

## Risk of gastroesophageal cancer among smokers and users of Scandinavian moist snuff

Kazem Zendehdel<sup>1,2\*</sup>, Olof Nyrén<sup>1</sup>, Juhua Luo<sup>1</sup>, Paul W. Dickman<sup>1</sup>, Paolo Boffetta<sup>3</sup>, Anders Englund<sup>4</sup> and Weimin Ye<sup>1</sup>

<sup>1</sup>Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

<sup>2</sup>Cancer Institute Research Center, Tehran University of Medical Sciences, Tehran, Iran

<sup>3</sup>International Agency for Research on Cancer (IARC), Lyon, France

<sup>4</sup>Swedish Work Environment Authority, Stockholm, Sweden

Although Scandinavian moist snuff (“snus”), no doubt, is a safer alternative to smoking, there is limited evidence against an association with gastroesophageal cancers. In a retrospective cohort study, we investigated esophageal and stomach cancer incidence among 336,381 male Swedish construction workers who provided information on tobacco smoking and snus habits within a health surveillance program between 1971 and 1993. Essentially complete follow-up through 2004 was accomplished through linkage to several nationwide registers. Multivariable Cox proportional hazards regression models estimated relative risks (RR) and 95% confidence intervals (CIs). Compared to never-users of any tobacco, smokers had increased risks for adenocarcinoma (RR = 2.3, 95% CI 1.4–3.7) and squamous cell carcinoma (RR = 5.2, 95% CI 3.1–8.6) of the esophagus, as well as cardia (RR = 2.1, 95% CI 1.5–3.0) and noncardia stomach (RR = 1.3, 95% CI 1.2–1.6) cancers. We also observed excess risks for esophageal squamous cell carcinoma (RR = 3.5, 95% CI 1.6–7.6) and noncardia stomach cancer (RR = 1.4, 95% CI 1.1–1.9) among snus users who had never smoked. Although confounding by unmeasured exposures, and some differential misclassification of smoking, might have inflated the associations, our study provides suggestive evidence for an independent carcinogenic effect of snus.

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Tobacco smoking is widely acknowledged as the main known cause of cancer-related death worldwide, estimated to be responsible for ~25% of all cancers in men and 4% in women.<sup>1</sup> Its relation to—among others—esophageal squamous cell carcinoma (ESCC) and adenocarcinoma (EAC) as well as stomach cancer is well established.<sup>2</sup> Snuff, particularly the moist Scandinavian variant (snus) with reduced levels of carcinogenic tobacco-specific nitrosamines (TSNAs), might help inveterate smokers stop or reduce their smoking habit. If acceptably safe, snus use might potentially be recommended to smokers in order to reduce risks for these cancers. Available investigations of snus use and risk of esophageal or stomach cancer are few but suggest an absence of risk elevation; only 1 study, published as an abstract,<sup>3</sup> found a statistically significant increased risk for esophageal cancer, while the other studies showed statistically nonsignificant relative risk estimates between 1.2 and 1.4 for esophageal cancer<sup>4–6</sup> and 0.9–1.1 for stomach cancer.<sup>6,7</sup> However, these studies generally had limited power and/or insufficient covariate information to rule out important positive or negative confounding by smoking intensity; there are good reasons for assuming that smokers smoke less if they also use smokeless tobacco.

We therefore studied the incidence of esophageal and stomach cancers in a large and highly exposed cohort of Swedish construction workers followed for up to 33 years from as far back as 1971. Snus exposure data were first analyzed without adjustment for smoking dose in order to evaluate the net effect of smoking and snus in combination (including the possible benefit conferred by a reduction in smoking dose). Then we tried to disentangle the independent effect of snus use by means of adjustment for smoking intensity. By virtue of the large sample size and the unprecedented exposure prevalence we could also investigate into these risks with reasonable statistical power in the stratum of never-smokers.

## Subjects and methods

### The cohort

The construction industry's Organization for Working Environment, Safety and Health, “Bygghälsan,” offered preventive health check-ups to all blue- and white-collar workers in the Swedish building industry between 1969 and 1993. In all, 361,280 individuals had records of at least 1 visit between 1971 and 1993. Since less than 5% of the participants were women, we restricted our investigation to male workers ( $n = 343,822$ ).

### Exposure information

During 1971–75 each cohort member filled out a 200-item questionnaire that included detailed questions about smoking and snus use. During the visits answers were double-checked by attending staff. After a pause during 1976 through 1977, the collection of smoking and snus information was resumed in 1978 but on a new form filled out directly by the staff. All data were compiled in a computerized central register. The data quality has been reviewed previously and was deemed to be satisfactory.<sup>8</sup> Because repeat visits were variable in number and timing among the cohort members, to a large extent driven by self selection, we only used the exposure information recorded at the first registered visit, which also marked the entry into the cohort.

### Follow-up

The national registration numbers (NRNs), unique personal identifiers assigned to all residents in Sweden, permitted follow-up through linkages to nationwide and essentially complete registers of cancer, causes of death, as well as to registers of the total population and migration. If a NRN could not be found in any of the latter 3 registers it was deemed to be erroneous and the record was excluded. The more than 98% complete cancer register,<sup>9</sup> established in 1958, has coded malignant neoplasms according to the 7th revision of International classification of diseases (ICD7) during the entire study period. The ICD7 code 150 (esophageal cancer) was broken down into EAC (code 096) and ESCC (code 146) using WHO/HS/CANC/24.1 histology codes,<sup>10</sup> and stomach cancer (ICD7 code 151) was subdivided into cardia (CSC) (151.1) and noncardia (N-CSC) (all other 151) cancer. Each cohort member contributed person-time from the date of first registered visit until the date of any diagnosis of cancer, death, emigration or December 31, 2004, whichever came first.

### Statistical analysis

We computed the incidence of esophageal and stomach cancer by smoking and snus consumption categories, standardized to the

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\*Correspondence to: Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Box 281, Stockholm SE-17177, Sweden. Fax: +46-831-4975. E-mail: kazem.zendehdel@ki.se

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TABLE 1—CHARACTERISTICS OF THE MALE SWEDISH CONSTRUCTION WORKERS COHORT

Age at entry (years)	Number of men	Person-years of follow-up	No. of ever-smokers (%)	No. of snus users (%)	No. of never-smoking snus users (%)
≤20	37,622	774,582	11,583 (31)	13,523 (36)	9561 (25)
20–29	117,460	2,662,862	57,917 (49)	40,748 (35)	20,887 (18)
30–39	74,046	1,783,956	49,656 (67)	19,231 (26)	5201 (7)
40–49	49,959	1,151,843	34,578 (69)	9698 (19)	2087 (4)
50–59	41,762	847,497	29,280 (70)	8265 (20)	2063 (5)
≥60	15,532	254,886	10,476 (67)	3319 (21)	1133 (7)
Overall	336,381	7,475,628	193,490 (58)	94,784 (28)	40,932 (12)

distribution of person–time experienced by the entire construction workers cohort using 5-year age categories.<sup>11</sup> Cox proportional hazards regression models estimated relative risks (RRs) and corresponding 95% confidence intervals (CIs) using attained age (in years) as the time scale. All models were adjusted for body mass index (BMI) at entry, categorized into quartiles. Calendar year of entry into the cohort and residential place (northern, middle or southern Sweden) was also considered as a covariate but both proved to be redundant. Smoking status (never, current or previous), smoking dose (0, 1–9, 10–19 and ≥ 20 g of tobacco per day) and time since quitting (<5 years and ≥5 years), reported at entry into the cohort, were categorized prior to the analyses based on what was perceived as relevant in relation to factual consumption habits and biological effects. To create a summary variable for total tobacco smoking, a cigarette and a cigar were equated to 1 and 6 g of tobacco, respectively, while pipe smoking was already reported in grams per week. We evaluated trends by creating semicontinuous variables from medians of categories; in these analyses the never-users of any tobacco were omitted. We also analyzed the effect of different smoking habits separately, *i.e.* cigarette only, pipe only and cigar only. We restricted the analyses of smoking effects to never-users of snus.

To study effects of snus use, we first compared cancer risks among all users to those among all nonusers, with adjustments only for attained age and BMI. Although we cannot exclude the possibility that preexisting smoking dose could have been linked to the inclination to take up snus use, the analyses that were unadjusted for smoking were thought to accommodate the assumed dose-limiting effect of adding snus use to the smoking habit. Hence, the estimates were interpreted as the net effect of the combined habit. Next we tried to disentangle independent associations of snus use by additional adjustment for smoking. These unadjusted and adjusted analyses were then repeated in the substratum of ever-smokers at time of entry. This was because it was assumed that any positive net effect of snus use would be particularly evident among smokers. In addition to attained age and BMI, we adjusted for smoking status (current or previous at entry into the cohort), dose and type of smoking tobacco (cigarette only, cigar only, pipe only, pipe and cigarette and other combinations). Evaluation of the proportional hazards assumption with graphs of scaled Schoenfeld residuals<sup>12</sup> revealed that the assumption did not hold for the association of snus use with stomach and esophageal cancers. As the RRs were diverging at age 70, we further estimated RRs in two age strata using age of 70 as cut-point. To control more efficiently for smoking we estimated the RRs among never-smoking snus users in comparison to never-users of any tobacco and adjusted only for attained age and BMI. Stata statistical software (release 9.1) was used in all analyses. This study was approved by the Regional Ethics Committee of Karolinska Institutet.

## Results

We removed 3,130 (0.9%) records because of invalid NRNs or inconsistencies found during record linkages. Moreover, we excluded 3,032 (0.8%) subjects due to missing information on BMI and—because we only considered first cancers—1,299 (0.3%) subjects with any cancer before entry into the cohort, leaving 336,381 workers for final analyses. They were followed for up to 33.5 years (mean 22.2) corresponding to 7,475,628 person-

years under observation. The mean age at entry was 34.7 years. Table I shows characteristics of the cohort members by age categories. Overall, 58% of the workers were current or former smokers at time of entry. The prevalence of snus use was 28% overall but higher among young workers. We observed 130 cases of EAC, 236 ESCC, 276 CSC and 1109 N-CSC.

## Smoking

Our observed associations between tobacco smoking and all 4 categories of esophagogastric cancer were in good accordance with the previous literature (Table II). With the possible exception of EAC, it appeared that pipe smoking was more strongly related to the risk of the studied cancers than were other types of smoking habits. We noted differential risk patterns for esophageal and stomach cancers after smoking cessation; while the risk of both major histological types of esophageal cancer fell to the unexposed level within 5 years of quitting, risks of CSC and N-CSC remained on increased and essentially unaltered levels even after 5–38 years.

## Snus use and esophageal adenocarcinoma

In a model that included the entire cohort and where snus users were compared to nonusers of snus, regardless of smoking status and with adjustments only for attained age and BMI, we found no increased risk among snus users (Table III). The risk before the age of 70 years tended to be slightly below that among nonusers and slightly above this risk among those who were older. Additional adjustment for smoking dose had only trivial effects on our estimates. In a model restricted to ever-smokers and unadjusted for smoking variables, the relative risk among snus users overall was 1.0 but it was 0.6 (95% CI 0.3–1.1) among workers who had not yet attained age 70 and 2.3 (95% CI 1.1–4.6) above this age. Further adjustment for smoking variables tended to increase the RRs values somewhat overall and in age strata, but the pattern was otherwise similar. In a model restricted to never-smokers the adjusted relative risk based on 1 exposed case, tended to be markedly lower than in the reference group, but the confidence interval was large and included unity (RR = 0.2, 95% CI 0.0–1.9).

## Snus use and esophageal squamous cell carcinoma

Models based on the entire cohort gave no indication of any overall increased or decreased risk for ESCC among snus users regardless of whether or not adjustments were made for smoking intensity (Table III). A restriction to smokers yielded a nonsignificant tendency toward decreased risk among snus users, relative to nonusers, but only before the age of 70 years. This risk reduction was attenuated after adjustments for smoking variables. However, we observed a significant 3.5-fold excess risk (95% CI 1.6–7.6) among isolated snus users relative to never-users of any tobacco. The excess was almost similar and statistically significant in both strata of attained age.

## Snus use and stomach cancer

Snus use had no significant effect on the risk of CSC, irrespective of analytic approach (Table IV), but in the analyses that included the entire cohort it was associated with borderline significant 10% excesses of N-CSC risks, regardless of whether or not

**TABLE II – SMOKING-ASSOCIATED RELATIVE RISKS (RR) AND 95% CONFIDENCE INTERVALS (CI) FOR ESOPHAGEAL AND STOMACH CANCERS AMONG MALE SWEDISH CONSTRUCTION WORKERS WHO WERE NEVER-USERS OF SNUS AT ENTRY INTO THE COHORT**

Tobacco habit	Person-years	Esophageal cancer				Stomach cancer			
		Adenocarcinoma		Squamous cell carcinoma		Cardia		Noncardia	
		IR <sup>1</sup>	RR (95% CI)	IR <sup>1</sup>	RR (95% CI)	IR <sup>1</sup>	RR (95% CI)	IR <sup>1</sup>	RR (95% CI)
Never-users of any tobacco	2,241,175	1.0	Reference	0.8	Reference	2.1	Reference	11.7	Reference
Ever-smokers	3,179,735	2.2	2.3 (1.4–3.7)	4.4	5.2 (3.1–8.6)	4.5	2.1 (1.5–3.0)	16.0	1.3 (1.2–1.6)
Current smokers <sup>2</sup>	2,352,918	2.7	2.9 (1.8–4.8)	6.4	7.6 (4.5–12.7)	4.8	2.3 (1.6–3.3)	16.5	1.4 (1.2–1.6)
<10 g/day	1,073,818	1.7	1.8 (0.9–3.2)	6.2	6.9 (4.0–11.8)	4.3	2.1 (1.4–3.1)	15.8	1.3 (1.1–1.6)
10–19 g/day	821,973	3.4	3.8 (2.1–6.7)	5.4	6.3 (3.5–11.1)	5.0	2.4 (1.6–3.7)	17.7	1.4 (1.2–1.8)
≥20 g/day	457,127	4.4	4.7 (2.5–9.0)	8.6	11.2 (6.2–20.2)	5.6	3.0 (1.8–5.0)	15.9	1.4 (1.1–1.9)
<i>p</i> value for trend <sup>3</sup>			0.001		0.2		0.1		0.3
Previous smokers <sup>4</sup>	753,339	1.4	1.2 (0.6–2.4)	0.7	0.9 (0.4–2.0)	3.9	1.8 (1.2–2.7)	15.0	1.3 (1.1–1.5)
Smoke free <5 yr	330,898	2.2	2.1 (0.9–4.9)	0.8	1.0 (0.3–3.5)	4.1	1.9 (1.1–3.4)	14.1	1.2 (0.9–1.6)
Smoke free ≥ 5 yr	422,441	0.7	0.8 (0.3–1.8)	0.6	0.8 (0.3–2.1)	3.6	1.7 (1.1–2.6)	15.7	1.3 (1.1–1.6)
<i>p</i> value for trend <sup>3</sup>			0.1		0.8		0.7		0.6
Smoking product <sup>5</sup>									
Cigarette only	2,196,928	2.5	2.6 (1.5–4.3)	3.7	4.5 (2.6–7.8)	3.7	1.7 (1.2–2.5)	15.2	1.3 (1.1–1.5)
Pipe only	381,783	0.9	1.1 (0.5–2.4)	7.8	8.3 (4.8–14.5)	6.3	3.1 (2.1–4.7)	18.1	1.5 (1.2–1.8)
Cigar only	44,518	1.1	1.2 (0.2–9.3)	4.9	5.8 (1.9–17.4)	–	–	13.5	1.0 (0.5–1.8)

All relative risk estimates were adjusted for attained age and body mass index.

<sup>1</sup>IR, Incidence rate per 100,000 person-years, standardized to the age distribution of person-years among all workers using 5-year age categories. <sup>2</sup>Observations with missing value for smoking intensity were excluded. <sup>3</sup>The never-users of any tobacco were omitted in the trend analyses. <sup>4</sup>Observations with missing value for time since cessation were excluded. Stratification was based on time prior to entry into the cohort. <sup>5</sup>All smokers (both current and former smokers) were used when analyzing relative risks for different smoking products.

**TABLE III – ASSOCIATION OF SNUS USE WITH ESOPHAGEAL CANCER BY HISTOLOGY AMONG MALE SWEDISH CONSTRUCTION WORKERS 1971–1993, FOLLOWED THROUGH 2004**

Tobacco habit	Number of men	Person-years	Adenocarcinoma			Squamous cell carcinoma		
			Number of cases	IR <sup>1</sup>	Relative risk (95% CI)	Number of cases	IR <sup>1</sup>	Relative risk (95% CI)
In the entire Cohort								
Non-users of snus	241,597	5,420,909	103	1.8	Reference	186	3.1	Reference
Snus users, adjusted only for BMI and attained age	94,784	2,054,718	27	1.7	1.0 (0.6–1.5)	50	3.2	1.1 (0.8–1.5)
<70-years-old <sup>2</sup>	81,377	1,945,373	14	0.7	0.7 (0.4–1.2)	28	1.4	0.9 (0.6–1.4)
≥70-years-old	13,407	109,345	13	11.8	1.6 (0.8–3.0)	22	20.1	1.4 (0.8–2.2)
Snus users, additionally adjusted for smoking intensity	94,784	2,054,718	27	1.7	1.0 (0.6–1.5)	50	3.2	1.0 (0.8–1.4)
<70-years-old <sup>2</sup>	81,377	1,945,373	14	0.7	0.7 (0.4–1.3)	28	1.4	0.9 (0.6–1.3)
≥70-years-old	13,407	109,345	13	11.8	1.7 (0.9–3.3)	22	20.1	1.4 (0.8–2.2)
Among ever-smokers								
Non-users of snus	139,638	3,179,735	83	2.2	Reference	170	4.2	Reference
Snus users, adjusted only for BMI and attained age	53,852	1,250,860	26	2.2	1.0 (0.6–1.5)	40	3.5	0.8 (0.6–1.2)
<70-years-old <sup>2</sup>	43,792	1,172,133	13	1.1	0.6 (0.3–1.1)	23	2.0	0.7 (0.4–1.1)
≥70-years-old	10,060	78,727	13	16.5	2.3 (1.1–4.6)	17	22.0	1.1 (0.6–1.9)
Snus users, additionally adjusted for smoking variables	53,852	1,250,860	26	2.2	1.3 (0.8–2.0)	40	3.5	1.2 (0.8–1.7)
<70-years-old <sup>2</sup>	43,792	1,172,133	13	1.1	0.8 (0.4–1.5)	23	2.0	1.0 (0.6–1.6)
≥70-years-old	10,060	78,727	13	16.5	2.9 (1.4–6.0)	17	22.0	1.6 (0.9–2.8)
Among never-smokers <sup>3</sup>								
Never-users of any tobacco	101,959	2,241,175	20	1.0	Reference	16	0.8	Reference
Users of snus only	40,932	803,858	1	0.2	0.2 (0.0–1.9)	10	2.6	3.5 (1.6–7.6)
<70-years-old <sup>2</sup>	37,588	7,73,240	1	0.2	0.6 (0.1–5.0)	5	1.6	3.7 (1.2–11.4)
≥70-years-old	3,347	30,618	0	–	–	5	15.6	3.1 (1.0–9.4)

<sup>1</sup>Incidence rate per 100,000 person years, standardized to the age distribution of person-years among all workers using 5-year age categories. <sup>2</sup>Since the observations were split by the attained age, each worker may contribute to both subcohorts, and thus the sum of the 2 subcohorts will exceed that in the main cohort. <sup>3</sup>Relative risks were adjusted for attained age and body mass index.

adjustments were done for smoking dose. These excesses were confined to workers above age 70, among whom statistically significant 40–50% risk elevations were observed. Moreover, a significant 40% overall excess risk (RR = 1.4, 95% CI 1.1–1.9) for N-CSC emerged among snuff using never-smokers, relative to never-users of any tobacco.

### Sensitivity analyses

Since we only used exposure information collected at entry into the cohort, there is a possibility that nonsmoking snus users, com-

pared to nonusers of any tobacco, were more inclined to take up smoking in the follow-up period. With the reservation that cross-sectional data across successive repeat visits may be sensitive to selection bias, we analyzed such data among 60,833 workers who reported being never-users of any tobacco at entry (with at least 2 visits and an average 3.3 repeat visits) and 21,436 who said that they were never-smoking snus users (3.7 repeat visits). In the former and latter group, respectively, 4,080 (6.7%) and 2,828 (13.2%) had at least 1 repeat record that indicated current or previous smoking, confirming that differential misclassification of smoking status is indeed a valid concern.

**TABLE IV** – ASSOCIATION OF SNUS USE WITH STOMACH CANCER BY SUBSITE AMONG MALE SWEDISH CONSTRUCTION WORKERS 1971 TO 1993, FOLLOWED THROUGH 2004

Tobacco habit	Cardia			Noncardia		
	Number of cases	IR <sup>1</sup>	Relative risk (95% CI)	Number of cases	IR <sup>1</sup>	Relative risk (95% CI)
In the entire cohort						
Non-users of snus	218	3.7	Reference	856	14.5	Reference
Snus users, adjusted only for BMI and attained age	58	3.7	1.0 (0.7–1.3)	253	16.4	1.1 (1.0–1.3)
<70-years-old	31	1.6	0.8 (0.6–1.2)	128	6.6	0.9 (0.8–1.1)
≥70-years-old	27	24.7	1.3 (0.8–2.0)	125	114.3	1.4 (1.2–1.8)
Snus users, additionally adjusted for smoking intensity	58	3.7	1.0 (0.8–1.4)	253	16.4	1.1 (1.0–1.3)
<70-years-old	31	1.6	0.9 (0.6–1.3)	128	6.6	0.9 (0.7–1.1)
≥70-years-old	27	24.7	1.3 (0.8–1.9)	125	114.3	1.5 (1.2–1.8)
Among ever-smokers						
Non-users of snus	174	4.5	Reference	615	16.2	Reference
Snus users, adjusted only for BMI and attained age	50	4.3	0.9 (0.7–1.3)	185	16.2	1.0 (0.9–1.2)
<70-years-old	28	2.4	0.8 (0.5–1.2)	96	8.6	0.8 (0.7–1.0)
≥70-years-old	22	28	1.2 (0.8–2.0)	89	113.1	1.3 (1.0–1.7)
Snus users, additionally adjusted for smoking variables	50	4.3	1.1 (0.8–1.6)	185	16.2	1.0 (0.9–1.2)
<70-years-old	28	2.4	1.0 (0.7–1.6)	96	8.6	0.8 (0.7–1.1)
≥70-years-old	22	28	1.4 (0.8–2.2)	89	113.1	1.4 (1.1–1.8)
Among never-smokers <sup>2</sup>						
Never-users of any tobacco	44	2.1	Reference	242	11.7	Reference
Users of snus only	8	2.0	0.9 (0.4–2.0)	68	17.4	1.4 (1.1–1.9)
<70-years-old <sup>2</sup>	3	0.9	0.6 (0.2–2.1)	32	9.7	1.2 (0.8–1.8)
≥70-years-old	5	16.5	1.3 (0.5–3.4)	36	115.6	1.7 (1.2–2.5)

<sup>1</sup>Incidence rate per 100,000 person years, standardized to the age distribution of person-year among all workers using 5-year age categories. <sup>2</sup>Relative risks were adjusted for attained age and body mass index.

In a sensitivity analysis, we extrapolated these proportions to the entire subcohorts of never-users of any tobacco and never-smoking snus users and assumed that workers with a positive smoking record at any point in time during follow-up were, in fact, smokers. Using the magnitude of smoking-disease associations shown in Tables II and III, we adjusted the observed associations between exclusive snus use and gastroesophageal cancers as proposed by Schneeweiss.<sup>13</sup> Taking the suspected misclassification into account, the relative risk for ESCC among never-smoking snus users would fall from 3.5 to 2.9 and, correspondingly, RRs for N-CSC would decrease from 1.4 to 1.37. We also estimated that at least 60% of the snus users would have to be smokers to shift a true null association with ESCC to the observed relative risk value, assuming no smoking misclassification among never-users of any tobacco. Moreover, not even 100% smoking prevalence among snus users would fully explain the observed association between exclusive snus use and noncardia stomach cancer.

## Discussion

This large retrospective cohort study with long and essentially complete follow-up confirms the well-established link between smoking and all major types of gastroesophageal cancer. It also provides new data suggestive of snus-associated carcinogenic risks. Although effectively confined to septuagenarians or older, never-smoking snus users overall had a statistically significant 40% excess risk of N-CSC compared to never-users of any tobacco. Although our data indicated that some differential misclassification of smoking status may have occurred at entry or during follow-up, despite several reports suggesting that exclusive snus users rarely take up smoking,<sup>14–17</sup> this misclassification is an unlikely explanation for our finding. We found little evidence of any net protective effect of snus use through its presumed reduction of smoking dose—neither in the mixed population of smoking and nonsmoking workers, nor among workers who were reportedly ever-smokers at entry into the cohort. Never-smoking snus users, further, had a substantially increased risk of ESCC when compared to never-users of any tobacco, again not likely explained by differential misclassification of smoking status. There was a nonsignificant tendency for a lower risk of ESCC among

smokers who also used snus, but the purported harm reduction by snus use<sup>18–20</sup> did not impress overall.

Generally, adjustments for smoking variables in analyses that also included smokers changed the unadjusted relative risk estimate surprisingly little. The main reason is that the proportions who reported being or having been smokers at entry were almost identical among users (56.8%) and nonusers (57.8%) of snus. Hence, based on the smoking information obtained at entry, the scope for confounding was limited to the observed variation among smokers in regard to smoking dose, smoking status (current or exsmoker) and type of smoking tobacco. If this information would not correctly reflect the relevant smoking exposure status, either because of erroneous reporting at entry or due to subsequent changes in habits (differential or nondifferential), residual confounding by smoking might be a concern.

We did, indeed, note certain weaknesses of the smoking information collected in 1971–75. Nonsmokers were not required to actively negate smoking. Instead, they were instructed to simply skip the smoking questions. All cohort members without answers to these questions were coded as nonusers. Thus, the never-smoker category may have contained some smokers, who skipped the smoking questions for other reasons than nonuse. As nonsmokers were instructed to move directly to the snus questions, where absence of any response was likewise coded as nonuse, it is conceivable that of all who skipped the smoking questions the proportion of negligent smokers who skipped it inadequately was greater when both sets of questions were skipped than when the snus questions were answered in the affirmative. Consequently, it was suspected that the reference category of never-smoking nonusers of snus may have contained more misclassified smokers than did the group classified as nonsmoking snus users. The sensitivity analysis using admittedly self-selected workers with 1 or several repeat visits did not support this suspicion, though.

None of the previous epidemiological studies on snus and esophageal cancer, 1 cohort study<sup>6</sup> and 2 population-based case-control studies,<sup>4,5</sup> has shown any significant excess risks, but the point estimates for the relative risk, multivariately adjusted for smoking dose, were above unity in all, ranging between 1.2<sup>4</sup> and 1.4.<sup>5,6</sup> Neither of the previous studies had sufficient power to analyze relative risk specifically for esophageal cancer in strata of

never-smokers. This was true also for the 2 studies that addressed the association between snus use and risk of stomach cancer.<sup>6,7</sup> These studies, 1 population-based case-control study<sup>7</sup> and 1 cohort study,<sup>6</sup> combined CSC and N-CSC, adjusted multivariately for smoking, and were both negative with RRs among ever-users, relative to never-users, of 0.9 and 1.1, respectively.

The observed departure from the proportional hazards assumption in our analyses pertaining to both esophageal and gastric cancer forced us to stratify our analyses by attained age (below and above age 70). This suggests effect modification by age. The RRs tended to be higher among workers who were older than 70, compared to those who were younger, consistent with a very long induction time. The oldest were also most exposed to snus from earlier parts of the 20th century. Such snus contained higher levels of carcinogenic TSNA's compared to the snus sold today.<sup>21</sup>

Some additional important caveats need to be highlighted. First, the analyses of some cancer sites in strata of never-smokers were based on small numbers (1, 10 and 8 snus-exposed cases of EAC, ESCC and CSC, respectively). Whereas the relative risk of ESCC among never-smoking snus users was statistically significant with a lower confidence limit of 1.6, chance could still have played a role, particularly since multiple significance testing was done in this study. Second, the lack of information about several con-

founding factors needs careful consideration. While alcohol is a candidate confounding factor for associations of tobacco use with ESCC and possibly also with CSC and unavailability of alcohol information is serious limitation, the weak or absent of association of alcohol use with N-CSC<sup>22</sup> makes such confounding unlikely. Since there is meager information about lifestyle differences between never-smokers who use snus and those who do not use snus, confounding from other unmeasured exposure cannot be confidently ruled out. The restriction to male construction workers—although a possible threat to the generalizability of our findings—allays concerns about confounding by gender, socioeconomic status and occupational exposures. Confounding by dietary factors remains a viable possibility, though.

Although some uncertainty remains regarding the causality and the strength of the association as well as the generalizability to other populations than Swedish men, we conclude that at present, Scandinavian snus cannot be considered to be without a carcinogenic risk.

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