comparable for both kinds of tobacco use.

In a cross-sectional study of the health status of this cohort, systolic and diastolic blood pressure values were found to be significantly higher among smokeless tobacco users than among either nonusers or smokers.[10] This difference was not significant at younger ages but became obvious in subjects older than 45 years. Smokers had the lowest prevalence of hypertension, as has been found in many other epidemiological studies.[22,25,26] The significantly higher prevalence of hypertension found among smokeless tobacco users, compared with cigarette smokers, could reflect differences in the pharmacodynamic effects of nicotine in smokeless tobacco users and smokers. The use of smokeless tobacco yields high blood concentrations of nicotine and more prolonged and more perpetual levels than smoking. These high concentrations might be accompanied by longer periods of cutaneous vasoconstriction, systemic venoconstriction, and increased muscle blood flow in smokeless tobacco users,[27] and it could be speculated that such mechanisms are more operative for the development of hypertension in smokeless tobacco users than in smokers.

The construction industry demands a high level of physical performance. Persons with decreased capacity are not hired or leave the industry; therefore, construction workers are physically fitter than average citizens of the same age. Because the study sample was drawn from active workers and not from company lists, which might include retired workers, the healthy worker selection could be expected to be more obvious among the workers who belonged to the higher age group at entry into the study. This situation could explain the more pronounced excess risk of cardiovascular mortality found among the younger tobacco users than among the older tobacco users in relation to nonusers in the same age group.

Since smoking—and probably also the use of smokeless tobacco—affects the cardiovascular system in an unfavorable way and leads to poorer physical performance, the above-mentioned selection process may also be related to tobacco habit, probably resulting in an underestimation of the strength of the relationship between tobacco use and cardiovascular mortality.

The results of this study support the hypothesis that smokeless tobacco users face a higher risk than nonusers of dying of ischemic heart disease and cerebrovascular disorders. Smokers still seem to be at the highest risk, and quitting smoking

considerably reduces the risk of cardiovascular events. Even though nicotine is the main substance common to both smokers and smokeless tobacco users, it remains to be elucidated in clinical studies and by laboratory experiments whether the higher risk of cardiovascular disease in smokeless tobacco users is caused by nicotine or by some other exposure related to smokeless tobacco. Data on vasoconstriction, arrythmias, release of stress hormones, atherogenic effects, or hypertension caused by the exposure to nicotine in smokeless tobacco might elucidate this matter. The higher risk of dying of cardiovascular disease in smokers than in smokeless tobacco users supports the idea that there are substances in tobacco smoke other than nicotine that are hazardous. Although the risk of dying of cardiovascular disease is lower for smokeless tobacco users than for smokers, the excess risks are sufficiently impressive to call for action to be taken against the use of smokeless tobacco. □

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