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Cancer and mortality among users and nonusers of snus

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Scandinavian moist snuff (snus) is claimed to be a safer alternative to smoking. We aimed to quantify cancer incidence among male snus users and to shed light on the net health outcome by studying their overall mortality. A cohort, comprised of 9,976 men who participated in a population-based survey, was compiled in 1973–74. Follow-up until January 31, 2002, was accomplished through record-linkages with nation-wide and essentially complete registers of demographics, cancer and causes of deaths. Adjusted relative risks among exposed relative to unexposed men were estimated using Cox proportional hazards regression. The cohort members contributed more than 220,000 person-years at risk for cancer. A statistically significant increase in the incidence of the combined category of oral and pharyngeal cancer among daily users of snus (incidence rate ratio 3.1, 95% confidence interval 1.5–6.6) was found. Overall mortality was also slightly increased (hazard ratio 1.10, 95% confidence interval 1.01–1.21). Although the combined previous literature on snus and oral cancer weigh toward no association, this population-based prospective study provided suggestive evidence of snus-related risks that cannot be lightly ignored.

Key words: epidemiology; cancer; mortality; smokeless tobacco

The carcinogenic potential of oral snuff, including the Scandinavian moist type (snus), has been evaluated and established by 2 working groups at the International Agency for Research on Cancer.[1] However, in view of the comparably low levels of tobacco-specific nitrosamines in snus and the idea of using snus as a way of reducing smoking dose among inveterate smokers,[2–4] possible health consequences of snus use is presently the topic of intense debate. Several Swedish case-control studies concluded that there was no significant association between use of snus and head and neck cancer,[5–7] while a significant excess risk of pancreatic cancer was reported from 2 recent cohort studies.[8,9] Moreover a moderately increased all-cause mortality was observed among snus-using male construction workers.[10]

We aimed to quantify cancer incidence among male snus users, and to shed light on the net health outcome by studying their overall and disease group-specific mortality.

Material and methods

The cohort

A cohort from Uppsala County, central Sweden, was established in 1973–74 as an emanation from a population-based survey investigation aimed at establishing the prevalence of oral lesions.[11] All residents of the municipalities of Enköping or Håbo aged 15 years or older during the year of examination (n = 30,118) were invited to participate. In the first round, a total of 18,659 (62% of all invited) individuals participated. Of those remaining, 2,292 were randomly selected for an intense recruitment effort, which resulted in another 1,674 (73%) examined participants. The total participation was 20,333 individuals constituting 68% of all invited (Fig. 1). All participants filled in a questionnaire about tobacco and alcohol consumption, and all underwent a clinical examination of the oral cavity, performed by one of the present authors (TA). For 121 individuals, the data from 1973 to 74 was lost. Since virtually no women were exposed to snus, we restricted our analysis to men (n = 9,976).

Follow-up

Follow-up for mortality and cancer incidence between 1973 and 2002 was accomplished through record-linkages with the nationwide and essentially complete registers of cancer,[12,13] causes of deaths[14] and total population,[15] using the individually unique National Registration Numbers, assigned to all Swedish residents and included in all registers, as identifiers.

Cancer diagnoses

We grouped the cancer diagnoses into the following 3 nested categories: a combined category of oral and pharyngeal cancer (ICD7: 140–148); smoking-related cancers according to Levitz *et al.*[16] including oral and pharyngeal cancer (ICD7: 140–148), oesophageal and gastric cancer (ICD7:150–151) pancreatic cancer (ICD7:157), laryngeal and pulmonary cancer (ICD7:161–162), cancer of the kidney, bladder and other urinary organs (ICD7:180–181); and any cancer (ICD7: 140–209). The list proposed by Levitz *et al.*[16] differs somewhat from that published by the International Agency for Research on Cancer[17] in that it does not include cancers of the nasal cavities and sinuses, liver, and myeloid leukemia.

As we only counted first cancers, individuals with a history of any cancer diagnosis before entry into the cohort in 1973–74 were excluded (n = 116). The follow-up for cancer thus comprised 9,860 men.

Causes of death

We grouped causes of death into the following 4 categories: Cancer deaths (ICD8, ICD9: 140–209, ICD10: C00–D48); cardiovascular deaths (ICD8, ICD9: 390–458, ICD10: I00–I99); and respiratory deaths (ICD8, ICD9: 460–519, ICD10: J00–J99) and all-cause mortality. The follow-up for mortality comprised all 9,976 men.

Statistical methods

In addition to computing crude incidence and mortality rates (the number of events divided by corresponding person-time), we analyzed data with Cox proportional hazard regression using attained age as the underlying time-scale. We estimated hazard ratios (HR) for cancer incidence and mortality, with 95% confidence intervals (CI), as measures of relative risk of cancer and death, respectively.

In the follow-up for mortality, person-time was calculated from the date (age) of first examination (1973–74) until the date (age) of death, emigration or end of follow-up (January 31, 2002), whichever occurred first. In the follow-up for cancer additional censoring took place at date of first cancer (any site).

Exposure to snus was categorized as never or ever daily use at entry into the cohort in 1973–74. The models were adjusted for

Abbreviations: CI, confidence interval; HR, hazard ratios; ICD, International Classification of Diseases; IR, incidence rate; MR, mortality rate; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N′-nitrosonornicotine; TSNA, tobacco-specific nitrosamines.

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smoking (never versus ever daily use), alcohol consumption (less than once a week versus once a week or more), and area of residence (rural, small municipality or town). All covariate information emanated from 1973 to 74. We also adjusted for calendar period (attained) in 5-year-intervals (1973–1977, 1978–1982, 1983–1987, 1988–1992, 1993–1997, 1998–2002). Since all participants entered at approximately the same time in 1973–74, calendar time was equivalent to time-in-study.

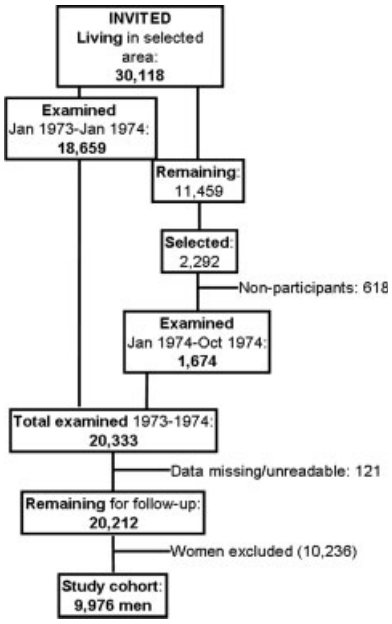

FIGURE 1 – Overview of the recruitment to the population-based cohort.

Nonproportionality of hazards (interaction between age [underlying time-scale] and covariates) was investigated using the Grambsch and Therneau test based on Schoenfeld residuals.[18] In cases of nonproportional hazards, separate covariate effects were fitted for 2 age strata, where the chosen cut-off age was 70 years for cancer analyses and 75 years for mortality analyses (since death occurs at higher ages than cancer). For respiratory deaths, the age cut-off was chosen as 80 years since virtually all these deaths occurred at advanced ages. The interaction between covariates and the dichotomized age-scale was further tested using likelihood ratio tests, and *p*-values are presented. Only participants with complete information on outcome and all covariates were included in the models. Stata version 9 was used for the statistical analyses.[19]

Results

At time of cohort accrual in 1973–74, 867 men (9%) were classified as ever daily users of snus (but never daily smokers), 5,309 (53%) as ever daily smokers (but never daily users of snus), and 692 (7%) as both ever daily smokers and ever daily users of snus. The cohort was followed for up to 29 years and the study participants contributed 223,528 and 231,542 person-years at risk for cancer and death, respectively (Table I). There were 237 ever-users of snus among the 1,575 individuals who were diagnosed with any first cancer. A total of 3,630 cohort members died and

TABLE I – NUMBER OF PARTICIPANTS, PERSON-YEARS, CRUDE INCIDENCE (IR) AND MORTALITY (MR) RATES BY SNUS USE, SMOKING AND SOME OTHER BACKGROUND FACTORS

	Any cancer[1]				All-cause mortality[2]	
	No of individuals (*n*)[3]	Person-years[4]	Cases (*n*)	CrudeIR[5]	Deaths (*n*)	Crude MR[6]
Snus use						
Never daily use	8,311	189,561	1,337	7.1	2,988	15.2
Ever daily use	1,548	33,944	237	7.0	641	18.3
Missing	1		1		1	
Smoking						
Never daily use	3,930	91,978	544	5.9	1,262	13.3
Ever daily use	5,930	131,550	1,031	7.8	2,368	17.4
Alcohol consumption						
No/low	1,447	29,895	228	7.6	703	22.6
Moderate/high	8,407	193,522	1,345	6.9	2,922	14.6
Missing	6		2		5	
Area of residence						
Rural	3,513	77,353	626	8.1	1,494	18.5
Small community	1,492	36,391	188	5.2	402	10.8
Town	4,855	109,784	761	6.9	1,734	15.3
Calender period (attained)						
1973–1977	9,860	42,127	175	4.2	457	10.7
1978–1982	9,298	44,676	260	5.8	632	13.8
1983–1987	8,559	40,999	241	5.9	641	15.2
1988–1992	7,872	37,447	299	8.0	674	17.3
1993–1997	7,115	33,658	323	9.6	656	18.5
1998–2002	6,353	24,622	277	11.3	570	21.6
Age (attained)						
14–24	1,625	8,656	2	0.2	7	0.8
25–34	3,832	26,891	8	0.3	22	0.8
35–44	5,374	44,964	25	0.6	56	1.2
45–54	6,449	48,433	100	2.1	163	3.3
55–64	6,192	42,499	288	6.8	358	8.2
65–74	4,675	31,700	555	18.0	849	24.8
75+	2,941	20,386	597	29.0	2,175	90.8

[1]Any cancer includes ICD7 codes 140–209.–[2]All cause mortality includes all ICD8, ICD9, and ICD10 codes.–[3]Number of cohort members in the cancer analysis ($n = 9{,}860$). Since we excluded 116 cohort members with prevalent cancer at time of entry in the cohort, the mortality analysis included a slightly larger number of individuals ($n = 9{,}976$). Their distributions across exposures categories were very similar to that exhibited here and are therefore not shown.–[4]The distribution of person-years across exposure categories differ marginally in the mortality analysis due to a slightly larger number of cohort members from start and absence if censoring at cancer incidence. The difference is so small that these data are not shown.–[5]Crude incidence rate of any cancer per 1,000 person-years.–[6]Crude mortality rate per 1,000 person-years.

TABLE II – INCIDENCE RATE RATIOS (IRR) FOR ANY CANCER, SMOKE-RELATED CANCER AND THE COMBINED CATEGORY OF ORAL AND PHARYNGEAL CANCER BY SNUS USE AND SMOKING, OBTAINED IN MODELS THAT INCLUDED ALL PARTICIPANTS AND IN MODELS RESTRICTED TO NEVER-SMOKERS

	Any cancer			Smoke-related cancer[1]				The combined category of oral and pharyngeal cancer[1]		
	Cases (*n*)	Crude IR[2]	HR[3] (95% CI)	Cases (*n*)	Crude IR[2]	HR (95% CI)		Cases (*n*)	Crude IR[2]	HR[4] (95% CI)
Snus use										
Never daily use	1,335	7.1	1.00 (ref)	422	2.2	1.0 (ref)		23	0.1	1.0 (ref)
Ever daily use	237	7.0	1.00 (0.87–1.15)	71	2.1	1.1 (0.8–1.4)		11	0.3	3.1 (1.5–6.6)
Smoking							Age <70 years			
Never daily use	544	5.9	1.00 (ref)	112	1.2	1.0 (ref)	Never	8	0.1	1.0 (ref)
Ever daily use	1,028	7.8	1.26 (1.13–1.40)	381	2.9	2.2 (1.8–2.7)	Ever	5	0.05	0.5 (0.1–1.4)
							Age ≥70 years			
							Never	3	0.2	1.0 (ref)
							Ever	18	0.9	5.6 (1.6–19.6)
Restricted to never smokers										
Snus use										
Never daily use	406	5.5	1.0 (ref)	73	1.0	1.0 (ref)		6	0.1	1.0 (ref)
Ever daily use	138	7.8	1.1 (0.9–1.4)	39	2.2	1.6 (1.1–2.5)		5	0.3	2.3 (0.7–8.3)

All models were adjusted for calendar period (attained), area of residence, alcohol consumption, and smoking or snus use; along with interaction terms where appropriate (see footnotes).

[1]For definitions, see text.–[2]Crude incidence rate per 1,000 person-years.–[3]Interaction term included in model: Age × calendar period (attained).–[4]Interaction term included in model: Age × smoking.

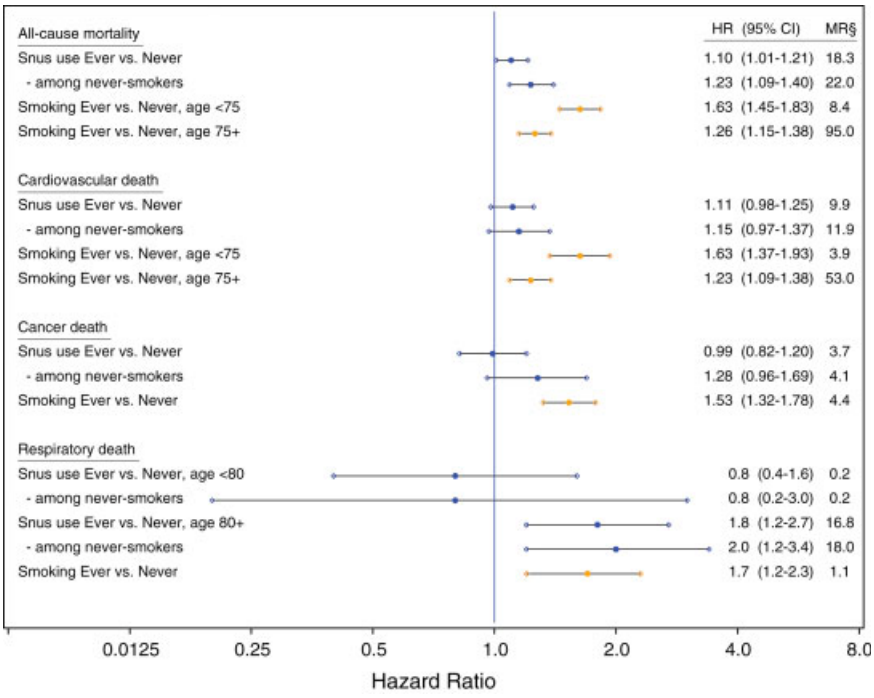

FIGURE 2 – Hazard ratios (HR) and mortality rates (MR) for all-cause mortality, cardiovascular deaths, cancer deaths, and respiratory deaths by snus use (blue) and smoking (yellow). Data are given for all participants and (in analyses of snus effects) for the substratum of never smokers. All models used attained age as the underlying time-scale and were adjusted for calendar period (attained), area of residence, alcohol consumption and smoking or snus use. Models for all-cause mortality (including model restricted to never-smokers) contained the following interaction terms: Age × smoking, age × area of residence, and age × alcohol consumption. Interaction terms in the models for cardiovascular deaths were: Age × calendar period, age × smoking and age × area of residence. In the models for cancer deaths the interaction terms were age × area of residence and age × alcohol consumption. Models for respiratory deaths had interaction terms for age × calendar period and age × snus use. § Crude Mortality rate per 1,000 person-years.

641 of them had reported snus use in 1973–74. Table I exhibits characteristics of the study cohort, including crude incidence rates of cancer and death by exposure categories.

Cancer incidence

While smokers exhibited a statistically significant 26% (95% CI 13–40%) excess incidence of cancer overall relative to never-smokers (Table II), no corresponding excess was observed among ever-users of snus relative to never-users (HR 1.00) in a model that included all cohort members and where mutual adjustments were made for smoking and snus use. A similar difference between smoking and snus use was evident in an analogous analysis where the outcome was smoking-related cancers; as expected, smokers had an increased risk (HR 2.2, 95% CI 1.8–2.7), whereas snus use, relative to nonuse of snus, was linked to a trivial and nonsignificant excess (HR 1.1, 95% CI 0.8–1.4). On the other hand, when the outcome was restricted to the combined category of oral and pharyngeal cancer a significant 3.1-fold (95% CI 1.5–6.6) risk elevation was revealed among ever-users of snus relative

to never-users, based on 11 exposed cases. In the analysis of the relationship between smoking and the combined category of oral and pharyngeal cancer, we observed a significant interaction ($p < 0.0015$) between smoking and attained age. We therefore proceeded with age-stratified analyses, which showed a substantial smoking-related excess (HR 5.6, 95% CI 1.6–19.6) confined to ever-smokers who had attained an age of 70 years or more, relative to never-smokers in the same age bracket.

We then restricted our analyses of snus effects to the never-smoker stratum in order to eliminate possible residual confounding from smoking dose. When total cancer incidence was the outcome, no excess incidence emerged among non-smoking ever-users of snus (HR 1.1, 95% CI 0.9–1.4) relative to individuals who had never smoked nor used snus, but a 60% excess of smoking-related cancers (HR 1.6, 95% CI 1.1–2.5) was significant (Table II). We were unable to statistically confirm a risk elevation for the combined category of oral and pharyngeal cancer, but the relative risk estimate was based on no more than 5 exposed cases (HR 2.3, 95% CI 0.7–8.3).

Mortality

We estimated relative risks for death of any cause, cancer death, cardiovascular death and respiratory death. In a model including all cohort members and where mutual adjustments were made for smoking and snus use, smoking was significantly linked to increased risks for all of the studied mortality outcomes (Fig. 2). Also snus use was associated with a statistically significant, albeit small, risk elevation for death of any cause (HR 1.10, 95% CI 1.01–1.21; Fig. 2). A trend toward a snus-associated excess of cardiovascular death of a similar magnitude did not attain statistical significance, while the risk of cancer death was close to that among never-users of snus. There was a significant ($p < 0.025$) interaction between snus use and attained age in the model with respiratory death as the outcome. Consequently, the risk for this outcome was analyzed separately in strata of age below versus equal to or above 80 years. A statistically significant excess risk among snus users, relative to never-users of snus, was noted in the older stratum (HR 1.8, 95% CI 1.2–2.7) but not in the younger.

Analyses of snus effects in strata of never-smokers generally produced relative risk estimates that were higher than those yielded in the models that included all cohort members. HR was statistically elevated 1.23 (95% CI 1.09–1.40) and 2.0 (95% CI 1.2–3.4) for death of any cause among all never-smoking users of snus and for respiratory death among such users who had attained an age of 80 years or more, respectively. Observed hazard ratios of 1.15 and 1.28 for cardiovascular death and cancer death, respectively, remained statistically nonsignificant.

We performed sensitivity analyses with restriction to men aged 25 years or above at entry into the cohort. It is unusual that people take up smoking above this age. The outcomes were (*i*) all cancer, (*ii*) the combined category of oral and pharyngeal cancer, and (*iii*) all-cause mortality, and the analyses were done in the total cohort as well as in the cohort of never smokers at entry. In all of these analyses, the results were essentially identical to those obtained in the exhibited main analyses without age restrictions (data not shown).

Discussion

The results of this population-based cohort study among Swedish men with essentially complete register-based follow-up and an accumulated person-time experience of more than 220,000 years suggest that snus use is not associated with an increased incidence of cancer overall but tentatively with an excess incidence of the combined category of oral and pharyngeal and of total smoking-related cancer. In analyses confined to never-smokers, where confounding from smoking dose is unlikely to occur, we observed relative risks of 2.3 (though based on 5 cases) and 1.6, respectively. In addition, statistically significant excesses were noted with regard to all-cause mortality and mortality due to respiratory diseases, the latter excess being limited to the very oldest.

The excess of the combined category of oral and pharyngeal cancer incidence is at odds with results from all of the more recent case-control[5–7,20] and cohort[8,9] studies of Scandinavian moist snus. However, since individuals who combine smoking with snus use may be exposed to a lower smoking dose and may increase their overall chances of subsequent abstinence compared to those who only smoke,[21] residual negative confounding from total cumulative smoking dose is an important concern. Indeed, while a Swedish case-control study found no significant relation between use of snus and overall risk of head and neck cancer, snus use among never-smokers (where this residual confounding is more likely to have been eliminated) was associated with an increased risk of 4.7 (95% CI 1.6–13.8).[5] In another study with prospective design and adjustment for smoking intensity through multivariate modeling[8] a 20% reduction in risk of lung cancer was noted, again suggesting residual negative confounding. Well in line with these indications are the consistently higher relative risk estimates in our analyses that were confined to the never-smoking stratum. We believe that the effect estimates for snus in these strata are less biased compared to the estimates obtained in analyses involving the total cohort of smokers and non-smokers and in which control for confounding by smoking is attempted through multivariate modeling. With only one exception,[5] previous studies did not have sufficient power to analyze snus effects in strata of never-smokers.

The presence of a range of carcinogens, among which the tobacco-specific nitrosamines (TSNAs) NNN and NNK appear to be the most important ones, is well established in smokeless tobacco.[22] Although TSNA levels in snus on the Swedish market have been greatly reduced since the 1980s,[23] the prerequisites for carcinogenicity are indisputably present. A recent report from the United States[24] provides evidence that users of smokeless tobacco may be exposed to NNK to a similar degree as are smokers. And others have shown that differences in current TSNA levels between American and Swedish moist snuff may not be substantial.[25] Therefore, while disagreeing with previous Scandinavian studies, our results may be biologically plausible but they have to be confirmed in further studies on Swedish moist snus.

Whether or not the observed increased overall mortality and the similarly sized, statistically nonsignificant excess of cardiovascular deaths can be attributed to snus use warrants further studies. Experimental data in both animals[26–28] and humans[29–31] have demonstrated that nicotine and smokeless tobacco, including Swedish moist snus[32,33] raise blood pressure and pulse rate, albeit the results are ambiguous as regards the risk of chronic hypertension. Two Swedish cohort studies indicated an approximately 40% excess risk of death[10] or incidence[34] from cardiovascular disease. Additional Swedish case-control data suggest that the excess of myocardial infarction might be confined to fatal cases,[35,36] in line with animal data showing an increased propensity for cardiac arrhythmias[37] and an increased size of experimentally induced myocardial infarctions after exposure to nicotine.[38,39] Previous epidemiological data on the risk of fatal cardiovascular disease, however, have been inconsistent, and the positive findings did not attain statistical significance.

Our observed excess risk of respiratory deaths, seemingly limited to the very oldest, is consistent with findings in the American Cancer Prevention Study.[40] The mechanisms, including the possibility of confounding, are yet to be established. The effect-modification by attained age might suggest that at least 60 years of exposure is required for the effect. An alternative possibility is that the very oldest were the ones who were most heavily exposed to snus from the distant past. If snus has become successively less detrimental to the general health it is conceivable that late effects might be seen only among octogenarians and older. The manufacturing processes for Swedish snus have changed over the decades and there are data to support that the levels of N-nitrosamines have diminished in the past 25 years.[23]

Strengths of our study include the prospective design with essentially complete follow-up, and the anchorage in the general population.

We restricted our analysis to first cancers only and excluded all potential cohort members who had a cancer documented in the nationwide cancer register, which goes as far back as 1958. A special feature of our study is that all cohort members were screened for oral cancer at time of entry into the cohort. Thus, there were no prevalent oral cancers at time of entry, and the possibility of reversed causation or selection bias vis-à-vis oral cancer is practically excluded.

An important caveat is the fact that the exposure information was collected in 1973–74, up to 29 years prior to the occurrence of studied outcomes. It is possible that the tobacco habits had changed after inclusion into the cohort. In a subcohort comprising 252 men tobacco habits were recorded both at entry (1973–74) and at reexamination in 1993–95.[41–43] Among the 22 who were never users of tobacco in 1973–74 nobody had taken up smoking, but 1 man had taken up daily snus use. Among 56 exclusively ever daily smokers in 1973–74 seven had become daily users of snus exclusively and 28 had stopped using tobacco. None of 60 exclusively snus users in 1973–74 had changed to smoking.

Since smoking is rarely taken up after age 25, the analyses that were restricted to never-smokers should not have been seriously affected by changes in smoking habits. Sensitivity analyses restricted to men who had attained the age of 25 before entry into the cohort, performed both among never-smokers at entry and in the entire cohort, confirmed that the results were practically identical to those obtained when younger men were also allowed in the cohort. If confounding by misclassified smoking due to changed habits during follow up would explain the observed excess risk among our snus users, it must be assumed that smoking exposure increased more among snus users than among nonusers of snus. This is highly unlikely.[44] A recent Swedish study reported a high probability of continuing snus use once the habit has been initiated.[45]

Of further concern is the unavailability of data on a range of conceivable confounding factors. Fortunately, relevant are only factors that are linked to the use of snus and which are not in the causal pathway between snus use and the studied outcomes. This probably rules out covert factors such as cholesterol levels, hypertension, but also even anthropometric measures, infections, and presence of diabetes. We were able to adjust for alcohol consumption. However, confounding by dietary pattern, physical activity and socioeconomic status could have shifted the relative risks in any direction. Although adjustments for area of residence could have reduced possible confounding by socioeconomic status somewhat, the absence of information on these potential confounding factors is an important limitation of our study.

Even though more than 220,000 person-years were under surveillance statistical precision is still a concern. The snus-related relative risks for the combined category of oral and pharyngeal cancer in the entire cohort and in the never-smoking substratum were based on no more than 11 and 5 exposed cases, respectively. This resulted in wide confidence intervals. Moreover, although the outcomes studied were strictly defined *a priori*, the analysis of multiple outcomes in multiple exposure strata may have produced some chance findings.

As 32% of the initially invited individuals chose not to participate, the external validity is somewhat uncertain. It is conceivable that a "healthy participant effect" was in operation so that the participants, on average, were healthier than the general Swedish population. Therefore, effect sizes might differ somewhat from what would have been observed if the entire population had participated. On the other hand, the "healthy participant effect" is likely to have slightly reduced the range of exposure to various lifestyle factors, thereby correspondingly limiting potential confounding from these factors.

In conclusion, our results are inconsistent with claims that the use of Scandinavian moist snus is without demonstrable risk. While relative risks of the studied outcomes are consistently lower than those associated with smoking, and the combined previous Scandinavian literature on snus and oral cancer has not shown any association, the possible snus-related risks are biologically plausible and warrant further exploration. Presently, they should not be categorically dismissed.

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References

1. Cogliano V, Straif K, Baan R, Grosse Y, Secretan B, El Ghissassi F. Smokeless tobacco and tobacco-related nitrosamines. Lancet Oncol 2004;5:708.
2. Foulds J, Kozlowski L. Snus—what should the public-health response be? Lancet 2007;369:1976–8.
3. Gartner CE, Hall WD, Vos T, Bertram MY, Wallace AL, Lim SS. Assessment of Swedish snus for tobacco harm reduction: an epidemiological modelling study. Lancet 2007;369:2010–14.
4. Rodu B, Jansson C. Smokeless tobacco and oral cancer: a review of the risks and determinants. Crit Rev Oral Biol Med 2004;15:252–63.
5. Lewin F, Norell SE, Johansson H, Gustavsson P, Wennerberg J, Biorklund A, Rutqvist LE. Smoking tobacco, oral snuff, and alcohol in the etiology of squamous cell carcinoma of the head and neck: a population-based case-referent study in Sweden. Cancer 1998;82:1367–75.
6. Schildt EB, Eriksson M, Hardell L, Magnuson A. Oral snuff, smoking habits and alcohol consumption in relation to oral cancer in a Swedish case-control study. Int J Cancer 1998;77:341–6.
7. Rosenquist K, Wennerberg J, Schildt EB, Bladstrom A, Hansson BG, Andersson G. Use of Swedish moist snuff, smoking and alcohol consumption in the aetiology of oral and oropharyngeal squamous cell carcinoma. A population-based case-control study in southern Sweden. Acta Otolaryngol 2005;125:991–8.
8. Boffetta P, Aagnes B, Weiderpass E, Andersen A. Smokeless tobacco use and risk of cancer of the pancreas and other organs. Int J Cancer 2005;114:992–5.
9. Luo J, Ye W, Zendehdel K, Adami J, Adami HO, Boffetta P, Nyren O. Oral use of Swedish moist snuff (snus) and risk for cancer of the mouth, lung, and pancreas in male construction workers: a retrospective cohort study. Lancet 2007;369:2015–20.
10. Bolinder G, Alfredsson L, Englund A, de Faire U. Smokeless tobacco use and increased cardiovascular mortality among Swedish construction workers. Am J Public Health 1994;84:399–404.
11. Axell T. A prevalence study of oral mucosal lesions in an adult Swedish population. Odontol Revy 1976;27:1–103.
12. Mattsson B, Wallgren A. Completeness of the Swedish Cancer Register. Non-notified cancer cases recorded on death certificates in 1978. Acta Radiol Oncol 1984;23:305–13.
13. Mattsson B, Rutqvist LE, Wallgren A. Undernotification of diagnosed cancer cases to the Stockholm Cancer Registry. Int J Epidemiol 1985;14:64–9.
14. Johansson LA, Westerling R. Comparing Swedish hospital discharge records with death certificates: implications for mortality statistics. Int J Epidemiol 2000;29:495–502.
15. Total Population Register: Statistics Sweden [Internet] 2005 [cited 2007 June 7]. Available from: www.scb.se.
16. Levitz JS, Bradley TP, Golden AL. Overview of smoking and all cancers. Med Clin North Am 2004;88:1655–75, xiii.
17. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Tobacco smoke and involuntary smoking. IARC Monogr Eval Carcinog Risks Hum 2004;83:1–1438.
18. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals,10.1093/biomet/81.3.515. Biometrika 1994;81:515–26.
19. StataCorp. Stata Statistical Software: Release 9, College Station, TX: StataCorp LP [Internet] 2005 [cited 2007 May 5]. Available from: www.stata.com.
20. Blomqvist G, Hirsch JM, Alberius P Association between development of lower lip cancer and tobacco habits. J Oral Maxillofac Surg 1991;49:1044–7; Discussion 8–9.

21. Gilljam H, Galanti MR. Role of snus (oral moist snuff) in smoking cessation and smoking reduction in Sweden. Addiction 2003;98: 1183–9.
22. WHO. Smokeless tobacco control. Report of a WHO Study Group. World Health Organ Tech Rep Ser 1988;773:1–81.
23. Osterdahl BG, Jansson C, Paccou A. Decreased levels of tobacco-specific N-nitrosamines in moist snuff on the Swedish market. J Agri Food Chem 2004;52:5085–8.
24. Hecht SS, Carmella SG, Murphy SE, Riley WT, Le C, Luo X, Mooney M, Hatsukami DK. Similar exposure to a tobacco-specific carcinogen in smokeless tobacco users and cigarette smokers. Cancer Epidemiol Biomarkers Prev 2007;16:1567–72.
25. Stepanov I, Jensen J, Hatsukami D, Hecht SS. Tobacco-specific nitrosamines in new tobacco products. Nicotine. Tobacco Res 2006;8:309–13.
26. Squires WG, Jr, Brandon TA, Zinkgraf S, Bonds D, Hartung GH, Murray T, Jackson AS, Miller RR. Hemodynamic effects of oral smokeless tobacco in dogs and young adults. Prev Med 1984;13:195–206.
27. Herman EH, Vick JA, Strong JM, Parker RJ, Geyer HM, III, Kramer ED, Higgins KM, Sistare FD. Cardiovascular effects of buccal exposure to dermal nicotine patches in the dog: a comparative evaluation. J Toxicol Clin Toxicol 2001;39:135–42.
28. Huckabee KD, Barnes RT, Williams AG, Jr, Fan WL, Downey HF. Effects of snuff on regional blood flow to the cheek and tongue of anesthetized dogs. Oral Surg Oral Med Oral Pathol 1993;76:729–35.
29. Fant RV, Henningfield JE, Nelson RA, Pickworth WB. Pharmacokinetics and pharmacodynamics of moist snuff in humans. Tobacco Control 1999;8:387–92.
30. Benowitz NL, Porchet H, Sheiner L, Jacob P, III. Nicotine absorption and cardiovascular effects with smokeless tobacco use: comparison with cigarettes and nicotine gum. Clin Pharmacol Ther 1988; 44:23–8.
31. Wolk R, Shamsuzzaman AS, Svatikova A, Huyber CM, Huck C, Narkiewicz K, Somers VK. Hemodynamic and autonomic effects of smokeless tobacco in healthy young men. J Am Coll Cardiol 2005; 45:910–14.
32. Bolinder G, Noren A, Wahren J, De Faire U. Long-term use of smokeless tobacco and physical performance in middle-aged men. Eur J Clin Invest 1997;27:427–33.
33. Hirsch JM, Hedner J, Wernstedt L, Lundberg J, Hedner T. Hemodynamic effects of the use of oral snuff. Clin Pharmacol Ther 1992;52:394–401.
34. Johansson SE, Sundquist K, Qvist J, Sundquist J. Smokeless tobacco and coronary heart disease: a 12-year follow-up study. Eur J Cardiovasc Prev Rehabil 2005;12:387–92.
35. Huhtasaari F, Lundberg V, Eliasson M, Janlert U, Asplund K. 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.
36. Hergens MP, Ahlbom A, Andersson T, Pershagen G. Swedish moist snuff and myocardial infarction among men. Epidemiology 2005; 16:12–16.
37. Mehta MC, Jain AC, Mehta A, Billie M. Cardiac arrhythmias following intravenous nicotine: experimental study in dogs. J Cardiovasc Pharmacol Ther 1997;2:291–8.
38. Villarreal FJ, Hong D, Omens J. Nicotine-modified postinfarction left ventricular remodeling. Am J Physiol 1999;276:H1103–H1106.
39. Sridharan MR, Flowers NC, Hand RC, Hand JW, Horan LG. Effect of various regimens of chronic and acute nicotine exposure on myocardial infarct size in the dog. Am J Cardiol 1985;55:1407–11.
40. Henley SJ, Thun MJ, Connell C, Calle EE. Two large prospective studies of mortality among men who use snuff or chewing tobacco (United States). Cancer Causes Control 2005;16:347–58.
41. Roosaar A, Johansson AL, Sandborgh-Englund G, Nyren O, Axell T. A long-term follow-up study on the natural course of snus-induced lesions among Swedish snus users. Int J Cancer 2006;119:392–7.
42. Roosaar A, Yin L, Johansson AL, Sandborgh-Englund G, Nyren O, Axell T. A long-term follow-up study on the natural course of oral leukoplakia in a Swedish population-based sample. J Oral Pathol Med 2007;36:78–82.
43. Roosaar A, Yin L, Sandborgh-Englund G, Nyren O, Axell T. On the natural course of oral lichen lesions in a Swedish population-based sample. J Oral Pathol Med 2006;35:257–61.
44. Rodu B, Stegmayr B, Nasic S, Cole P, Asplund K. Evolving patterns of tobacco use in northern Sweden. J Intern Med 2003;253: 660–5.
45. Furberg H, Lichtenstein P, Pedersen NL, Bulik C, Sullivan PF. Cigarettes and oral snuff use in Sweden: prevalence and transitions. Addiction. 2006;101:1509–15.