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A long-term follow-up study on the natural course of snus-induced lesions among Swedish snus users

Ann Roosaar[1,2]*, Anna L.V. Johansson[2], Gonilla Sandborgh-Englund[1], Olof Nyrén[2] and Tony Axéll[3]

[1]*Institute of Odontology, Karolinska Institutet, Stockholm, Sweden*
[2]*Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden*
[3]*Maxillofacial Unit, Halmstad Hospital, Halmstad, Sweden*

Snus-induced lesions (SILs) are mucosal changes that are regularly seen in users of moist snuff (snus). Their role in oral carcinogenesis remains undefined. Our aim was to assess the natural course of SILs over several decades. A cohort of 1,115 individuals with SILs, confirmed in 1973–1974 during a population-based survey was followed for 27–29 years through multiple record linkages with virtually complete population- and health registers. A sample (n = 267) of the cohort members were invited for reexamination after 19–22 years. Register-based follow-up through January 2002 revealed a total of 3 incident cases of oral cancer (standardized incidence ratio of 2.3, 95% CI 0.5–6.7), none of which occurred at the site of the original SIL. There was a strong association noted between the degree of SIL and current snus consumption. The SILs had disappeared in all 62 individuals who had permanently quitted using snus. In no case did we observe an important clinical change for the worse among individuals who had decreased their use or continued unabatedly. While the incidence of oral cancer in this cohort of individuals with SILs tended to be higher than expected, we conclude that cancers rarely occur at the site of lesions observed in the distant past.

Key words: epidemiology; oral cancer; oral mucosa; smokeless tobacco

Possible health consequences of smokeless tobacco use, especially cancer development in the oral cavity, have remained a longstanding issue of debate. Although the epidemiological literature on smokeless tobacco use and oral cancer risk lacks consistency, an American case–control study found evidence of a markedly increased incidence of oral cancer at sites presumed to be particularly exposed among dry snuff-using white women.[1] Snus—moist snuff that is typically placed as a quid inside the lips—is commonly used in Scandinavia; current prevalence among Swedish men is 22%.[2] In the US, moist snuff is the only smokeless tobacco product that shows increasing sales.[3] Habitual users of snus almost invariably develop typical lesions (snus-induced lesions - SILs) in the mucosa corresponding to the location of the quid.[4] These lesions have been shown to be reversible after cessation of the snus habit,[5] but some users exhibit histological features similar to dysplasia. The true nature of these changes is uncertain; some investigators consider them to be reactions due to irritation,[6,7] but there are no long-term follow-up data available.

Our aim, therefore, was to study the natural course of snus-induced lesions in a historic cohort established in 1973–1974, and followed up for 27–29 years with population register data and with a reexamination after 19–22 years.

Methods

During 1973–1974, a population-based prevalence study of oral mucosal lesions was carried out in Uppsala County in central Sweden.[8,9] All persons aged 15 years or older in 2 geographically well-defined areas, including a small town (Enköping) and a municipality (Bålsta), were invited to an examination of the oral cavity. Of 30,118 eligible individuals, 20,333 were examined and interviewed. Special efforts were made to document the validity and reliability of the findings primarily by means of repeated clinical examinations performed by the same operator.

The present follow-up study was restricted to a subset of the original 20,333 study participants, namely those coming from Bålsta, Enköping and 15 rural parishes surrounding Enköping and Bålsta. The total number of individuals initially examined in the selected areas was 16,144 (7,890 men and 8,254 women). At the initial examination in 1973–1974, SILs were recorded in 1,115 of the male participants. These men formed our study cohort in the present investigation. We restricted the study to men, since only 4 women had snus-induced lesions.

The study cohort was followed-up until January 31, 2002. Via the cohort members' National Registration Numbers—unique personal identifiers—we were able to link information from several nation-wide and essentially complete registers to the individuals. These registers were as follows: SPAR (a population register of addresses), the Causes of Death Register, the Migration Register and the Cancer Register. This enabled us to study occurrence of cancer in the study cohort up to January 31, 2002.

Furthermore, in 1993, a sample was drawn among cohort members who had not died or moved out of the selected areas for a face-to-face interview and clinical reexamination, performed by one investigator (AR) at local dental clinics. The interviews and reexaminations were performed during 1993–1995. Because of limited resources, not all of the 1,115 individuals were invited for reexamination, but only a sample. The sampling procedure differed between Enköping, Bålsta and the surrounding parishes. In Enköping and the 15 rural parishes, the selection was restricted to a few zip code areas chosen to preserve the sociodemographic distribution of the source population. In these zip code areas, all individuals were invited for reexamination. In Bålsta, the entire study cohort was selected and invited for reexamination. As the selection of subjects was unrelated to individual characteristics, and thus to outcome probability, it was deemed equivalent to random sampling, but it simplified the practical arrangements around the reexaminations. If a participant failed to attend the first appointment, at least 1 new appointment was offered. The participants were typically examined 4–8 weeks after the invitation. Standardized questions were asked about type(s) of tobacco used (smoking/snus) currently and in the past, number of cigarettes per day, amount of pipe tobacco expressed as grams/day, number of hours per day with the snus quid in place, type of snus (loose or portion-bag packs), brands and amount of snus expressed as grams/day. The questions about tobacco habits were identical to those used in 1973–1974,[9] with one exception: questions about the use of portion-bag pack snus had been added since this way of administration was first introduced after 1974. The reliability of tobacco consumption data in the 1973–1974 survey, assessed by means of a

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***Correspondence to:** Karolinska Institute, Institute of Odontology, Box 4064, S-141 04 Huddinge, Sweden. Fax: +46-8-746-76-88.
E-mail: ann.roosaar@ki.se
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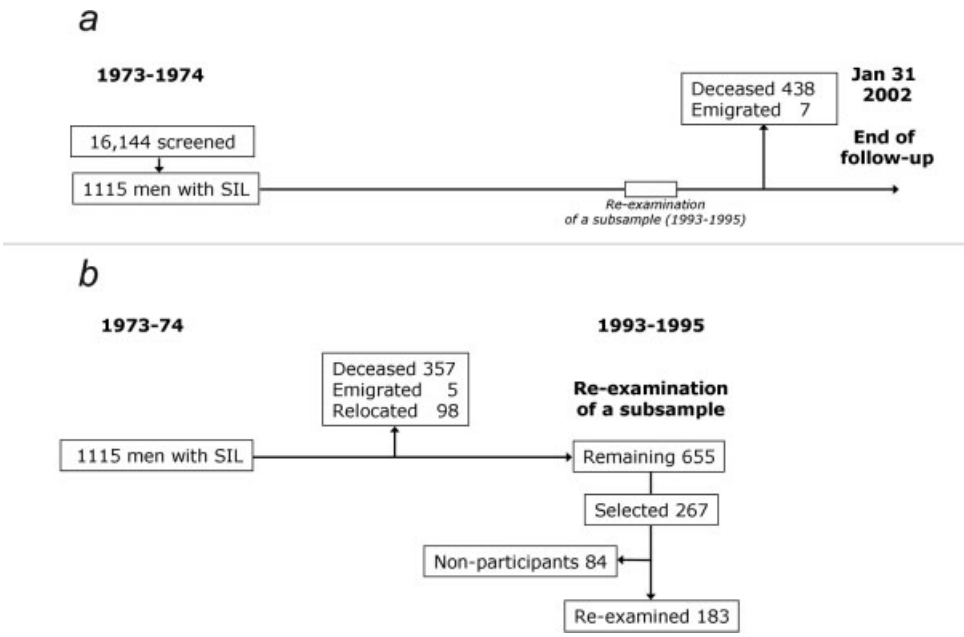

FIGURE 1 – (*a*) Overview of the follow-up study and (*b*) Selection of cohort members for reexamination in 1993–1995.

repeat interview after 2 weeks in 278 individuals, was found to be good, with a κ value[10] of 0.64, (95% CI 0.46–0.82).[11]

Clinical examination

Criteria for SILs were the same at follow-up in 1993–1995 as used in 1973–1974.[9]

Degree 1. A superficial lesion with a color similar to the surrounding mucosa and with slight wrinkling. No obvious mucosal thickening.
Degree 2. A superficial, whitish or yellowish lesion with wrinkling. No obvious thickening.
Degree 3. A whitish-yellowish to brown, wrinkled lesion with intervening furrows of normal mucosal colors, obvious thickening.
Degree 4. A marked yellowish to brown and heavily wrinkled lesion with intervening deep reddened furrows and/or heavy thickening.

Before the 1993–1995 fieldwork, the original examiner (TA) and the examiner at follow-up (AR) calibrated their diagnostic criteria. After having jointly reviewed a large number of clinical photos and assessed the presence or absence of SILs and the clinical degree of lesions found, the 2 investigators compared their independent assessments of a new set of photos. Inter- and intraexaminer agreement beyond chance was determined using κ statistics.[10] The interexaminer agreement was substantial with a κ value of 0.71; 95% CI 0.46–0.96 (weighted κ 0.81; 95% CI 0.63–0.98) and AR's intraexaminer agreement was 0.78; 95% CI 0.56–1.00 (weighted κ 0.85; 95% CI 0.69–1.00).

The reexaminations took place with the individual in a dental chair. The examiner knew that the participants had SILs in 1973–1974 but was unaware of the degree and exact site. The oral inspection was performed with the aid of 2 dental mirrors and with illumination provided by a dental halogen lamp. No biopsies were taken.

The ethics committee of the Medical Faculty, Uppsala University, approved the study. Informed consent was obtained from all participants.

Statistical methods

In the register-based follow-up for cancer analyses, we only considered first cancers and disregarded malignancies detected incidentally at autopsy. After having confirmed the validity of the National Registration Numbers through linkage with the registers for population, death and migration, person-time was calculated from the date of first examination until the date of death, occurrence of any cancer, emigration or end of follow-up (January 31, 2002), whichever occurred first. The standardized incidence ratio (SIR), the ratio of the observed to the expected number of cancers, was used to estimate relative risk for oral cancer (WHO ICD7 codes 141: tongue; 143: floor of the mouth; 144: other parts of oral cavity). The expected number of oral cancers was calculated by multiplying the observed person-time in gender-, 5 year age-, and calendar-year strata by cancer incidence rates in the corresponding strata, based on observed rates in the entire Swedish population. Confidence intervals (CI) of SIRs were calculated with the assumption that the observed number of events followed a Poisson distribution.[12]

In the analysis of the reexamined participants in 1993–1995, Fisher's exact test was used to test independence between degree of lesion found at reexamination and the exposures snus use in hours per day and gram per day. Age, smoking and alcohol user status were also tested for independence of degree of lesion. The missing value category was not included in the tests.[10]

Results

The 1,115 cohort members with SILs were followed for a total of 24,591 person years up to January 31, 2002. (Fig. 1*a*). Data from the Causes of Death Register revealed that 438 individuals had died during follow-up. The causes of death were as follows: cancer, 89 (20%); cardiovascular diseases, 199 (54%); respiratory diseases, 34 (8%); accidents, 21 (5%) and other causes, 58 (13%). Data from the Cancer Register revealed that a total of 3 incident oral cancer cases had occurred during follow-up, corresponding to a SIR of 2.3 (95% CI 0.5–6.7). Among the 3 individuals, 2 of them were concomitant daily smokers. Only 1 individual with oral cancer had succumbed to this cancer. Case record review revealed that none of the tumors (2 cancers of the tongue, 1 in the maxillary aspect of the gum, contra lateral to the initial lesion) occurred at the site of the SIL recorded in 1973–1974. These lesions were of degree II in 2 cases and degree III in 1 case.

At the time of the invitation to reexamination in 1993–1995, censoring due to death and emigration had occurred in 357 and 5

TABLE I – DESCRIPTION OF STUDY COHORT AND SUBGROUPS

	Total cohort n = 1,115 n (%)	Relocated/ emigrated n = 103 n (%)	Deceased 1993–1995 n = 357 n (%)	Nonparticipants 1993–1995 n = 84 n (%)	Reexamined n = 183 n (%)
Age at entry					
15–24	190 (17)	24 (23)	2 (1)	20 (24)	45 (25)
25–34	286 (26)	50 (48)	5 (2)	28 (33)	68 (37)
35–44	143 (13)	15 (15)	15 (4)	8 (10)	37 (20)
45–54	114 (10)	9 (9)	36 (10)	13 (15)	16 (9)
55–64	172 (15)	4 (4)	103 (29)	10 (12)	16 (9)
65–74	129 (12)	1 (1)	115 (32)	5 (6)	1 (1)
75–84	62 (6)	0 (0)	62 (17)	0 (0)	0 (0)
≥85	19 (2)	0 (0)	19 (5)	0 (0)	0 (0)
Smoking habit					
Never daily	515 (46)	41 (40)	220 (62)	34 (40)	60 (33)
Previous daily	165 (15)	17 (17)	24 (7)	13 (15)	40 (22)
Current daily	434 (39)	45 (44)	112 (31)	37 (44)	83 (45)
Missing	1 (0)	0 (0)	1 (0)	0 (0)	0 (0)
Residence					
Rural	250 (22)	14 (14)	97 (27)	23 (27)	45 (25)
Small municipality	202 (18)	29 (28)	53 (15)	30 (36)	84 (46)
Small town	663 (59)	60 (58)	207 (58)	31 (37)	54 (29)
Snus hours/day[1]					
0	85 (8)	10 (10)	35 (10)	7 (8)	10 (5)
1–6	666 (60)	60 (58)	176 (49)	49 (58)	115 (63)
7–15	288 (26)	28 (27)	120 (34)	20 (24)	46 (25)
16–24	31 (3)	2 (2)	16 (4)	3 (4)	2 (1)
Missing	45 (4)	3 (3)	10 (3)	5 (6)	10 (5)
Degree of lesion[2]					
1	166 (15)	19 (18)	38 (11)	14 (17)	34 (19)
2	319 (28)	27 (26)	102 (29)	27 (32)	50 (27)
3	555 (50)	49 (48)	188 (53)	36 (43)	94 (51)
4	67 (6)	6 (6)	28 (8)	6 (7)	3 (2)
Missing[3]	8 (1)	2 (2)	1 (0)	1 (1)	2 (1)
Alcohol use[4]					
Low	155 (14)	10 (10)	68 (19)	14 (17)	16 (9)
Moderate	771 (69)	80 (78)	208 (58)	59 (70)	130 (71)
High	189 (17)	13 (12)	81 (23)	11 (13)	37 (20)

[1]Number of hours with snus in the mouth per day.–[2]Grading according to scale by Axéll et al.[11]–[3]Individuals were registered as having snus-induced lesion with no data on grading.–[4]Low: no consumption or less than once a week, moderate: 1–2 times a week, high: >2 times a week.

individuals, respectively, and 98 cohort members had relocated to places where personal investigations were unfeasible (Fig. 1*b*). Of the remaining 655 (58%) men, 267 selected in a way that was deemed to be independent of outcome probability were contacted. They comprised 24% of the initial cohort of 1,115 men. Out of the 267 invited, 183 (68%) attended the reexamination (Fig. 1*b*). Reasons for nonparticipation among the 84 men who could not be examined were refusal/missed appointment (67%), no contact (25%) or physical or mental impediments (8%).

In Table I, the initial SIL cohort (n = 1115) is compared to the group that underwent reexamination in 1993–1995. As expected, relatively few individuals in the oldest age groups in 1973–1974 were reexamined since most of them had died. The reexamined group did not differ importantly from those still eligible in 1993–1995 with regard to age, degree of lesion hours per day with snus intraorally, smoking or alcohol habits. During the follow-up period, there had been a shift from living in a small town toward residence in small municipality. This shift was largely due to a difference in selection of individuals for reexamination in 1993–1995; in the small municipality, all eligible were selected, while a selection process that was deemed to be equivalent to random sampling was employed in the small town. Since place of residence was unrelated to outcome in preliminary analyses, the artificial shift from small town to small municipality was deemed to be unimportant. Among individuals selected in 1993–1995, the pattern of residence did not differ materially between participants and nonparticipants. Participating and nonparticipating individuals did not differ significantly with respect to initial degree of lesion. However, a slight difference was found in the small group (67 individuals) with degree 4 lesion. In the selected sample, 9 individuals with degree 4 lesion were among those to be reexamined. Only 3 of them attended the reexamination and they belonged to the 2 youngest age groups. The nonattending 6 individuals were distributed across the age groups.

The development over time for lesions among the reexamined individuals is described in Figure 2. All those with grade 0 at the reexamination in 1993–1995 had stopped using snus or reported change from daily to nondaily use.

The relationships of age at entry, smoking, alcohol and snus habits with SIL degree in 1993–1995 are shown in Table II. There were no significant differences between categories of SIL concerning age or alcohol use. Smoking status was inversely related to SIL degree ($p < 0.01$). There was a strong and statistically significant relation between SIL degree and current number of hours per day with snus intraorally ($p < 0.01$). A similarly strong association was noted with current consumption of snus per day in grams ($p < 0.01$).

Table III shows the association between changes in snus use and changes in SIL degree. The degree differed significantly ($p < 0.01$) between those who had stopped and those who had continued their snus habit, changed or unchanged. A decrease in lesion degree could be observed regardless of whether the individuals had lesions of grade 1–2 or 3–4 in 1973. As for change in hours per day with snus intraorally, no case showed an increase in lesion degree when number of hours was less or the same as in 1973–1974. In 8 cases (12%), there was an increase in the lesion grade related to increased dose. The lesions had become less pronounced in 19 (45%) and more pronounced in 4 (10%) of those who had changed their habit from loose snus to portion bag-packed snus. This tendency towards milder changes was not explained by decreases in amount of snus used or the time with the quid in place (data not shown).

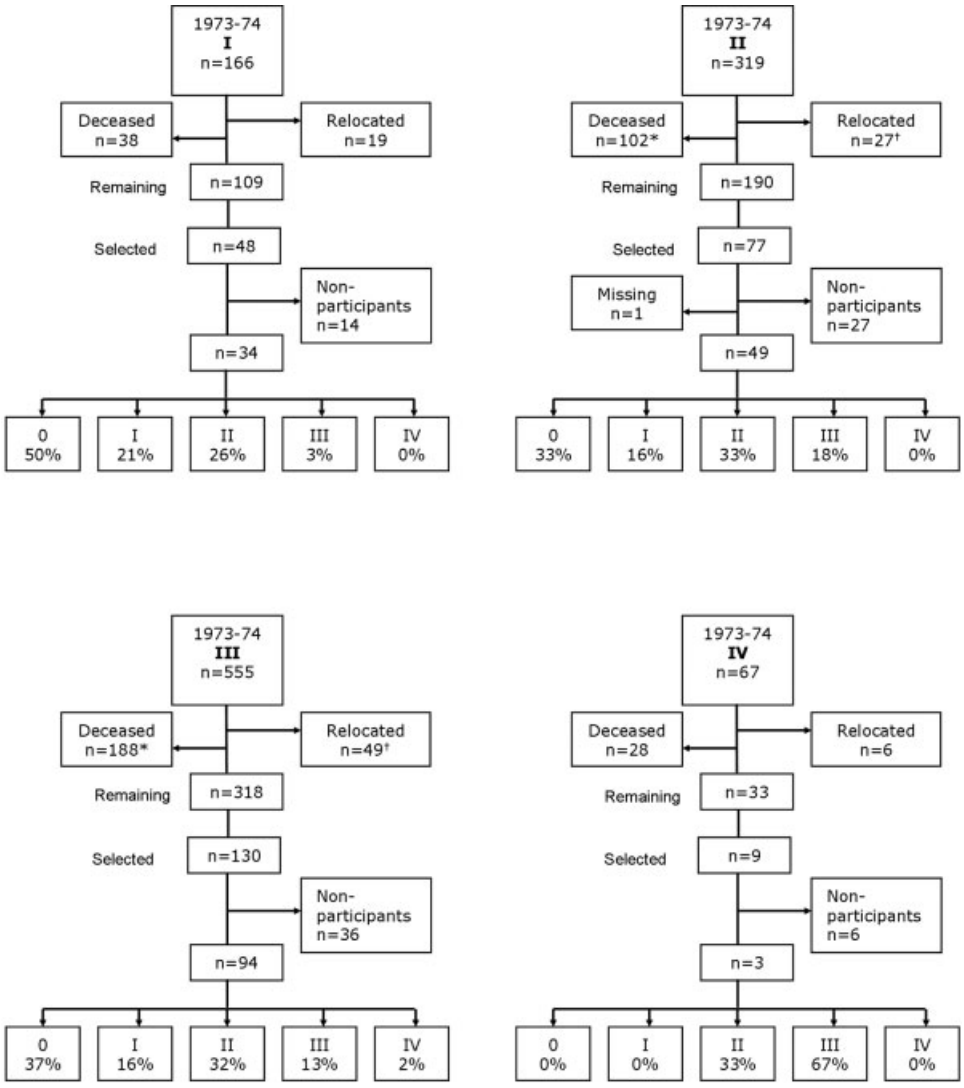

FIGURE 2 – Transmission patterns of participants with lesions (degree I, II, II and IV) from 1973–1974 to lesions (degree 0, I, II, III and IV) and lost to follow-up in 1994–1995. *Two of the deceased with lesion degree II and 1 of the deceased with lesion graded III were diagnosed with oral cancer. †One of the relocated with lesion degree II and 4 of the relocated with lesion graded III had emigrated.

Discussion

The results of this 27–29-year follow-up study of individuals with SIL, with clinical reexamination after 19–22 years, indicate that the lesions are rarely clinically progressive in the long term. Overall, there was a trend towards regression of the lesions, and they had disappeared in all 62 individuals who had quitted using snus at least 1 year prior to the reexamination. The most important determinant of presence and degree of SIL, even after 2 decades, was the current snus dose. Smoking and alcohol did not influence observed changes in lesion. While the course of the lesion appeared benign, however, the incidence of oral cancer overall tended to be higher than expected, albeit based on very small numbers. Although this may seem contradictory, our findings are consistent with a uniform risk in mucosal parts with and without SILs; the study was not powered to confirm a 2.3-fold excess at the sites of the SILs.

This is the first long-term follow-up of SILs in a representative population sample that did not seek medical or dental advice for oral symptoms or signs. The strengths include the prospective and population-based design, and the long observation time. The weaknesses are equally obvious, with losses to follow-up due to death and relocation, leading to censoring in a sizeable proportion of the cohort. If the natural course of snus-induced lesions would be different among cohort members who died, or in those who moved out of the area, our results might be biased. We find it unlikely that the course would be different in those who moved out, compared to those who stayed in the area. Old people and individuals with more severe lesions in 1973–1974, however, were overrepresented among those who died. It should therefore be emphasized that some reservation has to be made for the generalizability of our results to old individuals and those with the most advanced lesions at the time of diagnosis. It is notable, however, that in our limited data derived from those who survived and remained in the study until reexamination, the tendency towards improvement among old people and individuals with more advanced lesions appeared to be no different from the pattern in the entire sample.

The longer (nearly 30-year) follow-up for oral cancer was close to complete thanks to the ubiquitous National Registration Numbers in Sweden, combined with an efficient population administration. Essentially, all occurrences of cancer are ascertained in the more than 98% complete nation-wide Cancer Register,[13,14] all deaths are recorded in the Causes of Death Register[15] and all emigrations are recorded in the Migration Register. However, since the number of cancer cases was few, we acknowledge that the statistical precision of our SIR estimate is poor. The 95% confidence interval ranges from a 50% lower risk to an almost 7 times higher risk than in the age-, gender-, and calendar-period-matched Swedish population. Earlier studies from Sweden suggested no increased risk for cancer among snus users,[16,17] but in one of these studies,[16] there was a significant excess among nonsmoking snus users.

TABLE II – EXAMINED IN 1993–1995, BY SNUS-INDUCED LESION RECORDED IN 1993–1995

	Total $n = 182$ n (%)	Degree 0 $n = 70$ n (%)	Degree 1–2 $n = 86$ n (%)	Degree 3–4 $n = 26$ n (%)
Age at entry ($p = 0.4$[1])				
15–24	45 (25)	20 (29)	15 (17)	10 (38)
25–34	67 (37)	26 (37)	35 (41)	6 (23)
35–44	37 (20)	14 (20)	18 (21)	5 (19)
45–54	16 (9)	5 (7)	9 (10)	2 (8)
55–64	16 (9)	4 (6)	9 (10)	3 (12)
65–74	1 (1)	1 (1)	0 (0)	0 (0)
Smoking habit 1993–1995 ($p < 0.01$[1])				
Never daily	89 (49)	18 (26)	52 (61)	19 (73)
Previously daily	61 (33)	36 (51)	19 (22)	6 (23)
Current daily	32 (18)	16 (23)	15 (17)	1 (4)
Alcohol use[2] 1993–1995 ($p = 0.9$[1])				
Low	3 (2)	1 (1)	2 (2)	0 (0)
Moderate	136 (75)	54 (77)	61 (71)	21 (81)
High	40 (22)	14 (20)	21 (24)	5 (19)
Missing[3]	3 (2)	1 (1)	2 (2)	0 (0)
Snus hours/day[4] 1993–1995 ($p < 0.01$[1])				
0	66 (36)	62 (89)	4 (5)	0 (0)
1–2	2 (1)	0 (0)	2 (2)	0 (0)
3–6	19 (10)	0 (0)	15 (17)	4 (15)
7–15	70 (39)	2 (3)	51 (59)	17 (65)
16–24	15 (8)	0 (0)	11 (13)	4 (15)
Missing[3]	10 (6)	6 (9)	3 (4)	1 (4)
Snus, gram/day[5] 1993–1995 ($p < 0.01$[1])				
0	69 (38)	62 (89)	7 (8)	0 (0)
1–5	35 (19)	0 (0)	31 (36)	4 (15)
6–10	26 (14)	0 (0)	23 (27)	3 (12)
11–15	4 (2)	0 (0)	3 (5)	1 (4)
16–20	10 (6)	0 (0)	6 (7)	4 (15)
>20	31 (17)	2 (3)	16 (19)	13 (50)
Missing[3]	7 (4)	6 (9)	0 (0)	1 (4)

[1]Fisher's exact test of equal proportions across strata. Percentages do not add to 100% due to rounding.–[2]Low: no consumption or less than once a week, moderate: 1–2 times a week, high: >2 times a week.–[3]Missing values include no-answers and occasional users.–[4]Number of hours with snus in the mouth per day.–[5]Amount in grams with snus in the mouth per day.

TABLE III – CHANGE IN DEGREE OF LESION IN RELATION TO CHANGED OR UNCHANGED HABIT, ACCORDING TO TYPE OF SNUS (LOOSE OR PORTION-BAG PACKS) AND HOURS WITH SNUS INTRAORALLY, OVER TIME

	Degree in 1973–1974	Degree in 1993–1995		
		0	1–2	3–4
Stopped[1] ($n = 66$)	1–2	31 (97)	1 (3)	0 (0)
	3–4	31 (91)	3 (9)	0 (0)
Type of snus				
Continued use of	1–2	0 (0)	22 (79)	6 (21)
loose snus ($n = 68$)	3–4	1 (2)	25 (63)	14 (35)
Change to portion-bag	1–2	0 (0)	17 (81)	4 (19)
packs ($n = 42$)	3–4	1 (5)	18 (86)	2 (9)
Missing ($n = 4$)	1–2	2 (100)	0 (0)	0 (0)
	3–4	2 (100)	0 (0)	0 (0)
Hours with snus intraorally/day[2]				
Less ($n = 9$)	1–2	0 (0)	3 (100)	0 (0)
	3–4	0 (0)	5 (83)	1 (17)
Same ($n = 26$)	1–2	0 (0)	5 (100)	0 (0)
	3–4	1 (5)	14 (67)	6 (28)
More ($n = 66$)	1–2	0 (0)	27 (77)	8 (23)
	3–4	1 (3)	22 (71)	8 (26)
Missing ($n = 13$)	1–2	2 (25)	4 (50)	2 (25)
	3–4	2 (40)	2 (40)	1 (20)

[1]Stopped: ex- or nondaily users of either loose snus or portion bag packs.–[2]Defined as change in number of hours/day with snus intraorally from 1973–1973 to 1993–1995.

As we did not take biopsies, we could not study the microscopic changes and/or possible accumulation of genetic damage in the mucosal cells. Our findings, however, confirm the previously demonstrated reversibility of the macroscopically observable lesions with cessation of snus use.[5] A tendency towards regression was also noted among long-time users with unchanged snus habits over the years. A possible reason for this benign development of the lesion may be changes in the snus product over the years. Our data were unable to discern any particular aspects of snus use as more important than the others in the maintenance of snus-induced lesions. A previous study has indicated that hours per day may be most important.[18] Although not unequivocally supported by our

data, use of portion bag-packed snus may also affect the severity of the lesions; such use has previously been shown to be associated with less pronounced mucosal changes and less prevalent gingival retractions than loose snus.[18]

The results of this study suggest that SILs probably constitute no more than markers of current or recent snus consumption.[5] The follow-up time in our study greatly exceeds the follow-up time in previously published prospective studies.[5] Not even in the long term were there any indications of autonomous progression or malignant transformation of the snus-induced lesions. In our interpretation, the SILs may not be mandatory intermediate steps in snuff-associated oral carcinogenesis; in fact, it is uncertain if the risk in the affected mucosal areas is importantly higher than in other parts of the oral mucosa of snuff users. This interpretation might not be valid for other types of snuff; the strong association of oral cancer with snuff reported from South Carolina[1] seemed to be specific for intraoral sites that were particularly exposed. The local effects of less refined products, such as the Sudanese *toombak,* containing up to 1,000 times carcinogenic tobacco-specific nitrosamines NNN and NNK compared to Swedish moist snus, and linked to oral cancer risk,[19,20] could potentially be very different.

In conclusion, this essentially population-based study from Sweden suggests that oral cancers rarely occur at the site of SILs observed in the distant past. It appears that SILs are linked primarily to current snus consumption, and usually disappear after cessation.

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