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

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Summary

Background **Although classified as carcinogenic, snuff is used increasingly in several populations. Scandinavian moist snuff (snus) has been proposed as a less harmful alternative to smoking, but precise data on the independent associations of snus use with site-specific cancers are sparse. We aimed to assess the risks for cancer of the oral cavity, lung, and pancreas.**

Methods **Detailed information about tobacco smoking and snus use was obtained from 279 897 male Swedish construction workers in 1978–92. Complete follow-up until end of 2004 was accomplished through links with population and health registers. To distinguish possible effects of snus from those of smoking, we focused on 125 576 workers who were reported to be never-smokers at entry. Adjusted relative risks were derived from Cox proportional hazards regression models.**

Findings **60 cases of oral, 154 of lung, and 83 of pancreatic cancer were recorded in never-smokers. Snus use was independently associated with increased risk of pancreatic cancer (relative risk for ever-users of snus 2·0; 95% CI 1·2–3·3, compared with never-users of any tobacco), but was unrelated to incidence of oral (0·8, 95% CI 0·4–1·7) and lung cancer (0·8, 0·5–1·3).**

Interpretation **Use of Swedish snus should be added to the list of tentative risk factors for pancreatic cancer. We were unable to confirm any excess of oral or lung cancer in snus users.**

Lancet 2007; 369: 2015–20

Published Online May 10, 2007
DOI:10.1016/S0140-6736(07)60678-3

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Introduction

Use of snuff has become increasingly popular in several countries, but Sweden has the highest consumption, predominantly in the form of moist snuff (snus). The habit is especially gaining popularity in adolescents and women.[1] At present, however, the majority of users are men; at least 23% of Swedish men used snus in 2002.[2]

About 30 carcinogens have been identified in smokeless tobacco, and the tobacco-specific nitrosamines, formed from nicotine and related tobacco alkaloids, are thought to be particularly important.[3] The tobacco-specific nitrosamines with the greatest proportions in snuff (4-(nitrosomethylamino)-1-(3-pyridyl)-1-butanone [NNK] and N´-nitrosonornicotine [NNN]), have been implicated in the cause of tobacco-related cancers.[4–6] Comparative studies have generally shown lower concentrations of tobacco-specific nitrosamines in Swedish snus than in American snuff,[7] leading to a perception that the use of Swedish snus is a suitable alternative to smoking. Indeed, with a few exceptions,[8–10] studies of Scandinavian snus have shown no risk associated with use of this form of tobacco.[7] The Scandinavian experience differs from that in South Asia[11] and elsewhere,[12,13] where smokeless tobacco is an established risk factor for oral cancer. This inconsistency might be attributable to methodological aspects, such as inadequate control for confounding by cigarette smoking and alcohol use, which are strong risk factors for oral cancer.

Because of NNK's specificity for the lung in rodent cancer models,[14,15] lung cancer should be another concern in relation to smokeless tobacco. However, few studies have addressed this risk in human beings. The only study of Scandinavian snus and lung cancer showed a non-significantly decreased risk in snus users,[10] raising questions about residual confounding due to smoking. Epidemiological evidence[10,16–18] suggests that the use of smokeless tobacco, including Scandinavian snus,[10] might increase the risk of pancreatic cancer, but published data are based on few snus-exposed cases.

With a growing awareness of the health hazards associated with smoking, snus could become increasingly popular,[19,20] and the habit might spread to people who would otherwise refrain from tobacco use. Therefore, valid and precise epidemiological data on health risks associated with use of snus are urgently needed. We consequently did a prospective study in Swedish construction workers, with a high prevalence of exposure to snus, to address the association of snus use with oral, lung, and pancreatic cancer.

Methods

Setting and participants

The background of the Swedish construction worker cohort has been described previously.[21] Briefly, from 1969 through 1992, preventive health check-ups were offered to all workers in the Swedish building industry, and from 1971, the collected data were compiled in a computerised central

register. Each record also contained the participant's National Registration Number, a unique personal identifier assigned to every Swedish resident at birth or immigration. This identifier includes the date of birth.

Because of ambiguities in the coding of smoking status in the questionnaires used during 1971–75 (Zendehdel K, et al, unpublished), we restricted our analysis to workers with at least one visit in the 1978–92 period, when information on smoking and snus use was obtained through personal interviews by nurses. Because the group contained few women, we limited our analyses to men. Links with nationwide registers of the total population, emigration, and death enabled us to exclude records with incorrect National Registration Numbers (which could not be found in any of these registers), and men with a death or emigration date before entry. Links with the Swedish Cancer Register led to exclusion of men with cancer before entry. We also excluded men with incomplete tobacco exposure data.

Procedures

We only used exposure information obtained at the first visit, which defined entry into the cohort: snus user status (never, previous, or current), grams of snus per day (<10 g or ≥10 g), smoking status (never, previous, or current), grams of smoking tobacco per day (continuous), and body-mass index (BMI; <25, 25–29, or ≥30). The quality of exposure data has been reviewed previously and was deemed satisfactory.[21]

Follow-up was done through linking of records to the nationwide, and essentially complete, population and health registers previously mentioned. For correct censoring, dates of death were obtained from the Causes of Death register, and dates of emigration came from the Register of Domestic and International Relocations. The Cancer Register, established in 1958, codes malignant neoplasms according to the International Classification of Diseases, 7th edition, and includes information on more than 98% of all diagnosed cases in Sweden.[22,23] We used codes 140, 141, 143, and 144 for incident cases of oral cancer (not including cancers of the salivary glands, pharynx, or larynx), code 162 for lung cancer, and code 157 for pancreatic cancer. Each cohort member contributed person-time from the date of entry until the date of any first cancer diagnosis, migration, death, or December 31, 2004, whichever occurred first.

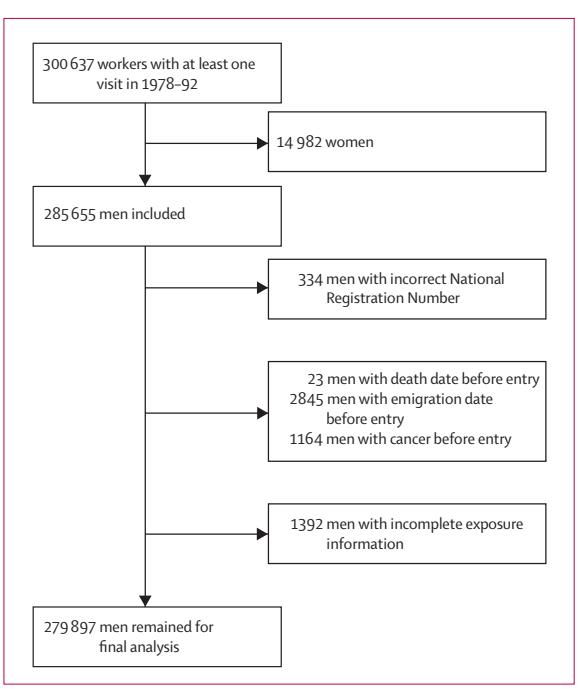

Figure: **Summary of inclusion and exclusion criteria and final cohort used for analysis**

Statistical analysis

All three cancers are highly age dependent. Therefore, we investigated age distributions in each exposure category. The associations between exposure variables and risk of cancer were expressed as relative risks (RRs) derived from Cox proportional hazards regression models, with attained age (continuous) as time scale. Initially, we fitted models in which the relative risks associated with smoking were adjusted for snus use, and in which relative risks linked to snus use were adjusted for smoking. To better control the strong confounding effect of smoking in our analyses of snus, we fitted models restricted to never-smokers. We adjusted for BMI in all our models. However, since BMI could conceivably be in the causal pathway, we also did analyses unadjusted for this factor. Tests for linear trend were done by creating a continuous variable from the median of the categories.

The assumption of proportional hazards was tested on the basis of the cumulative sums of Martingale residuals with the Kolmogorov-type supremum test,[24] in which 1000 realisations were used. Results indicated that the proportional assumption was satisfied for all models.

Role of the funding source

The funding source had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the paper for publication.

Results

The figure shows the numbers of eligible workers included in and excluded from the group for our analysis. Characteristics of the 279 897 men in our cohort, including smoking and snus use, are shown in table 1. Average age at entry was 35 years (SD 13). These men were followed-up for an average of 20 years (SD 6). At time of entry, 31% of the cohort members used or had previously used snus. The proportion of ever-smokers was greater for men older than 30 years than in younger

	Number	Person-years accumulated	Users of snus		Users of snus only		Smokers	
			Ever	Current	Ever	Current	Ever	Current
<30 years	122 820 (44%)	2 410 637	45 710 (37%)	41 501 (34%)	28 689 (23%)	27 122 (22%)	47 209 (38%)	37 066 (30%)
30–39 years	69 216 (25%)	1 492 628	21 194 (31%)	16 139 (23%)	5 505 (8%)	4 648 (7%)	46 538 (67%)	30 719 (44%)
40–49 years	45 065 (16%)	927 998	10 530 (23%)	7 700 (17%)	2 021 (4%)	1 711 (4%)	30 879 (69%)	18 990 (42%)
50–59 years	32 455 (12%)	612 408	6 262 (19%)	4 569 (14%)	1 043 (3%)	911 (3%)	22 593 (70%)	12 913 (40%)
≥60 years	10 341 (4%)	167 405	2 177 (21%)	1 601 (15%)	497 (5%)	426 (4%)	7 102 (69%)	3 621 (35%)
Total	279 897 (100%)	5 611 075	85 873 (31%)	71 510 (26%)	37 755 (13%)	34 818 (12%)	154 321 (55%)	103 309 (37%)

Table 1: **Baseline characteristics by age at entry**

	Number	Person-years	Oral cancer			Lung cancer			Pancreatic cancer		
			Cases	IR	RR (95% CI)	Cases	IR	RR (95% CI)	Cases	IR	RR (95% CI)
Never-users of any tobacco	87 821	1 751 072	50	3·1	1·0 (ref)	136	8·6	1·0 (ref)	63	3·9	1·0 (ref)
Ever-smokers	154 321	3 153 168	198	5·3	2·0 (1·4–2·7)	2062	54·7	7·2 (6·0–8·5)	385	10·2	2·8 (2·1–3·7)
Ex-smokers	51 012	1 069 923	48	3·1	1·1 (0·8–1·7)	329	19·8	2·6 (2·2–3·2)	105	6·3	1·8 (1·3–2·4)
Current smokers	103 309	2 083 245	150	6·9	2·5 (1·7–3·5)	1733	82·3	10·2 (8·6–12·2)	280	13·0	3·5 (2·6–4·6)

Combined use of snus and smoking tobacco was allowed in these analyses, but 37 755 men who used snus only were excluded. IR=incidence rate per 100 000 person years, standardised to age distribution of person-years experienced by all workers using 5-year age categories. *RR estimates obtained in models adjusted for attained age as time scale, BMI, and snus use.

Table 2: **Relative risks of oral, lung, and pancreatic cancer in relation to tobacco smoking status at entry**

men, whereas snus use was more common in those younger than 30 years, reflecting the spreading habit in the Swedish male population.

258 incident cancers of the oral cavity, 2216 of the lung, and 468 of the pancreas were recorded during follow-up. Of these, 60 oral, 154 lung, and 83 pancreatic cancers occurred in the 125 576 never-smokers.

We confirmed that tobacco smoking was a strong risk factor for all the studied cancers (table 2). The Cox regression models, which also included men who used snus simultaneously, were adjusted for attained age, BMI, and snus use. Removal of BMI from the models had little effect on the results (data not shown).

In analyses that included all cohort members, irrespective of smoking and snus user status, the adjusted relative risks for cancer in ever-users of snus, compared with never-users, were 0·7 (95% CI 0·5–0·9) for oral, 0·7 (0·6–0·7) for lung, and 0·9 (0·7–1·2) for pancreatic cancer. In analyses restricted to men who were never-smokers, ever-use of snus was associated with a significant increase of the risk for pancreatic cancer, compared with the risk in never-users of any tobacco (table 3). We also noted a significant dose-risk trend for pancreatic cancer with increasing amount of snus use (p=0·01). However, the point estimates for the two dose categories above zero (1–9 g and ≥10 g snus per day) did not differ greatly from each other. We did not observe an increased risk of oral cancer or lung cancer in men who used snus but did not smoke. Repeated analyses without adjustments for BMI produced similar results (data not shown).

Discussion

The main finding of this large cohort study was an increased risk of pancreatic cancer in never-smoking snus users compared with never-users of any tobacco, with some evidence for a dose-risk association. We did not detect any excess risk for cancer of the oral cavity or lung.

Our finding is at odds with the perception that use of Swedish moist snus has no demonstrable carcinogenic risk.[7] If valid, it will have important public-health implications, since snus has been proposed as a way to reduce harm in nicotine addicts.[19,20] The increase in risk is, however, in line with that reported in a cohort study from Norway[10]—the only published Scandinavian study on the association between use of smokeless tobacco and risk of pancreatic cancer. In that study, a significant 70% excess incidence was noted in ever-users relative to never-users of smokeless tobacco, after adjustment for smoking and alcohol use.[10,25] Some of the tobacco consumption was in the form of local chewing tobacco (skrå). In our cohort, the participants reported specifically about snus use, and use of other smokeless tobacco products was probably negligible. Results of several American studies of smokeless tobacco support our findings[16–18] although some do not.[26,27]

The excess risk was noticeable only in an analysis restricted to the never-smoking stratum. This analysis was defined a priori to eliminate residual confounding by smoking dose. Previous evidence, reinforced by observed data in the present study (not shown), suggests that individuals who combine smoking with snus use smoke

	Number	Person-years	Oral cancer			Lung cancer			Pancreatic cancer		
			Cases	IR	RR (95% CI)†	Cases	IR	RR (95% CI)	Cases	IR	RR (95% CI)
Tobacco use											
Never-users of any tobacco	87 821	1 751 072	50	3·1	1 (ref)	136	8·6	1 (ref)	63	3·9	1 (ref)
Ever-users of snus	37 755	698 542	10	2·6	0·8 (0·4–1·7)	18	6·4	0·8 (0·5–1·3)	20	8·5	2·0 (1·2–3·3)
Ex-users	2937	50 469	1	1·9	0·7 (0·1–5·0)	3	8·5	0·9 (0·3–3·0)	2	6·6	1·4 (0·4–5·9)
Current users	34 818	648 074	9	2·7	0·9 (0·4–1·8)	15	6·0	0·8 (0·4–1·3)	18	8·8	2·1 (1·2–3·6)
Snus consumed*											
1–9 g/day	6704	134 390	2	1·9	0·7 (0·2–2·8)	7	8·6	1·0 (0·5–2·1)	6	7·6	1·9 (0·8–4·3)
≥10 g/day	30 683	564 152	8	3·1	0·9 (0·4–2·0)	10	4·8	0·7 (0·4–1·3)	13	8·5	2·1 (1·1–3·8)
p for trend					0·8			0·2			0·01

Exposure status was that noted at entry. RR estimates obtained in models adjusted for attained age as time scale and BMI. IR=incidence rate per 100 000 person-years, standardised to age distribution of person-years experienced by all workers using 5-year age categories. *Analysis excluded 368 snus users without dose information, therefore totals for number of cases in dose-specific categories do not match exactly with corresponding totals of cases in ever-users.

Table 3: **Relative risks of oral, lung, and pancreatic cancer in relation to snus use in 125 576 never-smokers**

less and might increase their overall chances of subsequent abstinence, compared with those who only smoke.[28] Indeed, although findings of a Swedish case-control study[8] showed no significant relation between use of snus and overall risk of head and neck cancer in multivariate-adjusted analyses, snus use among never-smokers was associated with an almost five-times increased risk. In the Norwegian cohort study mentioned previously[10] a 20% reduction in risk of lung cancer was noted in multivariate-adjusted analyses, again suggesting residual negative confounding. The shift from a similar inverse association with lung cancer in our multivariate-adjusted analysis to a null result in the analysis restricted to never-smokers is in good agreement with the Norwegian data and provides further support for the concern about confounding. Hence, we believe that the estimate for snus in never-smokers is less biased than an estimate obtained in an overall analysis that also includes smokers and in which control for confounding by smoking is attempted through multivariate modelling. The absence of association with lung cancer in this stratum, in effect, confirms the absence of important confounding by smoking.

Efficient adjustment for smoking dose in snus-using smokers is expected to nullify any positive consequences of snus use conferred through its purported anti-smoking effects. The significant risk reductions for all three studied cancers among snus users noted in our conventional models that included the entire group, despite our attempts to adjust for smoking dose, suggest that the net effect of snus use in the studied population might be a reduced risk of cancer.

The apparent specificity for the pancreas as the target organ is biologically plausible. First, the carcinogenicity of tobacco-specific nitrosamines is remarkably organ-specific in animal experiments.[6] Although the lung and upper respiratory tract dominate as target organs, rats develop pancreatic adenocarcinoma when exposed to NNK or its metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) in drinking water.[14] Second, measurable amounts of NNK and NNAL have been documented in human pancreatic juice, in the case of NNK at significantly higher concentrations in smokers than in non-smokers.[29] Third, it is well established that NNK metabolites bind to DNA and induce activating point mutations in the RAS gene—mutations that are observed in 50–90% of all pancreatic adenocarcinomas.[30] Fourth, NNK acts as an agonist on β-adrenergic receptors, which activate signal transduction pathways that induce the formation of arachidonic acid and its mitogenic metabolites.[30] Fifth, Swedish data suggest a causal link between snus use and risk of type 2 diabetes,[31] and increasing evidence implicates insulin resistance and abnormal glucose metabolism as risk factors for development of pancreatic cancer.[32]

The absence of an increased risk for oral cancer in snus users confirms the negative results of published work on this particular type of smokeless tobacco.[8,10,33,34] However, residual negative confounding from smoking dose cannot be confidently excluded in these studies, as discussed above. An International Agency for Research on Cancer working party recently concluded, mainly on the basis of American and Asian data, that sufficient evidence exists that smokeless tobacco causes oral cancer in human beings.[13] With only ten cases among ever-users of snus in the never-smoker stratum, oral cancer was the least common cancer of the three studied in our analysis, making the estimates liable to chance variations.

In accord with our findings, previous epidemiological evidence on smokeless tobacco and lung cancer in developed countries has been essentially negative,[10,26,35] with few exceptions,[36] despite the strong link between exposure to tobacco-specific nitrosamines and formation of lung tumours in rodents.[6] The reasons for the discrepancy between animal and human data remain to be clarified; in our study, confounding from smoking dose is an unlikely explanation.

Our study has several strengths but also some limitations. An important strength is the cohort design, which essentially precludes the possibility that the cancer outcome could have affected the initial reports about, or the actual use of, the tobacco products of interest. One disadvantage of this design is that individuals' tobacco-use habits might have changed during follow-up. The repeat visits during follow-up varied in number and timing, and therefore were sensitive to self-selection bias. However, we used the smoking information recorded at these visits to investigate whether workers who were initially classified as never-smoking snus users might differ from those who were classified as never-users of any tobacco. We found that 2132 of 17 634 (12%) of never-smoking snus users were later recorded at some point in time as former or current smokers. The corresponding proportion in never-users of any tobacco was 2824 of 39 469 (7%). We used these data and the effect sizes derived from tables 2 and 3 in a sensitivity analysis according to Schneeweiss.[37] The suggested misclassification of smoking status affected our reported estimates no more than trivially (data not shown). In accord with a recent Swedish study that reported a high probability of continuing snus use once the habit has been initiated,[38] our data from the repeat visits suggested that dose of snus remained stable over time (data not shown).

Another strength is the completeness of follow-up. Furthermore, the large cohort size and the high prevalence of exposure to snus made it possible to obtain meaningful estimates in never-smokers. However, the statistical precision is still a weak point; the estimates for the three types of cancer in never-smoking ever-users of snus were based on few cases, with considerable risk for type 2 error in analyses for oral and lung cancer.

The scarcity of information about covariates in our database needs careful consideration. The restriction to male construction workers allays concerns about confounding by sex, socioeconomic status, and occupational exposures. Furthermore, it is hard to imagine any negative confounding that would have hidden a true association of snus with risk for oral and lung cancer. In the case of pancreatic cancer, we were unable to identify any established or suspected risk factor[39] other than smoking that might be linked to snus use, although confounding by dietary factors is a possibility. Another, more speculative, confounding factor could be passive smoking, but such an effect seems unlikely in view of the strength of the association and the absence of an increased risk for lung cancer.

At present, our results can be confidently generalised only to Swedish male construction workers. Although our relative risk estimates—if unbiased and unconfounded—might reflect a biological relation that can be generalised to other populations, measures that depend on the underlying baseline risk and exposure prevalence rates (eg, risk difference, numbers needed to harm, population attributable risk percentage, etc) could differ substantially between population groups. These measures are typically the ones that are most important for public-health consequences.

We conclude that our findings are probably internally valid. Although we have some reservations about statistical power, the oral use of snus does not seem to be linked to the risk for cancer of the oral cavity or lung, in agreement with some but contrary to other previous work on oral cancer. However, the habit seems, with slightly greater certainty, to be associated with an increased risk of pancreatic cancer. The overall consistency of combined available evidence suggests that the association with pancreatic cancer is real, but perhaps weaker than that noted for smoking. Therefore, oral use of snus should be added to the list of tentative risk factors for pancreatic cancer. The Swedish snus investigated in this cohort, despite its low concentrations of tobacco-specific nitrosamines in comparison with many other smokeless tobacco products, might not be an entirely safe product. Because of the special characteristics of the cohort, additional studies in populations with other patterns of use, not the least in women, are desirable—albeit difficult to accomplish, in view of the sample sizes needed—to put the implications for public health in perspective.

Contributors

JL participated in the conception and design of the study, analysis of the data, and drafting the manuscript. WY participated in the conception and design of the study and in the interpretation of results. KZ assisted with data analysis. JA coordinated the data collection. HOA and PB provided scientific suggestions. ON was the lead author in the overall conceptualisation and design of the study, and provided overall supervision for the article. Raw data were reviewed by JL, WY, and ON. All authors took part in reviewing and editing the entire manuscript, and approved the final version of the manuscript.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

This study was partly funded by a grant from the Swedish Cancer Society (4409-B00-01XAC).

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