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Use of moist oral snuff (snus) and pancreatic cancer: Pooled analysis of nine prospective observational studies

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While smoking is a well-established risk factor for pancreatic cancer, the effect of smokeless tobacco is less well understood. We used pooled individual data from the Swedish Collaboration on Health Effects of Snus Use to assess the association between Swedish snus use and the risk of pancreatic cancer. A total of 424,152 male participants from nine cohort studies were followed up for risk of pancreatic cancer 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. During 9,276,054 person-years of observation, 1,447 men developed pancreatic cancer. Compared to never-snus use, current snus use was not associated with risk of pancreatic cancer (HR 0.96, 95% CI 0.83–1.11) after adjustment for smoking. Swedish snus use does not appear to be implicated in the development of pancreatic cancer in men. Tobacco smoke constituents other than nicotine or its metabolites may account for the relationship between smoking and pancreatic cancer.

Pancreatic cancer is one of the most lethal malignancies.[1] In the year 2012, in Europe, there were 78,700 new cases and 77,900 deaths.[2] Pancreatic cancer incidence rates are higher in the Nordic countries and Central Europe than in other parts of the world.[3] Although the etiology of pancreatic cancer remains poorly understood, cigarette smoking is a well-established and modifiable risk factor.[1] A meta-analysis of 82 studies demonstrated that current and former smoking was associated with a 74% and a 20% increased risk of pancreatic cancer, respectively.[4] The mechanism explaining the increased risk of pancreatic cancer with cigarette smoking is unclear, but a role of nicotine or its metabolites cannot be ruled out.[5]

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Smokeless tobacco yields lower exposure to tobacco carcinogens compared with smoking, because it does not undergo combustion, but delivers an equivalent dose of nicotine.[6] Smokeless tobacco products vary with respect to packaging, modality of use and known impact on cancer risks.[7] Snus is a moist tobacco for oral use that is common in Scandinavian countries, where its use is increasing rapidly among young people.[8] According to national public health surveys, about 18% of Swedish men and 27% of Norwegian young men are daily users.[9] Except Sweden, the sale of snus is currently banned in the European Union (EU).[10] Swedish snus is known to deliver lower levels of carcinogenic tobacco-specific nitrosamines (TSNA) than North American smokeless tobacco products.[7]

Evidence regarding smokeless tobacco use and pancreatic risk is inconsistent.[11–15] The International Agency for Research on Cancer (IARC) and European Community Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) on the health effects of smokeless tobacco, in 2007 and 2008, respectively, concluded that smokeless tobacco products are carcinogenic to humans, and the

What's new?

While smoking is a well-established risk factor for pancreatic cancer, the effect of smokeless tobacco is less well understood. Smokeless tobacco like snus yields lower exposure to tobacco carcinogens compared with smoking, because it does not undergo combustion, but delivers an equivalent dose of nicotine. Using pooled individual data from the Swedish Collaboration on Health Effects of Snus Use, here the authors show that Swedish snus use does not appear to be implicated in the development of pancreatic cancer in men. Tobacco smoke constituents other than nicotine or its metabolites may account for the relationship between smoking and pancreatic cancer.

pancreas has been identified as the main target organ.[11,12] A meta-analysis of six studies (including two Scandinavian studies of Swedish snus) by Boffetta and colleagues,[13] also demonstrated a moderate risk increase, which emanated from the two included studies on snus use.[13] Two recent meta-analyses[14,15] of mainly European and North American case–control studies, however, did not find any association.

Assessing the effects of smokeless tobacco products may provide insights into carcinogenic mechanisms of smoking. Similar associations as for smoking would make a role of carcinogens not associated with combustion more likely. Hence, studies of snus are relevant not only to inform users and public health policy about the health consequences of snus but also on the long-term safety of nicotine (often administered as nicotine replacement therapy or via e-cigarettes).

The Swedish Collaboration on Health Effects of Snus Use consists of a group of Swedish investigators, who have conducted prospective studies where data on snus use has been collected.[16] The collaboration involves data from nine Swedish cohort studies,[17–25] of which only one[17] had published data on snus use and pancreatic cancer. We here take advantage of this large pooling project to investigate the impact of snus use on pancreatic cancer risk.

Material and Methods

Contributing studies and data collection

We used data from nine prospective cohort studies, including participants of varying ages, recruited at different periods from diverse geographic regions across Sweden with information on both snus use and tobacco smoking. Exclusion criteria were pancreatic cancer before study enrolment, age <18 years or missing information on body mass index (BMI) (Fig. 1). Since snus use is rare in women;[9] the study was restricted to men. Details on study design and data collection procedures of the individual studies have been reported elsewhere.[17–25]

Each cohort study provided individual participant data, and data harmonization and analyses were implemented centrally. 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).

Pancreatic cancer cases were identified from the Swedish Cancer Register[26] established in 1958.[26] Since the Swedish Cancer Register does not accept notifications from death certificates only, and therefore incompletely record pancreatic cancer because of their poor prognosis,[27,28] we complemented our case ascertainment with data from the Cause of Death Register. The Cause of Death Register covers all deaths in Sweden since 1961 and includes ICD-codes for the main and contributory causes of death.[29] Linkages were performed using the national registration number, a unique personal identifier assigned to all Swedish residents,[29] and pancreatic cancer cases were identified by the ICD-7 code 157 and ICD-10 code C25.

Information on tobacco use was collected at baseline using self-administered questionnaires in eight studies[17–20,22–25] and by a structured telephone interview in one study.[21] All studies contributed information on current snus use and seven on former snus use[17,19–21,23–25] while amount and duration of snus use were available from seven[17–21,24,25] and five studies,[17–19,24,25] respectively. Covariates collected at baseline included body mass index (BMI),[30] alcohol intake,[31] physical activity level[32] and type 2 diabetes.[33]

Information on height and weight, whether it was self-reported[20–23] or measured by health professionals,[17–19,24,25] was collected in all studies. Information on alcohol consumption was retrieved from all studies, except one.[17] Physical activity data was collected from seven studies,[19–25] and diagnosis of type 2 diabetes were identified in five studies[18,20–24] using several sources including self-reported data, record-linkage to the National Patient Register[34] (ICD-9 code 250 and ICD-10 code E11 and E14) and Prescribed Drug Register (as antidiabetics, code A10 according the Anatomic Therapeutic Chemical classification system).[35]

Smoking and snus use was categorized into never, former and current users (where noncurrent snus use was treated as never use in the studies[18,22] that did not have information on former snus use). Current snus use was further categorized according to the amount consumed per week (<4 cans, 4–6 cans, ≥7 cans) and duration (<5 years, 5–<10 years, 10–<15 years, 15–<20 years, ≥20 years) of use. Such information for smoking status was not available. Never-users of snus constituted the reference group.

Each cohort member contributed person-time from the date of entering into the study until the date of pancreatic cancer diagnosis, death, or the end of the study, whichever came first. Shared frailty models with random effects at the

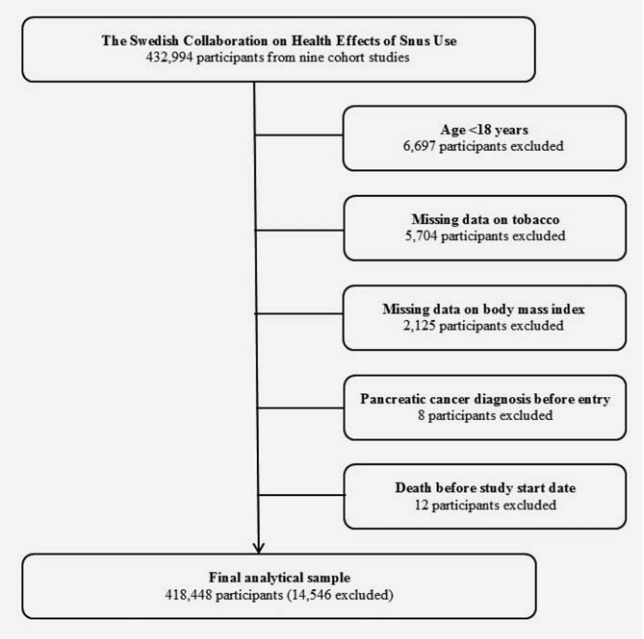

Figure 1. Derivation of the analytical sample.

study level were used to estimate hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) of pancreatic cancer in relation to tobacco use, using attained age (in years) as the time scale. The shared frailty model is an extension of the Cox proportional hazards model and accounts for within-study correlation by incorporating shared random effects. We tested for heterogeneity among included studies, using a Q-test and I^2 statistics.[36] In addition to the inherent adjustment for age, all models were adjusted for body mass index (BMI, kg/m^2), calculated as body weight (kilograms) by the height (meters) squared and used as a continuous variable and smoking (categorized as never, former or current smoking). Evaluation of the proportional hazards assumption with Schoenfeld's global test[37] revealed that smoking status variable did not satisfy the proportional hazards assumption. Modeling was therefore performed using an extended Cox regression analysis, with an inclusion of smoking as a time-varying covariate.

All tests were two-sided, and we considered $p < 0.05$ to be statistically significant. Stata statistical software (Version 13.0, Stata Corporation, and College Station, TX) was used for all analyses.

We conducted sensitivity analysis according to the following scenarios: (*i*) Using data from Cancer Register only. (*ii*) Excluding the Construction Workers Cohort, this dominates the results of our main analyses because of size. (*iii*) Adjusting for alcohol consumption (grams/week), physical activity ("<2 hrs of light activity per week," ">2 hrs of light activity per week," "1 to 2 hrs of at least moderate physical activity per week" and ">2 hrs of at least moderate physical activity per week") and type 2 diabetes (yes/no) in the subset of studies where this information was available.[18,20–24] (*iv*) Excluding cohorts[18,22] with no available information on former snus use, thus enabling correct classification of former snus use. (*v*) Restriction to never smokers, as an alternative approach to controlling for the potential confounding effect of tobacco smoking.

Results

Figure 1 shows the numbers of study participants meeting the inclusion criteria. Characteristics of the 418,448 men constituting our analytical sample, yielding 9,276,054 person-years of observation, are shown in Table 1. Period of recruitment and duration of follow-up ranged from 1978 to 2013 and from 5 to 35 years, respectively. Average age at entry was 40 years (range 18–99 years). A total of 1,423 incident cases of pancreatic cancer, including 424 solely identified from the Cause of Death Register, occurred during follow-up. At the time of entry, 30% of study participants had ever used snus.

Our main analyses, including the full analytical sample and adjusting for smoking status, did not support any relationship between snus use and pancreatic cancer risk (HR 0.93, 95% CI 0.82–1.06, comparing ever to never-snus users). Additionally, there was no indication that current snus use, regardless of its duration or intensity, affected the risk (Table 2). Study specific HRs of pancreatic cancer for current snus users as compared to never-snus users are shown in Figure 2. We observed a moderate degree of heterogeneity between studies (I^2 statistics 63%).

Sensitivity analysis

Table 3 presents the results from sensitivity analyses. The estimates did change when using data from Cancer Register only. Excluding the Construction Workers Cohort, the HR for pancreatic cancer in current snus users was 1.30 (95% CI 0.97–1.73) after adjustment for BMI and smoking status. In the subset of studies where further covariate information was available, additional adjustment for alcohol consumption, physical activity and interaction between alcohol consumption and smoking, yield the corresponding HR of 1.32 (95% CI 0.84–2.08), and a similar result was produced with adjustment for diabetes (data not shown). Lastly, when the analytical sample was restricted to never smokers, the adjusted HR of pancreatic cancer in current snus users was 1.07 (95% CI 0.77–1.50).

Discussion

Findings from this large pooling project, including nine prospective cohort studies and 1,423 incident cases, did not support any relationship between snus use and risk of pancreatic cancer in men regardless of timing, duration or intensity of use.

We judge prior evidence regarding the association between smokeless tobacco use and pancreatic cancer to be inconsistent.[11–15] This is in spite of conclusions from prior and well-recognized reviews, including the IARC Monograph

Table 1. Baseline characteristics of study participants in the Swedish Collaboration of Health Effects of Snus Use

Study	Study population	Data collection	Period recruitment	Male participants (*N*)	Person years of follow-up (*N*)	Mean age at recruitment (years)	Cases (*N*)	Current snus users (%)	Information available regarding snus use		
									Duration	Amount	Former use
Construction Worker Cohort (CWC)[17]	Construction workers, national	Questionnaire	1978–1993	273,604	7,699,364	34	1,025	26	Yes	Yes	Yes
Malmö diet and Cancer Study (MDCS)[18]	Population-based, Malmö City	Questionnaire	1991–1996	11,217	207,444	59	63	7	No	Yes	No
Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA)[19]	Population-based, Norrbotten and Västerbotten Counties	Questionnaire	1986–2004	4,474	57,109	48	14	23	Yes	Yes	Yes
National March Cohort (NMC)[20]	Participants in a charity walk, national	Questionnaire	1997	13,305	181,464	52	54	10	Yes	Yes	Yes
Screening Across the Lifespan Twin Study (SALT)[21]	Twins born in Sweden between 1926–1958, national	Structured telephone interview	1998–2002	17,923	174,124	56	85	15	Yes	Yes	Yes
Scania Public Health Cohort (Scania_PHC)[22]	Population-based, Scania County	Questionnaire	1999	5,837	54,647	48	3	20	No	No	No
Stockholm Public Health Cohort (Sthlm_PHC)[23]	Population-based, Stockholm County	Questionnaire	2002–2010	37,807	185,581	49	42	18	No	No	Yes
Västerbotten Intervention Programme (VIP)[24]	Population-based, Västerbotten County	Questionnaire	1992–2013	47,181	616,045	47	129	27	Yes	Yes	Yes
Work, Lipids and Fibrinogen Study (WOLF)[25]	Employees, Västernorrland, Jämtland, and Stockholm Counties	Questionnaire	1992–1997	7,100	100,276	42	8	23	Yes	Yes	Yes
All studies			1978–2013	418,448	9,276,054	40	1,423	24			

Table 2. Pooled hazard ratios and 95% confidence intervals for pancreatic cancer in relation to snus use

Use of snus at baseline	Number of cases	Hazard ratio[1]	95% Confidence interval
Never-users	1,103	Ref.	
Ever users	321	0.93	(0.82–1.06)
Former users	93	0.88	(0.71–1.10)
Current users	227	0.96	(0.83–1.11)
Amount (cans/week)[2]			
<4	91	0.87	(0.70–1.08)
4–6	83	1.16	(0.93–1.46)
≥7	48	0.87	(0.65–1.17)
Duration (years)[2]			
<5	27	0.82	(0.56–1.21)
5–<10	38	1.00	(0.72–1.39)
10–<15	41	0.99	(0.72–1.36)
15–<20	27	0.98	(0.67–1.44)
≥20	78	0.95	(0.75–1.19)

[1]All hazard ratio estimates were adjusted for attained age, smoking (never, former and current) and body mass index.
[2]Among current snus users only.

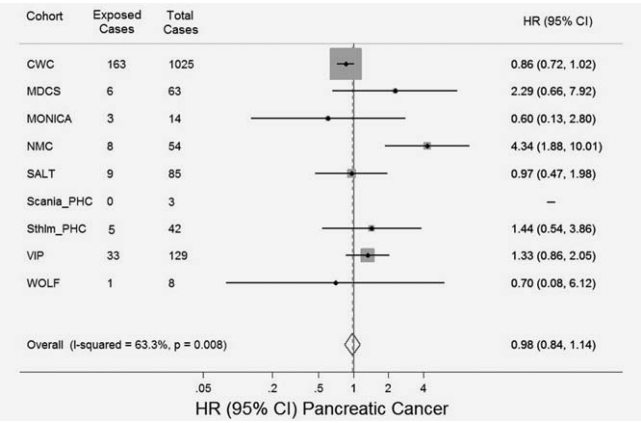

Figure 2. Study-specific hazard ratios (HR) and 95% confidence intervals (95% CI) of pancreatic cancer among current snus users versus never-snus users.

89,[11] an SCENIHR report[12] and a meta-analysis by Boffetta and colleagues.[13] IARC Monograph 89[11] based its review on four studies, including three from the US and one from Norway; a US cohort study[38] reporting a relative risk (RR) of 1.70 (95% CI 0.90–3.19) for ever users of smokeless tobacco after adjustment for smoking, a US case–control study[39] showing an association with chewing tobacco but not snuff, another US case–control study,[40] finding no overall association, but an apparent positive trend in risk with amount used. Lastly, a prospective cohort study of 10,136 Norwegian men recruited in 1966 and followed up to 2001,[41] reported no association with snus use in never smokers but an increased risk overall after adjustment for smoking (RR 1.67, 95% CI 1.12–2.50). The SCENIHR report additionally considered data from the Swedish Construction Workers Cohort,[17] which demonstrated an increased risk for snus use among never smokers (RR 2.00, 95% CI 1.20–3.30) but not any overall association (RR 0.90, 95% CI 0.70–1.20, with adjustment for smoking). In contrast to the Norwegian study, Boffetta and colleagues[13] meta-analysed the six studies cited above, resulting in a summary RR of 1.60 (95% CI 1.10–2.20) for any use of smokeless tobacco, but only based the analysis on the positive associations, *i.e.* the increased risk in never smokers from the Swedish Construction Workers Cohort[17] and overall increased risk in the Norway Cohorts Study,[41,42] while ignoring the reciprocal null associations. Further reviews, a pooled analysis by Bertuccio and colleagues[14] of eleven case–control and a meta-analysis by Lee and Hamling,[15] did not support any association between smokeless tobacco use and pancreatic cancer.

Although snus use was not associated with risk in smoking-adjusted models in the Swedish Construction Workers Cohort, with follow-up until 2004,[17] a twofold increased risk for ever or current snus users was observed when the sample was restricted to never smokers. We could replicate this result in our analyses, but the association was weaker and no longer statistically significant when the follow-up was extended until 2013 (HR 1.34, 95% CI 0.90–1.99). Restricting to never smokers, we stratified our analyses of the Construction Workers Cohort according to calendar period of follow-up. The HR in current snus users was 1.98 (0.97–4.03, based on four exposed cases) with follow-up from 1978 through 1994, but 1.11 (0.68–1.79, based on 27 exposed cases) in 1995–2013. The reason for this discrepancy is unclear, but may be due to increasing misclassification of exposure with longer follow-up (diluting any true associations), or to chance. The latter notion is sustained by our sensitivity analysis, excluding the Construction Workers Cohort, which was

Table 3. Pooled hazard ratios (HR) and 95% confidence intervals (CI) of pancreatic cancer in relation to snus use from sensitivity analyses

	Use of snus at baseline					
	Ever users		Former users		Current users	
Type of analysis	*n*	HR (95% CI)	*n*	HR (95% CI)	*n*	HR(95% CI)
Cases from Cancer Register only	250	0.97 (0.84–1.12)	73	0.95 (0.75–1.22)	177	0.98 (0.83–1.15)
Excluding Construction Workers Cohort	98	1.13 (0.87–1.45)	33	0.90 (0.61–1.31)	65	1.30 (0.97–1.73)
Controlling for additional potential confounders[1]	92	1.12 (0.76–1.63)	33	0.90 (0.51–1.59)	59	1.32 (0.84–2.08)
Excluding cohorts with no information on former snus use	315	0.93 (0.81–1.06)	93	0.88 (0.70–1.09)	222	0.95 (0.82–1.10)
Restriction to never smokers	50	1.04 (0.77–1.42)	9	0.92 (0.47–1.80)	41	1.07 (0.77–1.50)

[1]Additional adjustment for alcohol consumption, physical activity and interaction between alcohol consumption and smoking among the studies where this information was available (MONICA, NMC, SALT, Scania_PHC, Sthlm_PHC, VIP and WOLF).

not in support of any strong relationship between snus and pancreatic cancer risk.

Our study has several strengths. Its prospective design minimizes recall and selection bias, often afflicting retrospective studies. The latter bias is particularly problematic in studies of pancreatic cancer, since its high lethality imposes on case recruitment. Our study is also the largest to date, and we were hence able to explore dose-response relationships. To control for confounding by smoking, we used two approaches; multivariate modeling including current and former smoking as covariates, and restriction of the study population to never-smokers—both supporting a null association. In contrast to Boffetta and colleagues[41] and Luo and colleagues,[17] we had the opportunity to control for alcohol consumption, the level of physical activity as well as diabetes, and again the main findings did not change. We used both Swedish Cancer Register and the Cause of Death Register to identify cancer cases, thus maximizing case ascertainment.[26,43] Information on smoking and snus use was, however, self-reported, and only assessed at baseline. Although self-reports show high concordance with serum cotinine levels (a biomarker of smoking status) in cross-sectional data,[44] tobacco habits may change over the life-course. Yet, Swedish data show 70% of snus users at baseline continued use after 10 years.[45] Misclassification of tobacco use may nevertheless have biased our estimates of associations towards the null.

Tobacco smoking is a strong risk factor for pancreatic cancer.[46] Tobacco smoke contains high doses of carcinogenic TSNAs, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and *N*′-nitrosonornicotine (NNN), which may have specificity for the pancreas.[47] NNK metabolites can bind to DNA to form adducts and induce activating point mutations in the RAS gene,[48] which are thought to be the most common genetic alterations in the progression of pancreatic cancer.[49] Nitrosamine levels are substantially lower in Swedish snus than in tobacco smoke, as well as than in other types of smokeless tobacco products,[50] strengthening the plausibility of a null association between snus use and pancreatic cancer.

Our findings, from the largest sample to date, do not support a role of snus use in the development of pancreatic cancer in men. They, furthermore, point to tobacco smoke constituents other than nicotine or its metabolites, *i.e.* carcinogens associated with combustion, as the causal agent explaining the increased risk of pancreatic cancer in smokers.

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