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

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BACKGROUND. This case-referent study was conducted to elucidate the role of selected exogenous agents in the etiology of head and neck cancer. The factors studied were tobacco smoking, alcohol intake, the use of moist oral snuff, dietary factors, occupational exposures, and oral hygiene. In this first report, the authors discuss the impact of tobacco smoking, the use of oral snuff, and alcohol consumption.

METHODS. The study base was approximately 2 million person-years at risk and consisted of Swedish males age 40–79 years living in 2 geographic regions during the years 1988–1990. A total of 605 cases were identified in the base, and 756 controls were selected by stratified random sampling from population registries covering the base.

RESULTS. Among those who were tobacco smokers at the time of the study, the relative risk of head and neck cancer was 6.5% (95% confidence interval, 4.4–9.5%). After cessation of smoking, the risk gradually declined, and no excess risk was found after 20 years. The relative risk associated with alcohol consumption of 50 grams or more per day versus less than 10 grams per day was 5.5% (95% confidence interval, 3.1–9.6%). An almost multiplicative effect was found for tobacco smoking and alcohol consumption.

CONCLUSIONS. Tobacco smoking and alcohol intake had a strong interactive effect on the risk of squamous cell carcinoma of the head and neck. Moderate alcohol intake (10–19 grams per day) had little or no effect among nonsmokers. No increased risk was found for the use of Swedish oral snuff. ***Cancer* 1998;82:1367–75.** © *1998 American Cancer Society.*

KEYWORDS: tobacco smoking, alcohol, oral snuff, squamous cell carcinoma, head and neck cancer, esophageal cancer, case–referent study, epidemiology.

There is a geographic variation in the incidence of cancer of the head and neck among different countries of the world and among different regions within a country.[1] This indicates that environmental factors may play an important role in the pathogenesis of cancer of the head and neck. In Europe, Sweden has one of the lowest incidences of these cancers. In Sweden, the majority (two-thirds) of patients with squamous cell carcinoma of the head and neck are males. It has been shown previously that tobacco smoking and alcohol intake are major risk factors.[2–4] In Asia, chewing-tobacco causes a high incidence of oral cancers,[5] and in the U.S. there have been reports of oral snuff as a risk factor in oral cancer.[6,7] About 15% of all adult males in Sweden use, or have used for part of their lives, an oral snuff produced

mainly in Sweden. The snuff is a moist, nonfermented tobacco product originating from the species *Nicotinum tabacum*. It is placed on the gum under the upper lip and is rarely used outside the Scandinavian countries. The "Swedish" moist oral snuff is known to cause reversible white patches on the site of application.[8] The possible association of Swedish oral snuff with cancer of the head and neck has not yet been determined. However, due to potentially carcinogenic substances contained in Swedish oral snuff, a concern regarding such a possible association exists.

To identify possible factors involved in the etiology of cancer of the head and neck (oral cavity, oro- and hypopharynx, larynx, and the esophagus) among men, a population-based case–referent study was performed over 3 years in 2 defined geographic regions in Sweden. Tobacco smoking, oral snuff, alcohol, dietary factors, occupational exposures, and indicators of oral hygiene were investigated. In this first report, we discuss the impact of tobacco smoking, the use of oral snuff, and alcohol consumption.

MATERIALS AND METHODS

The study base was the person-time generated by all men born in Sweden, ages 40–79 years, living in (and included in the population registers of) the Stockholm county or the southern healthcare region of Sweden during the study period January 1988 through January 1991. Thus, the study base was approximately 2 million person-years at risk.

Cases

Efforts were made to identify all incident cases of cancer of the head and neck (squamous cell carcinoma of the oral cavity, oro- and hypopharynx, larynx, and esophagus) that occurred in the study base. Cancers occurring outside the study base were not included. The cases were identified at weekly multidisciplinary conferences at all of the six ear, nose, and throat departments (ENT) where almost all head and neck cancers in the two regions were treated. In addition, patients with esophageal cancers not diagnosed at the ENT departments were reported by all the departments of surgery in the two regions. To identify cases not presented at the conferences or reported from the departments of surgery, information was obtained every second week on the recent reports to the regional cancer registers in Stockholm and in the southern region. About 10% of the cases were identified in this way. Notification of the regional cancer registries about new cancer cases is compulsory for both clinicians and pathologists. Of all cancers of the head and neck, almost 99% are being registered in the regional cancer registries.[9] Cancers identified incidentally at autopsy were not included.

Referents

The referents were selected by stratified random sampling every 6 months during the study period from a computerized population register in each region. Stratification was by region (Stockholm and the southern region) and age (40–54, 55–64, and 65–79 years). The population registers are updated every month.

Interviews

Cases and referents were asked to participate in an interview on life-style and environment. Informed consent was obtained from each subject. The interview followed a structured questionnaire covering smoking history, the use of oral snuff, and alcohol intake as well as dietary factors (food frequencies) and indicators of oral hygiene (the number of toothbrushes used per year and the number of visits to a dentist per year) and occupational exposure. All interviews were conducted by two nurses, one in each of the two regions. The nurses were trained for health interviews and for treating cases and referents alike. Most of the cases were interviewed at the hospital. The cases were interviewed approximately 1 month after diagnosis. The delay was deliberate, to give the patients time to get used to the new medical situation. Referents were usually interviewed in their homes.

Smoking

Lifetime smoking histories included information on the time when a subject began or stopped smoking and the average number of cigarettes, cigarillos, cigars, and grams of pipe tobacco smoked per day during different time periods. Total consumption of smoking tobacco was calculated by adding the quantity of tobacco smoked during different time periods, considering 1 cigarette or cigarillo equivalent to 1 gram and 1 cigar equivalent to 5 grams of tobacco. The mean intensity of smoking was calculated by dividing the subject's total consumption by the duration of smoking. "Ever-smokers" were men who had ever regularly smoked at least 7 grams of tobacco per week. To avoid the possibility that cases would be classified as ex-smokers because they had stopped smoking due to insidious cancer symptoms, subjects were considered current smokers if they smoked 1 year prior to the time of the interview.

Oral Snuff

Oral snuff usage was recorded in a similar way as smoking history, considering men who had ever regularly used 1 package (50 grams) per week as ever-users

TABLE 1
Total Number of Cases Identified, Referents Selected, Numbers Interviewed and Lost, and Reasons for Nonparticipation in the Interviews

	No. (%) of cases	No. (%) of referents
Identified/selected	605 (100%)	756 (100%)
Lost (not interviewed)	60 (10%)	115 (15%)
Refused	17	80
Disabled	9	8
Dead	30	6
Not located	—	21
Other reasons	4	—
Interviewed	545 (90%)	641 (85%)

and men who used oral snuff 1 year prior to the time of the interview as current users. Total consumption, duration, and mean intensity of usage were calculated in the same ways as for smoking tobacco.

Alcohol Intake

Intake of alcoholic beverages 5 years prior to the time of the interview was assessed using a questionnaire slightly modified from Gerhardsson de Verdier et al.[10] It provided information on the intake of beer, wine, and hard liquor, using seven categories of consumption frequency, and the average amount consumed on each occasion. This information was translated into grams of alcohol per day using a data base at the Swedish National Food Administration.[11]

Data Analysis

The referents were selected to provide information on exposure frequencies in the person-time that generated the cases. The relative risk (RR, incidence rate ratio) was calculated by logistic regression analysis.[12] Adjustments were made according to study design for age (three categories) and region (two categories). In some analyses, adjustments were also made for tobacco smoking (current smokers, ex-smokers, and those who never smoked) or alcohol intake (<10, 10–19, 20–49, and ≥50 grams per day), or both. As a check of residual confounding, adjustments were also made for age in 5-year categories, duration of smoking, oral hygiene, and certain dietary factors. The EGRET (1988) computer program from the Statistics and Epidemiology Research Corporation was used to process the data.

RESULTS

A total of 605 cases were identified, and 756 referents were selected. Ninety percent of the cases and 85% of the referents participated in the interviews. Reasons for not participating are shown in Table 1.

The effect of smoking was similar when men who smoked cigarettes only (RR = 3.7, 95% confidence interval [CI] = 2.5–5.5) were compared with those who smoked cigarillos, cigars, or a pipe (RR = 4.1, 95% CI = 2.3–7.4) and those who mixed use of different smoking tobacco (RR = 4.1, 95% CI = 2.8–6.1). Due to there being only two pure cigar smokers in the material, it was not possible to perform the RR analysis for this subgroup. All smoking tobacco was considered together in Table 2, showing the RRs associated with different aspects of smoking. The risk was considerably lower for ex-smokers than for current smokers and was related to time since smoking cessation. No increased risk was found for men who had stopped smoking more than 20 years previously. There was also some association between risk and the mean intensity of smoking. Cessation of smoking was, however, more common among men who smoked only a few cigarettes or grams of tobacco per day than among men with a high daily consumption. To evaluate the impact of the mean intensity of smoking aside from smoking cessation, it was investigated in current smokers: RR = 6.1 (95% CI = 4.0–9.5) for men smoking <15 grams per day, RR = 6.1 (95% CI = 4.0–9.3) for men smoking 15–24 grams per day, and RR = 6.6 (95% CI = 3.4–12.7) for men smoking ≥25 grams per day. This suggested that aside from the effect of smoking cessation, there was little or no impact of mean smoking intensity. If so, the impact of total consumption would essentially reflect an effect of duration of smoking, because total consumption equalled mean intensity multiplied by duration of smoking. As shown in Table 3, smoking cessation and the duration of smoking each had a decisive impact on risk.

The cancer subsites in the interviewed cases were: the oral cavity in 128 cases, the pharynx in 138 cases (75 oropharynx and 63 hypopharynx), the larynx (mainly glottic) in 157 cases, and the esophagus in 123 cases. Analysis by cancer subsite showed similar results, although the relative effect of smoking was more pronounced for cancers of the pharynx and larynx than for cancers of the other subsites. For current smokers, the RRs (with 95% CIs) were as follows: for cancer of the pharynx, RR = 8.5 (4.0–18.2); larynx, RR = 7.5 (3.9–14.2); esophagus, RR = 5.2 (2.6–10.3); and oral cavity, RR = 4.9 (2.6–9.2). For men who had smoked 45 years or longer: pharynx, RR = 10.1 (4.6–22.1); larynx, RR = 7.6 (3.9–14.7); esophagus, RR = 5.4 (2.7–11.0); and oral cavity, RR = 6.3 (3.2–12.4).

Overall, the use of oral snuff had little or no effect on risk, as shown in Table 4. In an analysis performed with the reference category "never-tobacco-users," precision was very low, as there were only 9 cases and 10 referents who had ever used snuff but had never smoked

TABLE 2
Smoking[a] and Relative Risk of Head and Neck Cancer[b] in Swedish Men Ages 40–79 Years

			Relative risk (95% confidence interval) adjusted for	
Smoking	No. of cases	No. of referents	Design[c]	Design[c] + alcohol[d]
Never smoked	44	193	1.0	1.0
Ever smoked	501	448	5.0 (3.5–7.0)	4.0 (2.8–5.7)
Current smokers	385	214	8.4 (5.8–12.2)	6.5 (4.4–9.5)
Ex-smokers	116	234	2.1 (1.4–3.1)	1.9 (1.3–2.8)
Stopped smoking				
1–10 yrs ago	61	75	3.5 (2.2–5.7)	3.2 (2.0–5.2)
11–20 yrs ago	32	76	1.9 (1.1–3.1)	1.7 (1.0–2.9)
≥21 yrs ago	23	83	1.1 (0.6–2.0)	0.9 (0.5–1.7)
Age at start				
<15 yrs	110	77	6.5 (4.2–10.1)	5.0 (3.2–7.9)
15–19 yrs	257	220	5.2 (3.6–7.6)	4.0 (2.7–5.9)
20–24 yrs	101	102	4.4 (2.8–6.7)	3.8 (2.4–5.9)
≥25 yrs	33	49	2.8 (1.6–4.9)	2.6 (1.5–4.6)
Duration of smoking				
<30 yrs	50	156	1.3 (0.8–2.0)	1.2 (0.7–1.9)
30–44 yrs	168	148	4.9 (3.3–7.3)	3.9 (2.6–5.9)
≥45 yrs	283	144	9.3 (6.3–13.8)	7.2 (4.8–10.8)
Total consumption[e]				
<125 kg tobacco	53	145	1.6 (1.0–2.5)	1.5 (1.0–2.4)
125–250 kg tobacco	181	146	5.5 (3.7–8.2)	4.3 (2.9–6.5)
>250 kg tobacco	267	157	7.5 (5.1–11.0)	5.9 (4.0–8.8)
Intensity of smoking[e,f]				
<15 g tobacco/day	202	211	4.1 (2.8–6.0)	3.4 (2.3–5.1)
15–24 g tobacco/day	230	189	5.5 (3.8–8.1)	4.4 (2.9–6.5)
≥25 g tobacco/day	69	48	6.5 (4.0–10.7)	4.8 (2.9–8.1)
Deep inhalers[g]				
Yes	341	176	8.9 (6.1–13.0)	6.7 (4.5–10.0)
No	41	33	5.3 (3.0–9.3)	3.9 (2.1–7.0)

[a] Cigarettes, cigarillos, cigars, pipe.
[b] Squamous cell carcinoma of the oral cavity, oro- and hypopharynx, larynx, and esophagus.
[c] Age (40–54, 55–64, 65–79 yrs) and region (Stockholm and the South Sweden healthcare area).
[d] Four categories (<10, 10–19, 20–49, ≥50 g alcohol/day).
[e] One cigarette or cigarillo = 1 g, 1 cigar = 5 g.
[f] Total consumption divided by duration of smoking (g per day).
[g] Among current smokers. Data missing for 3 cases and 5 referents.

tobacco. The RR (95% CI) for ever-users of snuff was RR = 4.7 (1.6–13.8). For current users, RR = 3.3 (95% CI = 0.8–12.0), and for ex-users, RR = 10.5 (95% CI = 1.4–117.8), further illustrating the low precision. When former smokers were the reference category, the precision was higher, with 24 cases and 46 referents who had ever used snuff. For ever-users of snuff with this reference category, RR = 1.1 (95% CI = 0.6–1.9). For current users of snuff, RR = 1.4 (95% CI = 0.7–2.8), and for ex-users RR = 0.8 (95% CI = 0.4–1.8). With current smokers as a reference category, the RRs (95% CIs) were as follows: RR = 0.8 (0.5–1.2) for ever-users of snuff, RR = 0.6 (0.3–1.1) for current snuff users, and RR = 1.0 (0.5–2.0) for ex-users.

In an analysis by anatomic subsite, precision was again low. The RRs by subsites are shown in Table 5.

The effect of alcohol intake is illustrated in Table 6. The results suggest a gradual increase in the risk of cancer of the head and neck with increasing alcohol intake. However, moderate alcohol intake (10–19 grams per day) had little or no impact on the risk of cancer in ex-smokers and in men who never smoked (Table 7). Moderate alcohol consumption was found to increase the risk only among current smokers. The joint effect of a high alcohol intake (≥20 grams per day), with an RR of 4.2 and current smoking RR = 6.3, was nearly multiplicative: RR = 22.1.

TABLE 3
Duration of Smoking for Current Smokers and Ex-Smokers and Relative Risk of Head and Neck Cancer in Swedish Men Ages 40–79 Years

	Relative risk (95% confidence interval) No. of exposed cases/exposed referents	
Duration of smoking	Current smokers	Ex-smokers
≥45 yrs	7.3 (4.8–11.0)	4.4 (2.4–8.0)
	247/113	36/31
30–44 yrs	6.1 (3.8–9.8)	2.4 (1.5–4.0)
	120/74	48/74
<30 yrs	2.4 (1.1–5.3)	1.0 (0.6–1.7)
	18/27	32/129

Unexposed (never smokers): 44 cases/193 referents.
Relative risks are adjusted for age (40–54, 55–64, 65–79 yrs), region (Stockholm and the South Sweden healthcare area), and alcohol intake (<10, 10–19, 20–49, ≥50 g alcohol/day).

Analysis by subsite showed the strongest relative effect of alcohol for cancer of the esophagus (RR = 8.6, 95% CI = 3.8–19.2) and pharynx (RR = 8.5, 95% CI = 4.0–18.1) at an alcohol intake of ≥50 grams per day. For the other subsites, the corresponding effects were as follows: oral cavity, RR = 5.7 (95% CI = 2.8–11.9) and larynx, RR = 2.0 (95% CI = 0.9–4.7). The RRs were adjusted for design and smoking, as shown in Table 5.

To check for residual confounding, RRs for smoking, oral snuff, and alcohol (Tables 2, 4, and 5) were adjusted for age in 5-year categories, and RRs for snuff and alcohol (Tables 4 and 5) were also adjusted for duration of smoking. This, however, left the results virtually unchanged. In addition, adjustments for dietary intake of calories, protein, fat, carbohydrates, fibers, and vitamins and for indicators of oral hygiene had little or no impact on these results.

DISCUSSION

The possibility of bias due to identification of cases and selection of referents is important in any case–referent study. To avoid such bias in the current study, we made efforts to identify all incident cases of head and neck cancer that occurred during the study period in a population defined by age, gender, and residence. This was facilitated by close cooperation with the clinicians involved and by the availability of population-based cancer registries. In addition, the referents were selected from continuously updated registers of the base population for the purpose of obtaining a representative sample of the person-time that generated the cases.

The interviews were completed by 90% of the cases identified and by 85% of the referents selected. Thus, even a substantial difference in exposure between those interviewed and those not interviewed would only have changed our results modestly. To avoid differential misclassification, the interviewers were trained to ask the questions in such a way that any impact of the disease on the answers would be minimized. However, for medical reasons, there were differences in the interviews. The cases were mostly interviewed at the hospital and the referents were usually interviewed in their homes. The cases were interviewed about 1 month after diagnosis but had experienced symptoms for some time prior to diagnosis. Some cases could have reduced (or increased) their tobacco or alcohol consumption due to such symptoms. To avoid this source of bias, exposure information for cases and referents did not include smoking and oral snuff usage during the last year prior to the interview, and information was obtained on alcohol intake 5 years prior to the interview. However, smokers who have reduced their smoking tend to underreport their past smoking.[13] Thus, if our cases had reduced their smoking due to symptoms of disease, smoking cases could have underestimated the number of cigarettes they smoked per day in the past. This would result in some underestimation of the effect of mean intensity of smoking in the current study. Underreporting of alcohol intake is another possibility. Patients with a serious disease (our cases) could be less likely to underreport their alcohol intake than healthy subjects (our referents). If exposed referents were classified as unexposed, the effect of alcohol intake would be overestimated. If highly exposed referents were classified as moderately exposed, the effect of a high alcohol intake would also be overestimated, but the effect of moderate alcohol intake would be underestimated.

Tobacco smoking has previously been shown to increase the risk of several cancers, including squamous cell carcinoma of the head and neck. We found a fourfold increased risk for ever-users of smoking tobacco (RR = 4.0, 95% CI = 2.8–5.7) for all sites. This was well in accordance with the results of other studies.[14–17] Mean intensity of smoking had little or no impact, but the risk increased with the duration of smoking. Similarly, Rothman et al. found only a minor difference in risk according to mean intensity, whereas Brugere et al. found a strong correlation between intensity and risk.[17,18] However, whether the intensity indicated is the mean intensity or current intensity is unclear. In results similar to those of our study, Blot et al. found a smaller difference in risk regarding intensity of smoking as compared with duration of the habit. Their risk estimates were generally lower than ours.[14,18] Bundgaard et al. found that the risk of oral

TABLE 4
Oral Snuff Usage and Relative Risk of Head and Neck Cancer in Swedish Men Ages 40–79 Years

			Relative risk (95% confidence interval) adjusted for	
Oral snuff usage	No. of cases	No. of referents	Design[a]	Design[a] + alcohol[b] and smoking[c]
Never used	462	550	1.0	1.0
Ever used	83	91	1.1 (0.8–1.5)	1.1 (0.7–1.5)
Current users	43	50	1.0 (0.7–1.6)	1.0 (0.6–1.6)
Ex-users	40	41	1.2 (0.8–1.9)	1.2 (0.7–1.9)
Age at start				
<25 yrs	39	43	1.1 (0.7–1.7)	1.0 (0.6–1.6)
≥25 yrs	44	48	1.1 (0.7–1.7)	1.1 (0.7–1.8)
Duration of usage				
<30 yrs	52	59	1.1 (0.8–1.7)	1.0 (0.7–1.6)
≥30 yrs	31	32	1.1 (0.7–1.9)	1.1 (0.6–2.0)
Total consumption				
<125 kg	57	63	1.1 (0.8–1.7)	1.0 (0.7–1.6)
≥125 kg	26	28	1.1 (0.6–1.9)	1.1 (0.6–2.0)
Intensity of usage[d]				
≤50 g/week	45	57	1.0 (0.6–1.4)	0.8 (0.5–1.3)
>50 g/week	38	34	1.4 (0.9–2.3)	1.6 (0.9–2.6)

[a] Age (40–54, 55–64, 65–79 yrs) and region (Stockholm and the South Sweden healthcare area).
[b] Four categories (<10, 10–19, 20–49, ≥50 g alcohol/day).
[c] Three categories (never smokers, ex-smokers, current smokers).
[d] Total consumption divided by duration of usage (g per week).

TABLE 5
Oral Snuff Usage and Relative Risk of Head and Neck Cancer in Swedish Men Ages 40–79 Years by Site

	Oral cavity		Larynx		Esophagus		Pharynx	
Oral snuff usage	Cases/referents	RR[a]	Cases/referents	RR[a]	Cases/referents	RR[a]	Cases/referents	RR[a]
Never used	103/550	1.0	133/550	1.0	103/550	1.0	123/550	1.0
Ever used	25/91	1.4 (0.8–2.4)	24/91	0.9 (0.5–1.5)	19/91	1.2 (0.7–2.2)	15/91	0.7 (0.4–1.3)
Current users	10/50	1.0 (0.5–2.2)	15/50	1.0 (0.5–1.9)	10/50	1.1 (0.5–2.4)	8/50	0.7 (0.3–1.5)
Ex-users	15/41	1.8 (0.9–3.7)	9/41	0.8 (0.4–1.7)	9/41	1.3 (0.6–3.1)	7/41	0.8 (0.3–1.9)

[a] Relative risk (RR) (95% confidence intervals) are adjusted for age (40–54, 55–64, 65–79 yrs), region (Stockholm and the South Sweden healthcare area), smoking (never smokers, ex-smokers, current smokers), and alcohol intake (<10, 10–19, 20–49, ≥50 g alcohol/day).

cancer increased with current daily consumption of smoking tobacco, but also with lifetime consumption.[15] Tuyns et al., however, found that the risk increased with mean intensity.[19] For supraglottic cancer they found a RR of 2.8 (95% CI = 1.2–6.8) for a mean consumption of 1–7 cigarettes per day and a RR of 24.0 (95% CI = 11.8–48.7) for a mean consumption of more than 26 cigarettes per day. We found a tendency towards a higher RR for deep inhaling of tobacco smoke. This was also reported by Tuyns et al., but only for glottic cancer.[19] It is known that the risk of developing cancer of the head and neck decreases after smoking cessation. Blot et al. and Tuyns et al. found no excess risk after 10 years,[14,19] whereas Spitz et al. found no excess risk later than 15 years after cessation of smoking.[20] We found a gradual decrease in risk up to 20 years after smoking cessation in our study. Some differences were found in the magnitude of the effect for different subsites. This was also in accordance with previous results.[18,19] However, the number of cases in each subsite was small, and the results should therefore be interpreted with caution.

Alcohol intake may increase the risk of head and neck cancer, according to previous studies.[2–4,21–24] Even though alcohol per se is not mutagenic, possible mechanisms for alcohol-related carcinogenesis have

TABLE 6
Alcohol Intake and Relative Risk of Head and Neck Cancer in Swedish Men Ages 40–79 Years

Alcohol intake	No. of cases	No. of referents	Relative risk (95% confidence interval) adjusted for: Design[a]	Relative risk (95% confidence interval) adjusted for: Design[a] – smoking[b]
<10 g/day	185	363	1.0	1.0
10–19 g/day	117	156	1.6 (1.2–2.1)	1.3 (1.0–1.8)
20–49 g/day	171	101	3.8 (2.8–5.2)	2.7 (1.9–3.8)
≥50 g/day	72	21	8.4 (4.9–14.3)	5.5 (3.1–9.6)

[a] Age (40–54, 55–64, 65–79 yrs) and region (Stockholm and the South Sweden healthcare area).
[b] Three categories (never smokers, ex-smokers, current smokers).

TABLE 7
Smoking, Alcohol Intake, and Relative Risk of Head and Neck Cancer in Swedish Men Ages 40–79 Years

Smoking	Relative risk (95% confidence interval) No. of cases/no. of referents Alcohol intake: ≥20 g/day	10–19 g/day	<10 g/day
Current smokers	22.1 (13.0–37.8)	10.4 (5.9–18.3)	6.3 (3.7–10.5)
	196/62	84/51	105/101
Ex-smokers	5.4 (2.8–10.2)	2.2 (1.2–4.1)	2.4 (1.4–4.1)
	34/40	26/68	56/126
Never smoked	4.2 (1.8–9.7)	1.2 (0.5–3.1)	1.0
	13/20	7/37	24/136

Relative risks are adjusted for age (40–54, 55–64, 65–75 yrs) and region (Stockholm and the South Sweden healthcare area).

been discussed by Kato and Nomura.[25] In our study, RR = 5.5 (95% CI = 3.1–9.6) for consumption of more than 50 grams per day, compared with less than 10 grams per day, after adjustment for smoking. A dose-dependent increased risk was found for tumors in the oral cavity, pharynx, and esophagus. These results seemed to be in accordance with other studies.[2,3,26–28] Even though not completely comparable, the magnitude of RRs in our study regarding alcohol consumption were similar to those of other studies. We found different RRs for different subsites of the head and neck. This is also known from others. No significant increased risk was found for tumors in the larynx, even at the highest dose level, suggesting a local effect of alcohol on the mucosa of the upper digestive tract. In this study, supraglottic cancer was not analyzed separately, as the patients in Sweden with supraglottic cancer represent only about 20% of all patients with laryngeal cancer. Others have found an increased risk for supraglottic tumors of the larynx from alcohol consumption.[3,29] Modest consumption of alcohol only had a minor impact on the risk of head and neck cancer. Franchesi et al. got the same result in their study.[2] Hedberg et al. found a significant increase of laryngeal carcinoma among alcoholics as measured by the Michigan alcoholism screening test, even after adjustment for cigarette smoking.[29] We did not classify our patients as alcoholics or nonalcoholics.

Notable is the almost multiplicative effect of combined high exposure to both tobacco smoking and alcohol, with an RR of 22.1 (95% CI = 12.9–37.8). This result has also been found by others.[3,14,15,30,31] Maier et al., for example, found that heavy smoking and drinking together increased the risk 146 times, and Bundegaard et al. found a multiplicative effect (with RR = 80) for more than 20 grams tobacco smoked and more than 5 drinks per day.[3,15] The mechanism behind the pathogenesis is largely unknown. However, there is circumstantial evidence for a genetic link to DNA repair. An increase in numeric and structural chromosomal rearrangements in the normal mucosa of smokers compared with nonsmokers has been recorded.[32] A defect in DNA repair might explain the impact of alcohol on cancer induced by tobacco smoking. On the molecular level, it has been shown that the frequency of p53 mutations among patients with squamous cell carcinoma of the head and neck are higher in smokers than in nonsmokers and even higher in smokers who also drink alcohol.[33] The magnitude of the RR associated with tobacco smoking and alcohol consumption varies among different studies. This may partly be due to differences in the consumption patterns in different parts of the world. We did not investigate the impact of different kinds of smoking tobacco, as the vast majority of smokers in Sweden smoke blond tobacco (dark tobacco is used by less than 1%

of the smoking population). We also did not categorize exposure according to different types of alcoholic beverages, as there is as yet no convincing evidence that nonethanolic ingredients in alcoholic beverages are of any importance in the etiology of head and neck cancer.[2,4]

Of special interest to the Nordic countries is "Swedish" oral snuff. It is a moist, nonfermented tobacco, mainly produced from dark Virginia tobacco mixed with Kentucky tobacco. It is a special Scandinavian product used mainly in Sweden and to a lesser extent in the other Nordic countries. Outside this geographic area this snuff is virtually not used at all. It is sometimes said that 15% of all males in Sweden use or have used Swedish oral snuff. In our material, 14% of the referents and 15% of the cases had used or were current users of Swedish oral snuff. The consumption is highest among males and the habit is most common in the North of Sweden. This geographic area is a low incidence area for head and neck cancers. In the areas with the highest incidence of cancer of the head and neck (the urban areas of Stockholm, Gothenburg, and Malmö), the consumption of oral snuff is lower. In comparison with countries where oral snuff is seldom used, Sweden has a much lower incidence of head and neck cancer, especially cancer of the buccal mucosa and gingiva.[1] Within the European Union, a discussion is taking place over the role of oral snuff in the etiology of cancer with special concern for cancer of the head and neck. The concern is especially important, as this type of oral snuff is believed to be widely used among male teenagers and it is often being regarded as an alternative to cigarette smoking. Oral snuff contains *N*-nitrosamines with carcinogenic potential. Reports from the U.S. have indicated an increased risk of oral cancer associated with the use of oral snuff,[6,7] and the International Agency of Research on Cancer has concluded that nonsmoking tobacco is hazardous.[34] The prohibition of oral snuff by the European Union member nations has been urged. Sweden has so far been an exception to this prohibition. In our study, relative risks were usually close to RR = 1. Age at start, total number of years of use, and total amount used in a lifetime had little or no impact on RR. A high intensity of usage (>50 grams/week) was associated with moderately, but not significantly, elevated risks: RR = 1.7 (95% CI = 0.8–3.9) for cancer of the oral cavity and RR = 1.9 (95% CI = 0.8–3.9) for cancer of the esophagus. The snuff is known to produce ulceration at the place of application on the gum under the upper lip. Also, white lesions often appear at the place of application. There is no clinical evidence that these lesions transform into malignancies, and the mucous tissue normalizes after cessation of snuff dipping.[8] On the contrary, as mentioned before, cancers of the gingiva or buccal mucosa are very rare, with only 14 cases a year on average in the Stockholm area (1990–1993). Of these, none were located inside the upper lip. The difference in results between the studies by Winn et al. and ours might be related to differences in study techniques.[6,7] The studies by Winn et al. involved referents selected from among patients admitted to hospital for reasons other than cancer. These patients do not necessarily represent the true use of oral snuff in the study base. Also, no consideration of chronic iron deficiency anemia was taken, although it is known that chronic anemia among women can produce squamous cell carcinoma of the upper gastrointestinal tract. The fact that different types of oral snuff contain different amounts of carcinogenic agents, due to both the ingredients used and the production process,[34] is also a plausible explanation for the different results. It is noteworthy that the RR (47.5) for the use of oral snuff found by Winn et al. was based on small numbers of individuals. Before forming public health recommendations or regulations, the RR for squamous cell carcinoma of the head and neck associated with Swedish oral snuff compared with tobacco smoking, as well as the possibility of other yet unknown health risks, has to be considered.

In conclusion, we confirm others' findings of a dose-dependent excess risk of cancer of the head and neck from tobacco smoking and alcohol consumption among Swedish males. Moderate alcohol intake had little or no effect among nonsmokers. No significantly increased RR was found for the use of Swedish oral snuff.

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