*Acta Oto-Laryngologica*, 2005; 125: 991–998

Taylor & Francis
Taylor & Francis Group

**ORIGINAL ARTICLE**

# 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

KERSTIN ROSENQUIST[1], JOHAN WENNERBERG[2], ELSY-BRITT SCHILDT[3], ANNA BLADSTRÖM[4], BENGT GÖRAN HANSSON[5] & GUNILLA ANDERSSON[1]

[1]*Department of Oral Surgery and Oral Medicine, Faculty of Odontology, Malmö University, Malmö, Sweden, Departments of* [2]*Otorhinolaryngology, Head and Neck Surgery and* [3]*Oncology and* [4]*Southern Swedish Regional Tumour Registry, Lund University Hospital, Lund, Sweden, and* [5]*Section of Medical Microbiology, Department of Laboratory Medicine, Malmö University Hospital, Lund University, Malmö, Sweden*

**Abstract**

*Conclusions*. The results of this study confirm that both smoking of tobacco and alcohol consumption are risk factors for oral and oropharyngeal squamous cell carcinoma (OOSCC). The use of moist snuff had no effect on the risk of OOSCC, probably due to the low levels of tobacco-specific N-nitrosamines in Swedish moist snuff. *Objective*. The aims of this population-based case-control study in southern Sweden were to establish risk estimates for cigarette and alcohol consumption and to evaluate whether Swedish moist snuff is a risk factor for OOSCC. *Material and methods*. Between September 2000 and January 2004, 132/165 consecutive cases (80%) diagnosed with OOSCC and 320/396 matched controls (81%) were investigated. All subjects were interviewed and examined according to a standardized protocol. *Results*. Individuals who drank $\geq$350 g of alcohol/week showed an increased risk of OOSCC (OR 2.6; 95% CI 1.3–5.4). Total lifetime consumption of tobacco for smoking ($>$250 kg) had a dose–response effect on the risk of OOSCC (OR 4.7; 95% CI 2.4–9.1). We found no increased risk of OOSCC associated with the use of Swedish moist snuff (OR 1.1; 95% CI 0.5–2.5).

**Keywords:** *Cigarettes, epidemiology, human papillomavirus, mucosal lesions, oral cancer, smokeless tobacco, spirits*

## Introduction

The incidence of squamous cell carcinoma in the oral cavity varies in different parts of the world. Oral and oropharyngeal squamous cell carcinomas (OOSCCs) are less common types of tumour in Sweden, but the number of new cases is increasing [1,2]. In 2002, 290 Swedish men and 194 Swedish women were diagnosed as having OOSCC, corresponding to 1.2% and 0.9% of all cancer cases in men and women, respectively [3]. It has been reported in a number of studies [4–10] that smoking of tobacco and alcohol consumption are major risk factors for oral cancer. In Asia, chewing tobacco is associated with a high incidence of oral cancer [11,12], while there are conflicting data regarding other smokeless tobacco products [5,10,13–16].

The consumption of alcohol in Sweden has increased in both men and women during the past 5 years. In 2002, the registered percentage consumptions of different types of alcohol (converted into pure alcohol) were 39% beer, 41% wine and 20% hard liquor (spirits). The type of alcohol varied between the sexes and consumption was almost twice as high in men as in women. Individuals aged 18–29 years had the highest alcohol consumption, while the 50–75 years age group had the lowest [17].

Smoking habits in Sweden have changed in recent decades. Cigarette sales peaked in 1975, with 1800 cigarettes being sold per year per person aged $>$15 years. The corresponding figure for 2002 was 1030 cigarettes. Cigarette consumption decreased in both men and women during this period, although the

Correspondence: Kerstin Rosenquist, RN, DDS, MDS, Department of Oral Surgery and Oral Medicine, Faculty of Odontology, Malmö University, SE-205 06 Malmö, Sweden. Tel: +46 40 6658441. Fax: +46 40 6658439. E-mail: Kerstin.Rosenquist@od.mah.se

*(Received 10 March 2005; accepted 12 May 2005)*

ISSN 0001-6489 print/ISSN 1651-2551 online 
DOI: 10.1080/00016480510043440

decrease was more pronounced in men. Interestingly, smoking in Sweden is more common today among women than men (19% and 14%, respectively), which is exceptional from an international perspective [17]. In 2004, 1.1 million people in Sweden smoked on a daily basis. On average, 16% of the population aged 18–84 years were smokers and the habit was most common between the ages of 45 and 64 years [18].

Use of snuff is widespread in Sweden, and consumption increased considerably between 1970 and 2002. In 1970 the average Swede aged >15 years consumed 394 g of snuff per year, and in 2002 the corresponding figure was 924 g [17]. In 2004, ≈800 000 Swedes were daily users of snuff: 22% of the male population and 3% of the female population [18]. The habit is most common in men and women aged 35–44 years (29% and 6%, respectively).

This paper is part of a population-based case-control study evaluating possible risk factors associated with OOSCC. Our aim was to establish risk estimates for tobacco in terms of smoking and alcohol consumption and to evaluate whether Swedish moist snuff is a risk factor for OOSCC.

## Material and methods

### *Cases*

This population-based case-control study was carried out in the Southern Healthcare Region of Sweden, which has a population of ≈1.6 million. The study period was September 2000 to January 2004 inclusive. The cases considered eligible were individuals with OOSCC [International Classification of Diseases—seventh revision codes 141 (tongue), 143 (floor of the mouth), 144 (oral cavity, not otherwise specified) and 145 (oropharynx)] born in Sweden and without a previous cancer diagnosis, with the exception of skin cancer. The cases were identified at weekly multidisciplinary meetings held at the ENT departments of the two university hospitals in the region, where almost all patients with oral cancer are treated. A total of 132 patients, 91 males (median age 59 years; range 36–87 years) and 41 females (median age 69 years; range 33–87 years), were examined, corresponding to 80% of all cases with OOSCC during the recruitment period.

### *Controls*

Individuals born in Sweden with no previous cancer diagnosis with the exception of skin cancer and who were living in the Southern Healthcare Region of Sweden were eligible as controls. Three controls per case were selected from the Swedish Population Register by means of stratified random sampling. The matching criteria were: age ±3 years; sex; and county. A total of 320 controls, 215 males (median age 60 years; range 36–89 years) and 105 females (median age 66 years; range 33–89 years), were examined, corresponding to 81% of the eligible controls. A detailed description of the recruitment procedure and drop-outs will be published in a forthcoming paper.

### *Examination procedure*

The same person (K. R.), a Registered Nurse and Dental Surgeon, interviewed and examined all cases and controls according to a standardized protocol. Questions were asked regarding medical history, medication, reactivated herpes labialis infection, oral sexual habits, use of tobacco and alcohol consumption. A thorough investigation of the individual's oral hygiene, dental status and oral mucosa was performed. A general assessment of the marginal bone level and the periapical status was made from panoramic radiographs. Cell samples from the oral cavity were collected for human papillomavirus (HPV) DNA analysis. The risk of OOSCC in relation to other risk factors (some lifestyle factors, oral hygiene, dental status, mucosal lesions and HPV) will be presented in forthcoming papers.

### *Alcohol*

The average frequency of alcohol intake per week and the amounts of light beer, medium strong beer, strong beer, wine, white and dark hard liquor drunk on each occasion were recorded. Alcohol was analysed in terms of the total quantity drunk in grams per week, which was calculated by converting the frequencies and amounts into grams per week for each type of alcohol, and then adding them. We analysed alcohol as a categorical variable defined as either low (<70 g/week), medium to high (70–349 g/week) or very high (≥350 g/week). The amounts of pure alcohol contained in different beverages are as follows: a bottle (330 ml) of light beer (2.25%) contains 6.5 g, a bottle (330 ml) of medium strong beer (3.5%) contains 9.1 g, a bottle (330 ml) of strong beer (4.5%) contains 12 g, 1 glass (150 ml) of wine (13%) contains 15 g and a drink (60 ml) of hard liquor (40%) contains 19 g. The low consumption group (<70 g/week) drinks ≈1 bottle of wine or ≈4 drinks of hard liquor per week. This group was used as the reference group.

*Smoking*

The average daily consumption of cigarettes, cigarillos, cigars and pipe tobacco were recorded, together with the period of smoking. Smoking of tobacco was analysed as the total amount used in kilograms during the lifetime of the individual. The total amount of tobacco smoked was calculated by multiplying the average amount of use by the duration of use for the separate smoking products, and adding these quantities. Total lifetime consumption was scored as either low ($<125$ kg), moderate (125–250 kg) or high ($>250$ kg). One cigarette is equivalent to 1 g of tobacco, one cigarillo to 3 g and one cigar to 5 g. One pack of pipe tobacco is equivalent to 50 g of tobacco. We also analysed cigarette consumption separately, but not other smoking products, as the number of users was too few to allow proper analysis. Habits regarding the use of hashish and marijuana were also recorded.

*Swedish moist snuff*

Snuff manufacture in Sweden started in the early 18th century. During the following centuries, the use of snuff increased in Sweden. At first, snuff was used as a fine dry powder which was inhaled through the nose. From the beginning of the 19th century, moist snuff has been used intraorally in the form of a quid.

In 1983, the manufacture of moist snuff in Sweden changed from fermentation to a heat treatment process. Today, Swedish snuff is manufactured from dark air-cured ground tobacco which, after the addition of salt and water, is subjected to a heat treatment process in which most of the volatile nitrosamines are distilled off. This process renders the product practically free of microorganisms, thereby lowering the risk of nitrite formation and the subsequent formation of tobacco-specific N-nitrosamines (TSNA).

The most common way of using snuff in Sweden is to deposit 1–2 g of loose snuff or a portion bag of snuff (1 g) in the vestibule of the upper lip. Both products are produced from ground tobacco, contain $\approx$50% water and 0.8–0.9% nicotine and are alkaline (pH 7.9–8.6) [19]. According to Österdahl et al. [20], the level of TSNA in Swedish moist snuff ranges from 0.15 to 3.0 μg/g wet weight, with a mean content of 1.0 μg/g.

In our study, an interview was performed which included questions on snuff habits, i.e. present or previous snuff use, form of snuff used, duration of snuff use, daily consumption of snuff and whether the quid was placed at one or more sites. Subjects who had stopped taking snuff at least 6 months before the interview were recorded as ex-users. Users of fermented snuff were implicitly defined as those who had been snuff users in 1983 or earlier. Information was also collected on other tobacco habits (e.g. chewing of tobacco), but this was not analysed.

In current snuff users, mucosal changes at the site(s) where the snuff quid was regularly placed were recorded and classified according to the degree of clinical severity using a four-point scale. This scale, designed by Axéll [21], is based on clinical criteria, including wrinkling, thickening and colour changes of the oral mucosa.

*Statistical methods*

The association between the factors studied and OOSCC was analysed by means of standard case-control methodology. All covariates were evaluated separately in univariate analyses. In addition, multivariate logistic regression methods were used for joint modelling of the impact of multiple factors and for adjustment of potential confounders. Associations between factors were analysed in cross-tables by means of Pearson's $\chi^2$ statistics using the hypothesis that the rows and columns in a two-way table were independent, or using Fisher's exact test when appropriate. In the following, statistical significance refers to a $p$-value of $<0.05$ and CIs refer to 95% confidence limits. Unless otherwise stated, adjusted ORs are presented. All analyses were performed using the statistical software package STATA, version 8.2 (StataCorp, College Station, TX).

The study was approved by the Ethics Committee of Lund University (approval No. LU 315-00).

## Results

*Alcohol*

The cases had higher consumption of alcohol than the controls. The median ages of the consumption groups were as follows: $<70$ g/week, 66 years (range 33–89 years); 70–349 g/week, 60 years (range 33–89 years); and $\geq 350$ g/week, 60 years (range 42–87 years). Compared to the lowest consumption group ($<70$ g/week), individuals with a very high consumption of alcohol ($\geq 350$ g/week), corresponding to 4.5 bottles of wine (3.38 l) or 18 drinks of hard liquor (1.08 l), showed an increased risk of OOSCC (OR 2.6; CI 1.3–5.4), while there was no increased risk for the moderate to high consumption group (OR 0.6; CI 0.4–1.0) (Table I).

*Smoking*

Individuals who smoked 11–20 cigarettes/day were at increased risk of developing OOSCC (OR 2.4; CI 1.3–4.1), as were individuals who smoked $>20$

Table I. Characteristics and estimated ORs for alcohol consumption for cases with OOSCC and matched controls. The totals do not add up in some cases because of missing values.

| | | | | Univariate analysis | | | Multivariate analysis[b] | | |
|---|---|---|---|---|---|---|---|---|---|
| Alcohol consumption (g/week) | No. of cases | No. of controls | Total | OR | 95% CI | *p* | OR | 95% CI | *p* |
| <70[a] | 49 | 124 | 173 | 1.0 | | | 1.0 | | |
| 70–349 | 44 | 168 | 212 | 0.7 | 0.4–1.1 | 0.1 | 0.6 | 0.4–1.0 | 0.1 |
| ≥350 | 39 | 23 | 62 | 4.7 | 2.4–9.0 | <0.001 | 2.6 | 1.3–5.4 | <0.001 |
| Total | 132 | 315 | 447 | | | | | | |

[a]Reference.
[b]Adjusted for total amount of tobacco smoked.

cigarettes/day (OR 2.8; CI 1.3–6.1). Individuals with low cigarette consumption (≤10/day) showed no increased risk (OR 1.1; CI 0.6–2.1).

With regard to lifetime consumption of tobacco by smoking, the median age of individuals who had never smoked was 66 years (range 33–89 years). It was 59 years (range 33–86 years) for those who had smoked <125 kg, 62 years (range 42–86 years) for those who had smoked 125–250 kg and 61 years (range 39–89 years) for those who had smoked >250 kg. An increased risk of OOSCC with an increase in the amount of tobacco consumed was also apparent in the analyses of total consumption of tobacco by smoking (OR 1.1, CI 0.6–2.0; OR 1.8, CI 1.0–3.5; and OR 4.7, CI 2.4–9.1 for the three grades of consumption, respectively) (Table II).

Lifetime consumption of tobacco by smoking was lower for women than for men, with average values of 140 and 214 kg, respectively. In spite of this, the risk was higher for women than men (interaction term between female gender and smoking tobacco: OR 1.8, CI 0.7–4.9).

Fourteen individuals (5 cases and 9 controls), all ex-users, reported hashish and/or marijuana use. Hashish had been used by five males (two cases and three controls) and two females (one case and one control), and marijuana by two male controls. Both products had been used by four males (two cases and two controls) and by one female control. No analyses of these data were performed as there were too few subjects.

We found no synergistic effect between high alcohol consumption and tobacco smoking on the risk of OOSCC (interaction term between >250 kg of tobacco and very high alcohol consumption: OR 0.4, CI 0.1–1.1).

### *Swedish moist snuff*

A total of 85 subjects, 83 males and 2 females (median age 55 years; range 34–87 years), had used snuff. Of these, 41 were former and 44 present users. The median age for individuals who had never used snuff was 64 years (range 33–89 years). Details of different snuff factors are given in Table III. More than three-quarters of snuff users had been exposed to fermented snuff. More individuals had used loose snuff (12 cases and 38 controls) than portion bags

Table II. Characteristics and estimated ORs for smoking of tobacco for cases with OOSCC and matched controls. The totals do not add up in some cases because of missing values.

| | | | | Univariate analysis | | | Multivariate analysis[b] | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. of cases | No. of controls | Total | OR | 95% CI | *p* | OR | 95% CI | *p* |
| Cigarette consumption (cigarettes/day) | | | | | | | | | |
| Never smoked[a] | 41 | 154 | 195 | 1.0 | | | 1.0 | | |
| 1–10 | 21 | 74 | 95 | 1.2 | 0.6–2.2 | 0.6 | 1.1 | 0.6–2.1 | 0.7 |
| 11–20 | 49 | 71 | 120 | 3.0 | 1.8–5.1 | <0.001 | 2.4 | 1.3–4.1 | <0.001 |
| >20 | 20 | 21 | 41 | 4.2 | 2.0–8.6 | <0.001 | 2.8 | 1.3–6.1 | <0.001 |
| Total | 131 | 320 | 451 | | | | | | |
| Total tobacco consumption (kg) | | | | | | | | | |
| Never smoked[a] | 34 | 141 | 175 | 1.0 | | | 1.0 | | |
| <125 | 23 | 92 | 115 | 1.1 | 0.6–2.0 | 0.8 | 1.1 | 0.6–2.0 | 0.8 |
| 125–250 | 24 | 51 | 75 | 2.2 | 1.2–4.1 | <0.001 | 1.8 | 1.0–3.5 | 0.1 |
| >250 | 47 | 35 | 82 | 6.5 | 3.5–12.0 | <0.001 | 4.7 | 2.4–9.1 | <0.001 |
| Total | 128 | 319 | 447 | | | | | | |

[a]Reference.
[b]Adjusted for total consumption of alcohol.

Table III. Characteristics and estimated ORs for usage of Swedish moist snuff in cases with OOSCC and matched controls. The totals do not add up in some cases because of missing values.

| | | | | Univariate analysis | | | Multivariate analysis[b] | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. of cases | No. of controls | Total | OR | 95% CI | *p* | OR | 95% CI | *p* |
| Moist snuff usage | | | | | | | | | |
| Never used[a] | 112 | 255 | 367 | 1.0 | | | 1.0 | | |
| Had used | 20 | 65 | 85 | 0.7 | 0.4–1.2 | 0.2 | 0.7 | 0.3–1.3 | 0.2 |
| Total | 132 | 320 | 452 | | | | | | |
| Ex-users | 7 | 34 | 41 | 0.5 | 0.2–1.1 | 0.1 | 0.3 | 0.1–0.9 | <0.001 |
| Current users | 13 | 31 | 44 | 1.0 | 0.5–1.9 | 0.9 | 1.1 | 0.5–2.5 | 0.8 |
| Fermented snuff | 16 | 49 | 65 | 0.7 | 0.4–1.4 | 0.3 | 0.7 | 0.3–1.4 | 0.7 |
| Non-fermented snuff | 4 | 16 | 20 | 0.6 | 0.2–1.7 | 0.3 | 0.6 | 0.2–1.9 | 0.4 |
| Duration (years) | | | | | | | | | |
| <30 | 16 | 52 | 68 | 0.7 | 0.4–1.3 | 0.2 | 0.6 | 0.3–1.3 | 0.2 |
| ≥30 | 4 | 13 | 17 | 0.7 | 0.2–2.2 | 0.5 | 0.8 | 0.2–2.8 | 0.7 |
| Exposure time (h/day) | | | | | | | | | |
| ≤10 | 15 | 38 | 53 | 0.9 | 0.5–1.7 | 0.7 | 0.7 | 0.3–1.5 | 0.4 |
| >10 | 5 | 27 | 32 | 0.4 | 0.2–1.1 | 0.1 | 0.5 | 0.2–1.6 | 0.3 |
| Consumption (g/day) | | | | | | | | | |
| 1–14 | 8 | 21 | 29 | 0.9 | 0.4–2.0 | 0.7 | 0.9 | 0.3–2.5 | 0.9 |
| >14 | 5 | 10 | 15 | 1.1 | 0.4–3.4 | 0.8 | 1.7 | 0.5–5.7 | 0.4 |

[a]Reference.
[b]Adjusted for total consumption of alcohol and smoking of tobacco.

(7 cases and 26 controls). About two-thirds of individuals ($n=65$) did not place the quid at the same site on a regular basis.

Overall, we found no risk effect for OOSCC for any of the snuff habits studied (Table III): current users (OR 1.1; CI 0.5–2.5); ex-users (OR 0.3; CI 0.1–0.9); fermented snuff (OR 0.7; CI 0.3–1.4); >10 h/day (OR 0.5; CI 0.2–1.6); or at least 30 years of use (OR 0.8; CI 0.2–2.8). In fact, the only factor that showed a tendency towards an increased risk of OOSCC was consumption of >14 g/day (OR 1.7; CI 0.5–5.7). Three individuals, all males (one case and two controls), reported use of chewing tobacco.

### *Snuff and clinical lesions*

Snuff was being used currently by 44 individuals (13 cases and 31 controls). They all showed clinical lesions: 5 individuals (2 cases and 3 controls) showed degree 1 lesions; 15 (4 cases and 11 controls) degree 2 lesions; 18 (6 cases and 12 controls) degree 3 lesions; and 6 (1 case, 5 controls) degree 4 lesions. Those who used snuff for >10 h/day developed more pronounced lesions ($p=0.01$), while consumption of >14 g/day was not significantly associated with higher-degree lesions ($p=0.07$). Neither a long duration (≥30 years) of use ($p=0.8$) nor placing the quid at the same site ($p=0.8$) had an influence on the severity of lesions.

### *HPV*

HPV DNA was found in mouthwash samples from each of eight snuff users (low-risk type in two controls; high-risk type in five cases and one control). No association was found between use of snuff and HPV DNA ($p=0.8$), or between smoking of tobacco and the presence of HPV DNA ($p=0.2$). Moreover, multivariate analyses with adjustment for HPV had minor effects on the estimated ORs of alcohol, tobacco for smoking and snuff (data not shown).

### *Other risk factors*

Oral status and lifestyle factors (other than alcohol and tobacco consumption) and HPV infection did not affect any of the conclusions of risk of OOSCC due to alcohol consumption, tobacco smoking or use of Swedish moist snuff.

## Discussion

In Sweden, population registers and cancer registers covering the whole population are available. This makes Sweden especially suitable for studies with a case-control design. Using population-based registers to collect material lowers the risk of selection bias. Also, almost all of the patients with OOSCC in the southern part of Sweden are treated at the two university hospitals where this study was performed. Using the Swedish National Population Register, the

controls were drawn randomly from the same region of residence as the cases, which strengthens the study. The participation rate was 80% for both cases and controls.

Lifestyle factors such as alcohol and tobacco consumption are difficult to study. There is always a risk of under-reporting tobacco use as well as alcohol intake. In this study, information on individual exposure to tobacco and alcohol was collected in a uniform way, and by the same person for all cases and controls. We chose to estimate lifetime consumption of alcohol and tobacco to avoid a possible effect of changes in consumption due to symptoms resulting from the tumour. However, as in previous studies [4–10], our data confirm that very high alcohol intake increases the risk of OOSCC. Moreover, in agreement with other studies [4–10], we also found that the risk of OOSCC increased with the amount of tobacco smoked. Lewin et al. [5] found a synergistic effect between alcohol consumption and tobacco smoking on the risk of SCC of the head and neck. We found no interaction between high alcohol consumption and tobacco smoking on the risk of OOSCC. The inclusion of hypopharynx, larynx and oesophageal cancer in the study by Lewin et al. [5] may explain these differences. Furthermore, our study sample was quite small, which limits the possibility of detecting any significant interactions.

Muscat et al. [8] found that the risk of oral cancer associated with tobacco smoking was higher for women than men. Their finding is supported by our study, as the amount of tobacco smoked in our study was lower among female smokers but the risk was somewhat higher, indicating a gender difference in smoking-related susceptibility to OOSCC. Also, it has been shown that women are at higher risk of lung cancer than men for a given level of smoking. Harris et al. [22] found a relative risk of 1.7, i.e. of the same magnitude as that found in this study.

The results of studies on the risk of OOSCC associated with the use of smokeless tobacco worldwide vary widely [5,10–12,14,16]. This is probably mainly due to the fact that different products with different potential for malignant transformation of the oral mucosa are used, even though they are all called snuff. Consequently, it is very important to state the content of different products as carefully as possible, as we have done in this study.

Environmental factors such as fertilization of the soil and climate in the area where the tobacco is grown can have an influence on the amount of nitrate in the tobacco. A high moisture level makes it easier for bacteria to transform nitrate to nitrite which, under unfavourable conditions during curing and storage, can react with the alkaloids (nicotine, nor-nicotine) in the tobacco, resulting in the formation of TSNA, which are the most abundant carcinogens identified in unburned tobacco.

Since 2002, Swedish snuff has been manufactured from dark air-cured tobacco, while dark fire-cured tobacco is still used in the USA and Sudan [15,23]. The smoke affects the chemical composition, leading to an increased risk of nitrosamine formation. The heat treatment process, which has been used in Sweden since 1984, gives a product with a low level of volatile nitrosamines, while the fermentation process, as used in the USA, for example, is more difficult to control, which increases the risk of formation of TSNA. In moist snuff from the USA, the TSNA level is somewhat higher (two to six times) than that in Swedish moist snuff [20,23]. The TSNA level in dry snuff bought in the USA is reported to be 20–600 times that of Swedish moist snuff [23], which is likely to be at least one explanation for the increased risk associated with snuff dipping found by Winn et al. [16], as the women in that study used dry snuff according to Banbury report No. 23 [24]. That a very high level of TSNA increases the risk of OOSCC was also shown in a study of toombak users in Sudan [14]. Toombak, a variety of fermented moist snuff, contains concentrations of TSNA that are 100-fold higher than those in Swedish moist snuff [15].

The way snuff products are stored can also have an effect on the level of TSNA. Brunnemann et al. [25] reported that the TSNA level was increased by 30–130% when moist snuff produced in the USA was stored at room temperature for 6 months, while snuff produced in Sweden did not show any increase in TSNA level. Based on their observations, they suggested that snuff should be stored refrigerated by wholesalers and retail stores.

No increased risk of oral cancer in current users of Swedish moist snuff was found in our study (OR 1.1; CI 0.5–2.5). This result is in agreement with two previous Swedish case-control studies: those of Lewin et al. [5] (OR 1.0; CI 0.5–2.2) and Schildt et al. [10] (OR 0.7; CI 0.4–1.1). However, Lewin et al. [5] demonstrated a tendency towards an increased risk in ex-users (OR 1.8; CI 0.9–3.7), as did Schildt et al. [10] (OR 1.5; CI 0.8–2.9), although we did not observe this in our study (OR 0.3; CI 0.1–0.9). The cases and controls in the previous studies were recruited between 1988 and 1991 [5] and between 1980 and 1989 [10]. In a retrospective study [13] based on information from records reported to the Swedish cancer register between 1962 and 1971, an incidence of oral cancer of 0.5 cases/100 000/year in male users of fermented Swedish moist snuff was reported. Most cases were found in men aged 71–80 years. In our study, use of

fermented snuff, defined as snuff use before 1984 when the fermentation process was abolished, did not constitute any increased risk (OR 0.7; CI 0.3–1.4) of OOSCC, despite the fact that most of the subjects had used fermented snuff. In the three Swedish studies mentioned above [5,10,13] the levels of TSNA were not declared. Based on the findings of our study, and the TSNA level in fermented moist snuff from the USA [20,23], it seems reasonable to assume that the cancer cases in the previous Swedish studies [5,10,13] were due to the consumption patterns of the individual snuff users rather than the fermentation process. In our study, increased exposure time to moist snuff did not increase the risk of OOSCC (OR 0.5; CI 0.2–1.6). The amount of snuff used showed a slight tendency towards increased risk (OR 1.7; CI 0.5–5.7), which is in agreement with the results of Lewin et al. [5] (OR 1.4; CI 0.9–2.3).

Daily exposure time (h/day) is more important for the development of snuff dipper's lesion of a higher degree at the site where the quid is placed than the amount of snuff used (g/day) or the duration of the habit (years), which is in agreement with the findings of Andersson et al. [19]. There appears to be no correlation between the severity of lesions and oral carcinoma. The scale used for clinical grading of the snuff dipper's lesion is based only on changes in the surface of the oral mucosa, while marked histomorphological changes, such as dysplasia, cannot be predicted by the clinical appearance. In our study, one man developed a carcinoma at the site where he had put his snuff quid for 22 years. He had also smoked 20 cigarettes/day for the past 10 years. In individual patients, presumably with considerable exposure to moist snuff over many years and a smoking habit as well, the snuff dipper's lesion may develop into an oral cancer. However, on the whole there is no increased risk of oral cancer from use of Swedish moist snuff according to our results.

In agreement with several previous studies, our results show that smoking tobacco and consumption of alcohol are risk factors for oral cancer. One interesting observation is that women seem to have a higher risk of OOSCC than men for a given level of smoking. The risk associated with smoking was 1.8 in women compared to men and, although this was not significant, this should be interpreted bearing in mind that in each stratum of tobacco consumption women had a consumption level that was two-thirds that of men. A difference in the susceptibility of the upper aerodigestive tract between men and women is supported by the finding that, among lung cancer patients, the levels of aromatic/hydrophobic DNA adducts were higher in females than males when adjusted for smoking dose [26].

When it contains a high level of TSNA, as in dry snuff and moist snuff from Sudan, snuff also carries an increased risk of developing OOSCC. The level of TSNA in Swedish moist snuff is very low, even with storage, which is probably why its use does not increase the risk of OOSCC, as documented in this study.

## Acknowledgements

This work was supported by the Cancer Foundation of Malmö University Hospital, the Gunnar Nilsson Cancer Foundation, the Berta Kamprad Foundation, the Swedish Dental Society, the Faculty of Odontology, Malmö University, the Alfred Österlund Foundation, the Swedish Cancer Society and the King Gustaf V Jubilee fund.

## References

[1] Annertz K, Anderson H, Biorklund A, Moller T, Kantola S, Mork J, et al. Incidence and survival of squamous cell carcinoma of the tongue in Scandinavia, with special reference to young adults. Int J Cancer 2002;101:95–9.

[2] Östman J, Anneroth G, Gustafsson H, Tavelin B. Malignant oral tumours in Sweden 1960–1989—an epidemiological study. Eur J Cancer B Oral Oncol 1995;31B:106–12.

[3] The National Board of Health and Welfare. Cancer incidence in Sweden, 2002, Stockholm, Sweden. http://www.sos.se/FULLTEXT/42/2003-42-11/summary.htm

[4] Bundgaard T, Wildt J, Rydenberg M, Elbrand O, Nielsen J-E. Case-control study of squamous cell cancer of the oral cavity in Denmark. Cancer Causes Control 1995;6:57–67.

[5] Lewin F, Norell S, Johansson H, Gustavsson P, Wennerberg J, Biorklund A, et al. 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] Macfarlane G, Zheng T, Marshall J, Boffetta P, Niu S, Brasure J, et al. Alcohol, tobacco, diet and the risk of oral cancer: a pooled analysis of three case-control studies. Eur J Cancer B Oral Oncol 1995;31B:181–7.

[7] Marshall J, Graham S, Haughey B, Shedd D, O'Shea R, Brasure J, et al. Smoking, alcohol, dentition and diet in the epidemiology of oral cancer. Eur J Cancer B Oral Oncol 1992;28B:9–13.

[8] Muscat J, Richie JJ, Thompson S, Wynder E. Gender differences in smoking and risk for oral cancer. Cancer Res 1996;56:5192–7.

[9] Rothman K, Keller A. The effect of joint exposure to alcohol and tobacco on risk of cancer of the mouth and pharynx. J Chron Dis 1972;25:711–6.

[10] Schildt E-B, 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.

[11] Balaram P, Sridhar H, Rajkumar T, Vaccarella S, Herrero R, Nandakumar A, et al. Oral cancer in southern India: the influence of smoking, drinking, paan-chewing and oral hygiene. Int J Cancer 2002;98:440–5.

[12] Dikshit R, Kanhere S. Tobacco habits and risk of lung, oropharyngeal and oral cavity cancer: a population-based case-control study in Bhopal, India. Int J Epidemiol 2000; 29:609–14.
[13] Axéll T, Mörnstad H, Sundström B. Snuff and cancer of the oral cavity. Läkartidningen 1978;75:2224–6.
[14] Idris A, Ahmed H, Malik M. Toombak dipping and cancer of the oral cavity in the Sudan: a case-control study. Int J Cancer 1995;63:477–80.
[15] Idris A, Ibrahim S, Vasstrand E, Johannessen A, Lillehaug J, Magnusson B, et al. The Swedish snus and the Sudanese toombak: are they different? Oral Oncol 1998;34:558–66.
[16] Winn D, Blot W, Shy C, Pickle L, Toledo A, Fraumeni JJ. Snuff dipping and oral cancer among women in the southern United States. N Engl J Med 1981;304:745–9.
[17] Swedish Council for Information on Alcohol and other Drugs. CAN report No. 71. 2003. http://www.can.se/docs/press_rapporter/CAN_RS_71.pdf
[18] Part of Sweden's Public Health Objective NO 11. Reduced use of tobacco – how far have we come? Statistics, October 2004. National Institute of Public Health, Stockholm, Sweden.
[19] Andersson G. Snuff-induced changes associated with the use of loose and portion-bag-packed Swedish moist snuff. A clinical, and histological follow-up study [Thesis]. Malmö, Sweden: Lund University; 1991.
[20] Österdahl B, Jansson C, Paccou A. Decreased levels of tobacco-specific N-nitrosamines in moist snuff on the Swedish market. J Agric Food Chem 2004;52:5085–8.
[21] Axéll T. A prevalence study of oral mucosal lesions in adult Swedish population [Thesis]. Malmö, Sweden: Lund University; 1976.
[22] Harris R, Zang E, Anderson J, Wynder E. Race and sex differences in lung cancer risk associated with cigarette smoking. Int J Epidemiol 1993;22:592–9.
[23] 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.
[24] Winn DM. Smokeless tobacco in oral/pharynx cancer: The role of cofactors. In: Hoffmann D, Harris CC (Eds). Mechanisms in tobacco carcinogenesis. Banbury report No. 23. Cold Spring Harbor Laboratory, N.Y. 1986.
[25] Brunnemann K, Qi J, Hoffmann D. Aging of oral moist snuff and the yields of tobacco-specific N-nitrosamines (TSNA). American Health Foundation, Valhalla, N.Y. 2001. http://www.tobacco.org/News/010622BostonRE.html
[26] Ryberg D, Hewer A, Phillips D, Haugen A. Different susceptibility to smoking-induced DNA damage among male and female lung cancer patients. Cancer Res 1994; 54:5801–3.