ORIGINAL ARTICLE

No association between moist oral snuff (snus) use and oral cancer: pooled analysis of nine prospective observational studies

MARZIEH ARAGHI[1] , MARIA ROSARIA GALANTI[1,2], MICHAEL LUNDBERG[1],
ZHIWEI LIU[3], WEIMIN YE[3], ANTON LAGER[1,2], GUNNAR ENGSTRÖM[4],
LARS ALFREDSSON[5], ANDERS KNUTSSON[6], MARGARETA NORBERG[7],
PATRIK WENNBERG[8], YLVA TROLLE LAGERROS[9,10], RINO BELLOCCO[3,11],
NANCY L. PEDERSEN[3], PER-OLOF ÖSTERGREN[12] & CECILIA MAGNUSSON[1,2]

[1]Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden, [2]Centre for Epidemiology and Community Medicine, Stockholm Health Care District, Sweden, [3]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Sweden, [4]Department of Clinical Sciences, Lund University, Sweden, [5]Institute of Environmental Medicine, Karolinska Institutet, Sweden, [6]Department of Health Sciences, Mid Sweden University, Sweden, [7]Department of Public Health and Clinical Medicine, Umeå University, Sweden, [8]Division of Family Medicine, Umeå University, Sweden, [9]Clinical Epidemiology Unit, Karolinska Institutet, Sweden, [10]Clinic of Endocrinology, Metabolism and Diabetes, Karolinska University Hospital Huddinge, Sweden, [11]Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milan, Italy, and [12]Social Medicine and Global Health, Lund University, Sweden

Abstract

Aims: Worldwide, smokeless-tobacco use is a major risk factor for oral cancer. Evidence regarding the particular association between Swedish snus use and oral cancer is, however, less clear. We used pooled individual data from the Swedish Collaboration on Health Effects of Snus Use to assess the association between snus use and oral cancer. *Methods:* A total of 418,369 male participants from nine cohort studies were followed up for oral cancer incidence through linkage to health registers. We used shared frailty models with random effects at the study level, to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) adjusted for confounding factors. *Results:* During 9,201,647 person-years of observation, 628 men developed oral cancer. Compared to never-snus use, ever-snus use was not associated with oral cancer (adjusted HR 0.90, 95% CI: 0.74, 1.09). There were no clear trends in risk with duration or intensity of snus use, although lower intensity use ($\leqslant$ 4 cans/week) was associated with a reduced risk (HR 0.65, 95% CI: 0.45, 0.94). Snus use was not associated with oral cancer among never smokers (HR 0.87, 95% CI: 0.57, 1.32). **Conclusions: Swedish snus use does not appear to be implicated in the development of oral cancer in men.**

Keywords: Oral cancer, incidence, smokeless tobacco, snus

Background

In 2012, 529,500 new cases of cancers of the oral cavity and pharynx, and more than 300,000 deaths were reported worldwide [1]. Oral cancers are predominantly squamous cell carcinomas of the lip or oral cavity. Its incidence varies greatly worldwide, with low rates in most Western countries while being among the most common cancers on the Indian subcontinent and in other parts of Asia [1]. Tobacco and alcohol consumption and human papillomavirus (HPV)-infections are established risk factors for oral cancer [2].

Smokeless tobacco is not burned and can be used orally or nasally. Oral smokeless-tobacco products are sucked or chewed. Snuff is a general term for finely cut or powdered, sometimes flavoured tobacco, which can be prepared as moist or dry snuff (this

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latter can be inhaled through nasal passages) [3]. Smokeless-tobacco products contain nicotine and other alkaloids in addition to carcinogens such as nitrosamines, nitrosoamino acids, aldehydes and metals, but in varying doses depending, for example, on manufacturing methods and brands [3, 4]. Globally, a wide variety of different smokeless-tobacco products are used. Chewing tobacco is common throughout much of Southeast Asia and the Western Pacific, while in Sweden moist oral snuff, also known as snus, is the main product used [3]. Because of this variation, the global interpretation of epidemiological studies on health effects of smokeless tobacco use is complicated.

Results from four meta-analyses [3, 5–7] indicates that any type of smokeless tobacco (chewing or snuff) is significantly associated with an increased risk of oral cancer in the USA and South Asia. The International Agency for Research on Cancer (IARC), in 2007, hence concluded that there is strong evidence that smokeless tobacco causes cancer of the oral cavity [8]. The relationship between use of the Swedish snus and oral cancer is, however, less clear [9–15].

In 2018, 18% of Swedish men and 4% of Swedish women and 25% of Norwegian men and 14% of Norwegian women, were daily snus users [16, 17]. Snus use has been proposed as a smoking cessation aid, thus, it is important to fully understand the contribution of snus use to cancer incidence. The Swedish Collaboration on Health Effects of Snus Use (SCHESU) consists of a group of Swedish investigators, who have conducted prospective studies where data on snus use has been collected. The SCHESU has previously investigated the impact of snus use on multiple health outcomes such as pancreatic cancer [18], colorectal cancer [19], diabetes [20] and Parkinson's disease [21]. The present SCHESU involves data from nine Swedish cohort studies [9, 22–29], of which only one [9] had published data on snus use and oral cancer. We here take advantage of this large pooling project to investigate the impact of snus use on oral-cancer risk.

Materials and method

Contributing studies and data collection

We used data from nine prospective cohort studies, including participants of varying ages, recruited at different time periods from diverse geographic regions across Sweden. Exclusion criteria were age less than 18 years, missing information on body mass index (BMI) or tobacco, or being diagnosed with oral cancer, or death prior to study enrolment. Of the included studies, five were population-based [22, 23, 26–28], two were occupational cohorts [9, 29], one included participants in a charity-walk [24], and one was a twin study [25]. The cohorts are described in detail in Table I. Details on study design and data collection procedures of the individual studies have been reported elsewhere [9, 22–29]. Since snus use is rare in women, the study was restricted to men [16].

Information on tobacco use was collected at baseline using self-administered questionnaires in seven studies [22–24, 26–29] and by a structured phone interview and personal interviews by nurses in two studies [9, 25]. All studies contributed information on current snus use and seven [9, 23–25, 27–29] on former snus use while amount and duration of snus use was available from seven [9, 22–25, 28, 29] and six studies [9, 23–25, 28, 29], respectively. Detailed information on snus use assessment across studies has been summarized in Table II. Information on height and weight, whether it was self-reported or measured by health professionals, was collected in all studies. Moreover, information on educational level and alcohol consumption was available and retrieved from all studies, except one [9]. Each cohort member contributed person-time from the date of entering into the study until the date of oral cancer diagnosis, death, or the end of the study, whichever came first. The Swedish National Cancer Register, established in 1958 and shown to be 98% complete, has coded malignant tumours according to the seventh revision of International Classification of Diseases (ICD7) [30]. In this study, we used the ICD7 codes 140, 141, 143 and 144 to identify incident cases of oral cancer (not including cancers of the salivary glands, pharynx, or larynx). Linkages were performed using the personal identity, a unique national identifier assigned to all Swedish residents. The specific studies were approved by their respective regional ethical vetting boards, and approval for the pooling project was granted by the Stockholm Regional Ethical Review Board (registration number 2009/971-31/3).

Statistical analyses

Smoking and snus use were categorized into never, former and current use (where non-current snus use was treated as never-use in the studies that did not have information on former snus use). These data were collected at baseline and no follow-up data on tobacco-use habits were available. Snus use (excluding former use) was further, where possible (see also Table II), categorized according to amount consumed per week ($\leq$ 4 cans, 5–6 cans, $\geq$ 7 cans) and duration ($\leq$ 4 years, 5–9 years, 10–14 years, 15-19 years, $\geq$ 20 years) of use. Such information for smoking status

Table I. Baseline characteristics of study participants in the Swedish Collaboration of Health Effects of Snus Use.

Study	Population	Data collection	Period of recruitment	Current snus users at baseline (%)	Last follow-up with register data	Male participants (n)	Person years of follow-up (n)	Mean age at recruitment (years)	Cases (n)
Construction Worker Cohort (CWC) [9]	Construction workers, national	Questionnaire	1978–1993	26	2013	273,604	7,696,573	34	475
Malmö diet and Cancer Study (MDCS) [21]	Population-based, Malmö City	Questionnaire	1991–1996	7	2013	11,208	193,165	59	47
Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) [22]	Population-based, Norrbotten and Västerbotten Counties	Questionnaire	1986–2004	23	2008	4472	55,843	49	3
National March Cohort (NMC) [23]	Participants in a charity walk, national	Questionnaire	1997	10	2010	13,289	168,374	53	12
Screening Across the Lifespan Twin Study (SALT) [24]	Twins born in Sweden between 1926,1958, national	Structured telephone interview	1998–2002	15	2010	17,909	173,595	56	41
Scania Public Health Cohort (Scania_PHC) [25]	Population-based, Scania County	Questionnaire	1999	20	2008	5835	52,783	48	4
Stockholm Public Health Cohort (Sthlm_PHC) [26]	Population-based, Stockholm County	Questionnaire	2002–2010	18	2011	37,780	180,018	49	8
Västerbotten Intervention Programme (VIP) [27]	Population-based, Västerbotten County	Questionnaire	1992–2013	27	2013	47,172	582,232	47	36
Work, Lipids and Fibrinogen Study (WOLF) [28]	Employees, Västernorrland, Jämtland, and Stockholm Counties	Questionnaire	1992–1997	23	2009	7100	99,064	42	2
All studies			1978–2013	24	2008–2013	418,369	9,201,647	40	628

Table II. Snus habit assessment across included cohorts.

	Construction Worker Cohort (CWC) [9]	Malmö diet and Cancer Study (MDCS) [21]	Determinants in Cardiovascular Disease (MONICA) [22]	National March Cohort (NMC) [23]	Screening Across the Lifespan Twin Study (SALT) [24]	Scania Public Health Cohort (Scania_PHC) [25]	Stockholm Public Health Cohort (Sthlm_PHC) [26]w	Västerbotten Intervention Programme (VIP) [27]	Work, Lipids and Fibrinogen Study (WOLF) [28]
Information at baseline									
Current snus use	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
If yes, please record the exact question asked	'Have you tried snus? "yes" or "no"' At 'what age?. . . . years of age' 'For how many years did you use snus?'	'Do you use snus? "yes" or "no"' 'How many packages of snus do you consume every week?'	'Do you use snus? "yes" or "no"' '. . .packs per week'	'Have you taken snuff regularly (at least once a week during more than six months)? "yes" or "no"'	'Do you use snus regularly and/or occasionally? "yes" or "no"'	'Do you use snus? "yes" or "no"'	'Do you currently use snus? "yes" or "no"'	'Have you ever used snus? "Yes, I use snus, . . . box per week"'	'Are you a current snuff user? "yes" or "no"'
Information about start-point of snus use	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes
If yes, please record the exact question asked	At 'what age?. . . . years of age'	-	'For how many years have you been using snus?'	'How old were you when you began snus use regularly'	'How old were you when you first start using snus?'			'Age of starting of snus. . .'	'Years of snus use'
Does 'Ever used' defined as current plus former use	Yes	Only current	Yes	Yes	Yes	Only current	Yes	Yes	Yes
Do any of the studies distinguish between daily and occasional use of snus use?	No	No	No	No	Yes	No	No	No	No
Former snus use	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes
If yes, define how former use was defined	'Not use of any tobacco 5 or more years prior to data of baseline data collection'	-	'I used to but not now'	'Tins per week during different ages in life'	'Not use snus currently'		'Not current users'	'I used to use snus'	'I am not current snus user'
Average amount of snus use	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
If yes, please record the exact question(s) asked	'Snus use in grams per day. . .'	'Pack of snus per week. . .'	'How much snus do you use per week?'	'Number of tins per week'	'Number of packs per week'			'Yes, I use snus, . . .box per week'	'number of packs per week'

was not available. Never-users of snus constituted the reference group.

Shared frailty models (gamma distributed) with random effects at the study level were used to estimate hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) of oral cancer in relation to tobacco use, using time from baseline to end of follow-up as the time scale. The shared frailty model is an extension of the Cox proportional hazards model and accounts for between study correlation by incorporating shared random effects [31]. Participants were followed from baseline until index date of oral cancer diagnosis, date of death, or end of follow-up, whichever came first. In addition to the inherent adjustment for age, all models were adjusted for BMI, calculated as body weight in (kilograms) by the height (in metres) squared and used as a continuous variable, and smoking (where possible, categorized as never, former or current smoking) [32]. The underlying assumption of proportional hazards was tested using Schoenfeld's global test. Stata statistical software (Version 13.1, Stata Corporation, and College Station, TX, USA) was used for all analyses.

We conducted a sensitivity analysis according to the following scenarios: (a) excluding the Construction Workers Cohort, since this cohort constituted 61.5% of the total sample size; (b) restriction to never smokers, as an alternative approach to control for the potential confounding effect of tobacco smoking; (c) adjusting for alcohol consumption ((grams/week), low, medium and high (in tertiles)) [33] and educational level (≤ 9 (compulsory), 10–11 (secondary or high school) and ≥ 12 years (university or above) of education) [34] in the subset of studies where this information was available; (d) excluding cohorts [22, 26] with no available information on former snus use, thus enabling correct classification of former snus use.

Results

After exclusions of 14,625 subjects, including those being under 18 years old ($n = 6697$), missing information on BMI ($n = 2125$), missing information on tobacco variables ($n = 5705$), having a prior history of colorectal cancer ($n = 87$), or a death date before entry ($n = 11$), 418,369 men constituted the analytical sample yielding 9,201,647 person-years of observation (Figure 1). Characteristics of the participants from the various cohorts included in the collaboration are shown in Table I. Period of recruitment and duration of follow-up ranged from 1978 to 2013 and from 5 to 35 years, respectively. The mean age at entry was 40 years (range 18–99). A total of 628 incident cases of oral cancer occurred during follow-up.
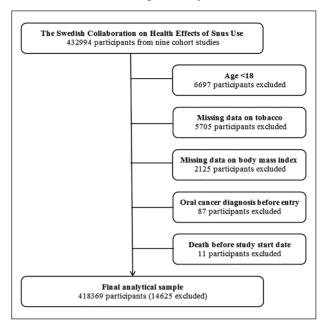

Figure 1. Derivation of the analytical sample.

At time of entry, 30% of study participants had ever used snus.

The main analyses including the full analytical sample, adjusting for smoking status and BMI did not support any association between ever-snus use and oral cancer (HR 0.90, 95% CI: 0.74, 1.09, compares ever- to never-snus users). The current users of snus had a statistically non-significant 21% lower risk of oral cancer than the never users (HR 0.79, 95% CI: 0.63, 1.00). Additionally, there was no clear trend with duration; while lower intensity use (≤ 4 cans/week) was associated with a reduced risk (HR 0.65, 95% CI: 0.45, 0.94) (Table III).

Sensitivity analyses

Table IV presents the results from sensitivity analyses. Excluding the Construction Workers Cohort, the HR for oral cancer in current snus users was 0.79 (95% CI: 0.46, 1.37) after adjustment for BMI and smoking status. Snus use was furthermore not associated with oral-cancer risk in analysis restricted to never smokers (HR 0.93, 95% CI: 0.59, 1.44). The results from other sensitivity analyses scenarios including adjustment for educational level and alcohol consumption, and excluding cohorts with no information on former snus use were generally similar to the overall findings.

Discussion

This large pooling project, including nine prospective cohort studies and 628 incident cases, does not

support the notion that use of Swedish snus increases the risk for oral cancer among men. Indeed, current users had a seemingly reduced such risk which, however, is difficult to interpret in light of lacking dose-response relationships and biological rationale. Our results contrast convincing evidence of an increased risk of oral cancer with use of other types of oral smokeless tobacco, including those commonly used in the USA, India, Pakistan and Sudan, but are in line with most studies from the Nordic Countries.

Table III. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) for oral cancer in relation to snus use (*n* = 418,369).

Use of snus at baseline	Number of cases	HR[a]	95% CI	HR[b]	95% CI
Never-users[c]	485	Ref.		Ref.	
Ever-users	143	0.89	(0.73, 1.07)	0.90	(0.74, 1.09)
Former users	51	1.20	(0.89, 1.60)	1.20	(0.89, 1.61)
Current users	92	0.77	(0.62, 0.97)	0.79	(0.63, 1.00)
Amount (cans/week)[d]					
≤ 4	31	0.71	(0.49, 1.02)	0.65	(0.45, 0.94)
5–6	29	0.77	(0.53, 1.13)	0.83	(0.56, 1.21)
≥ 7	30	0.83	(0.57, 1.22)	0.97	(0.66, 1.41)
Duration (years)[e]					
≤ 4	13	0.64	(0.36, 1.11)	0.67	(0.38, 1.17)
5–9	20	0.80	(0.50, 1.26)	0.86	(0.54, 1.35)
10–14	19	0.83	(0.52, 1.32)	0.86	(0.54, 1.37)
15–19	8	0.57	(0.28, 1.16)	0.60	(0.29, 1.21)
≥ 20	30	0.99	(0.68, 1.44)	0.97	(0.67, 1.42)

[a] Hazard ratio estimates were adjusted for attained age.
[b]Hazard ratio estimates were adjusted for attained age, smoking (never, former and current) and body mass index.
[c]Never users of snus.
[d]Among current snus users only. The information was only available for following studies: CWC, MDCS, MONICA, NMC, SALT, VIP, and WOLF.
[e]Among current snus users only. The information was only available for following studies: CWC, MONICA, NMC, SALT, VIP, and WOLF.

In a previous report from the Swedish Construction Workers Cohort [9] from 279,897 male in 1978–1992 with follow-up until 2004 with 248 cases of oral cancer, snus users had a relative risk of oral cancer of 0.8 (95% CI: 0.4, 1.7) after restriction to never smokers. This result was replicated in the current study with complete follow-up until end of 2013 with total 475 cases of oral cancer during 35 years of follow-up (HR 1.0, 95% CI: 0.6, 1.7). In a cohort study by Boffetta and colleagues [10], snus use was not associated with oral cancer (RR 1.10, 95% CI: 0.50, 2.41) after adjusting for age and smoking. Similarly, two case-control studies by Rosenquist and colleagues [11] (odds ratio (OR) for ever-snus use 0.7, 95% CI: 0.3, 1.3) and Schildt and colleagues [12] (OR for current snus use 0.7, 95% CI: 0.4, 1.2) found no increased risk for development of oral cancer associated with the use of Swedish snus.

In contrast, results from an additional Swedish cohort [13] showed an elevated risk for ever daily use of snus compared to never daily use of snus controlling for smoking (HR 3.1, 95% CI: 1.5, 6.6) based on 11 exposed cases. Among never-smokers in the cohort, the HR for ever daily use of snus was 2.3 (95% CI: 0.7, 8.3) [13]. In a another small Swedish study [14] among men with snus-induced lesions, a relative risk of 2.3 (95% CI: 0.5, 6.7) was reported in relation to snus use, but none of the cancers had developed at the site of the lesions. In a case-control study [15], the OR for cancers of the oral cavity, pharynx and oesophagus combined in relation to current snus use was 1.0 (95% CI: 0.7, 1.6). In the subgroup of never-smokers, the OR for ever-users of snus was, however, 4.7 (95% CI: 1.6, 13.8).

The reason for the discrepancy between these findings is unknown, but all studies but the Construction Workers Cohort were based on small

Table IV. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) of oral cancer in relation to snus use from sensitivity analyses (*n* = 418,369).

Type of analysis	*n*	Use of snus at baseline				
		Ever users	Former users		Current users	
		HR[a] (95% CI)	*n*	HR[a] (95% CI)	*n*	HR[a] (95% CI)
Excluding Construction Workers Cohort	31	0.96 (0.63, 1.48)	15	1.27 (0.72, 2.26)	16	0.79 (0.46, 1.37)
Restriction to never smokers[b]	28	0.87 (0.57, 1.32)	3	0.58 (0.18, 1.83)	25	0.93 (0.59, 1.44)
Controlling for additional potential confounders[c]	31	0.95 (0.61, 1.49)	15	1.26 (0.70, 2.28)	16	0.78 (0.44, 1.38)
Excluding cohorts[d] with no information on former snus use	142	0.97 (0.79, 1.18)	51	1.26 (0.93, 1.71)	91	0.86 (0.67, 1.09)

[a]Adjusted for attained age, smoking (never, former and current) and body mass index.
[b]The reference is never users of any tobacco.
[c]Additional adjustment for alcohol consumption, and educational level, among the studies where this information was available (MONICA, NMC, SALT, Scania_PHC, Sthlm_PHC, VIP and WOLF).
[d]MDCS and Scania_PHC.

numbers. Furthermore, studies were concerned with different subsites of the head and neck cancers (e.g. oral cavity, nasopharynx/paranasal sinuses, oropharynx, hypopharynx and larynx). It is possible that snus use is associated with cancers of the hypopharynx and larynx, where saliva (and hence carcinogens from snus) tends to accumulate, but not with cancers of the oral cavity. Differential and insufficient control for confounding factors, in particularly of smoking, may also explain inconsistencies in study results. In fact, residual confounding by smoking may also explain the seemingly reduced risk among current snus users from our analysis including smokers. This is since dual smokers and snus users smoke less on average than exclusive smokers, and since we could only adjust for smoking status categorized as never, former or current. Our analysis restricted to never-smokers, supporting a null association, is less likely to be biased from confounding by smoking dose. This may be the reason behind the seemingly reduced risk among current smokers in our sample, while the analysis restricted to never-smokers, supporting a null association, is likely to have eliminated residual confounding by smoking dose.

The present study has several strengths, including its large sample size, and a diverse study population. Additionally, its prospective design minimizes recall and selection bias, often afflicting retrospective studies. In addition to control for confounding by smoking, with two approaches, that is multivariate modelling, and restriction of the study population to never-smokers – we had the opportunity to further control for educational level and alcohol, and again the main findings did not change. The study also has several limitations. The main limitation is that the information on smoking and snus use was self-reported and only assessed at baseline. This may produce biased estimates of the association between snus use and oral cancer as a result of measurement error (true effect of snus use cannot be retrieved due to behaviour changes during long-period follow-up). A recent Swedish study showed that 70% of snus users at baseline and 55% of smokers continued their tobacco use habit after 10 years, which indicates that using snus is a more stable habit than is smoking [35]. Moreover, snus was found to be the most stable form of tobacco use among a cohort of 3407 men and women over 13 years of follow-up [36]. We were unable to control for all potentially confounding factors, including for example, HPV infections and occupational exposures (e.g. wood dust or nickel) [2]. Finally, we could not address the association between snus use and oral cancer among women because of their low prevalence of use.

Our findings, from the largest sample to date, do not support a role of Swedish snus use in the development of oral cancer in men. Risk from Swedish snus is clearly less than from smokeless tobacco products used in North America and South Asia, but this does not imply that snus is harmless. As long as the knowledge of the health effects of long-term use of snus is limited, recommendation to use snus as smoking cessation support is questionable.

ORCID iD

Marzieh Araghi https://orcid.org/0000-0003-3896-6401

References

[1] Shield KD, Ferlay J, Jemal A, et al. The global incidence of lip, oral cavity, and pharyngeal cancers by subsite in 2012. *Ca-Cancer J Clin* 2017;67:51–64.
[2] Ram H, Sarkar J, Kumar H, et al. Oral cancer: Risk factors and molecular pathogenesis. *J Maxillofac Oral Surg* 2011;10:132–137.
[3] Boffetta P, Hecht S, Gray N, et al. Smokeless tobacco and cancer. *Lancet Oncol* 2008;9:667–675.
[4] Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). *Health Effects of Smokeless Tobacco Products*. European Commission, 2008.
[5] Lee PN and Hamling J. Systematic review of the relation between smokeless tobacco and cancer in Europe and North America. *BMC Med* 2009;7:36.
[6] Weitkunat R, Sanders E and Lee PN. Meta-analysis of the relation between European and American smokeless tobacco and oral cancer. *BMC Public Health* 2007;7:334.
[7] Gupta B and Johnson NW. Systematic review and meta-analysis of association of smokeless tobacco and of betel quid without tobacco with incidence of oral cancer in South Asia and the Pacific. *Plos One* 2014;9:e113385.
[8] IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Smokeless Tobacco and Some Tobacco-specific N-Nitrosamines. *Personal Habits and Indoor Combustions 89*, http://monographs.iarc.fr/ENG/Monographs/vol100E/mono100E-8.pdf (2007, accessed 30 December 2019).

[9]　Luo J, Ye W, Zendehdel K, et al. Oral use of Swedish moist snuff (snus) and risk for cancer of the mouth, lung, and pancreas in male construction workers: a retrospective cohort study. *Lancet* 2007;369:2015–2020.

[10]　Boffetta P, Aagnes B, Weiderpass E, et al. Smokeless tobacco use and risk of cancer of the pancreas and other organs. *Int J Cancer* 2005;114:992–995.

[11]　Rosenquist K, Wennerberg J, Schildt EB, et al. Use of Swedish moist snuff, smoking and alcohol consumption in the aetiology of oral and oropharyngeal squamous cell carcinoma. A population-based case-control study in southern Sweden. *Acta Oto-Laryngol* 2005;25:991–998.

[12]　Schildt EB, Eriksson M, Hardell L, et al. Oral snuff, smoking habits and alcohol consumption in relation to oral cancer in a Swedish case-control study. *Int J Cancer* 1998;77:341–346.

[13]　Roosaar A, Johansson ALV, Sandborgh-Englund G, et al. Cancer and mortality among users and nonusers of snus. *Int J Cancer* 2008;123:168–173.

[14]　Roosaar A, Johansson ALV, Sandborgh-Englund G, et al. A long-term follow-up study on the natural course of snus-induced lesions among Swedish snus users. *Int J Cancer* 2006;119:392–397.

[15]　Lewin F, Norell SE, Johansson H, 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;82:1367–1375.

[16]　Public Health Agency of Sweden. *Tobacco Habits*, https://www.folkhalsomyndigheten.se/livsvillkor-levnadsvanor/alkohol-narkotika-dopning-tobak-och-spel-andts/tobak/utvecklingen-av-bruket/bruk-av-cigaretter-snus-och-e-cigaretter-i-den-vuxna-befolkningen/ (2018, accessed 30 December 2019).

[17]　Statistics Norway. *Smoking habits*, https://www.ssb.no/en/statbank/list/royk (2018, accessed 30 December 2019).

[18]　Araghi M, Galanti MR, Lundberg M, et al. Use of moist oral snuff (snus) and pancreatic cancer: Pooled analysis of nine prospective observational studies. *Int J Cancer* 2017;141:687–693.

[19]　Araghi M, Galanti MR, Lundberg M, et al. Smokeless tobacco (snus) use and colorectal cancer incidence and survival: Results from nine pooled cohorts. *Scand J Public Healt* 2017;45:741–748.

[20]　Carlsson S, Andersson T, Araghi M, et al. Smokeless tobacco (snus) is associated with an increased risk of type 2 diabetes: Results from five pooled cohorts. *J Intern Med* 2017;281:398–406.

[21]　Yang F, Pedersen NL, Ye WM, et al. Moist smokeless tobacco (Snus) use and risk of Parkinson's disease. *Int J Epidemiol* 2017;46:872–880.

[22]　Manjer J, Carlsson S, Elmstahl S, et al. The Malmo Diet and Cancer Study: Representativity, cancer incidence and mortality in participants and non-participants. *Eur J Cancer Prev* 2001;10:489–499.

[23]　Eriksson M, Holmgren L, Janlert U, et al. Large improvements in major cardiovascular risk factors in the population of northern Sweden: The MONICA study 1986-2009. *J Intern Med* 2011;269:219–231.

[24]　Trolle Lagerros Y, Hantikainen E, Mariosa D, et al. The Swedish National March Cohort. *Int J Epidemiol* 2017;46:795–795e.

[25]　Pedersen NL, Lichtenstein P and Svedberg P. The Swedish Twin Registry in the third millennium. *Twin Res* 2002;5:427–432.

[26]　Carlsson F, Merlo J, Lindstrom M, et al. Representativity of a postal public health questionnaire survey in Sweden, with special reference to ethnic differences in participation. *Scand J Public Health* 2006;34:132–139.

[27]　Svensson AC, Fredlund P, Laflamme L, et al. Cohort profile: The Stockholm Public Health Cohort. *Int J Epidemiol* 2013;42:1263–1272.

[28]　Norberg M, Wall S, Boman K, et al. The Vasterbotten Intervention Programme: Background, design and implications. *Glob Health Action* 2010;3:1.

[29]　Alfredsson L, Hammar N, Fransson E, et al. Job strain and major risk factors for coronary heart disease among employed males and females in a Swedish study on work, lipids and fibrinogen. *Scand J Work Env Hea* 2002;28:238–248.

[30]　Barlow L, Westergren K, Holmberg L, et al. The completeness of the Swedish Cancer Register: A sample survey for year 1998. *Acta Oncol* 2009;48:27–33.

[31]　Therneau TM and Grambsch PM. *Modeling survival data. Extending the Cox Model*. New York: Springer-Verlag, 2000, p. 346.

[32]　Sadri G and Mahjub H. Tobacco smoking and oral cancer: a meta-analysis. *J Res Health Sci* 2007;7:18–23.

[33]　Goldstein BY, Chang SC, Hashibe M, et al. Alcohol consumption and cancers of the oral cavity and pharynx from 1988 to 2009: An update. *Eur J Cancer Prev* 2010;19:431–465.

[34]　Conway DI, Petticrew M, Marlborough H, et al. Socioeconomic inequalities and oral cancer risk: A systematic review and meta-analysis of case-control studies. *Int J Cancer* 2008;122:2811–2819.

[35]　Norberg M, Lundqvist G, Nilsson M, et al. Changing patterns of tobacco use in a middle-aged population: The role of snus, gender, age, and education. *Global Health Action* 2011;4:693–704.

[36]　Rodu B, Stegmayr B, Nasic S, et al. Evolving patterns of tobacco use in northern Sweden. *J Intern Med* 2003;253:660–665.