uicc
global cancer control

IJC
International Journal of Cancer

Smoking, snus use and risk of right- and left-sided colon, rectal and anal cancer: a 37-year follow-up study

Caroline Nordenvall[1], Per J. Nilsson[2,3], Weimin Ye[1] and Olof Nyrén[1]

[1] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, SE-171 77 Stockholm, Sweden
[2] Division of Coloproctology, Center of Surgical Gastroenterology, Karolinska University Hospital, Stockholm, Sweden
[3] Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

Although some authorities consider smoking to be an established risk factor for colorectal cancer, the international literature is not entirely consistent. Further, only 1 study has addressed the association with smokeless tobacco and none with Scandinavian moist snuff (snus). This retrospective cohort study included 336,381 male Swedish construction workers with detailed information on tobacco use at cohort entry in 1971–1992. Complete follow-up through 2007 was accomplished by means of linkage to population and health registers. Hazard ratios (HRs) and 95% confidence intervals (CIs) derived from Cox proportional hazards regression models estimated relative risks, adjusted for age and body mass index. Subjects who were never-users of any tobacco served as reference. After up to 37 years of follow-up, pure smoking was associated with a marginally increased risk of colon cancer (HR 1.08, 95% CI 0.99–1.19), a modestly elevated risk of rectal cancer (HR 1.16, 95% CI 1.04–1.30) and a substantial excess risk of anal cancer (HR 2.41, 95% CI 1.06–5.48). Snus use was not significantly associated with an increased risk of colorectal or anal cancer, although the point estimate for colon cancer was similar to that observed among smokers. Swedish data provide meager support for the association between tobacco use and colorectal cancer. A general tendency among Swedish men to quit smoking in recent decades might have attenuated true associations. A link between smoking and anal cancer was confirmed.

While smoking is a well-established risk factor for anal cancer,[1] its role in the etiology of colon and rectal cancer remains controversial despite a large number of scientific reports. Following breast cancer among women and prostate cancer among men, colorectal cancer is the 2nd most common type of cancer in both the sexes in Sweden and the 3rd most common cause of cancer death.[2,3] Colorectal cancer is the 3rd most common cancer in both the sexes in the United States,[4] and in Europe, 412,900 cases were diagnosed and 207,400 deaths were registered in 2006.[5] Hereditary syndromes, like familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC), are estimated to account for up to 10% of all cancer cases, whereas the rest may be caused by environmental and lifestyle factors.[6] Smoking is a known risk factor for adenomas in the colon and rectum,[7,8] the precursor of most tumors,[9] with a relative risk larger than 2 for current compared to never smokers.[8] The inability to establish a firm association between smoking and colorectal cancer has different explanations such as inclusion of adenomas in the control group.[7,10,11] Smoking has also been proposed to be an initiator of the tumorigenesis, and follow-up for a long time would be needed to observe an association.[12]

Sweden has the world's highest prevalence of Scandinavian moist snuff (snus) use and 22% of Swedish males are daily users of snus.[13] One previous study has investigated the association between smokeless tobacco, in this case chewing tobacco, and colorectal cancer; it reported a significantly increased risk of rectal cancer among users but not of colon cancer.[14] The association between snus use and anal cancer has not been studied.

Data from the Swedish cohort of construction workers have previously showed no increased risk of colon cancer and a slightly increased risk of rectal cancer among smokers, but a long-term effect could not be excluded.[15] The aim of our study with up to 37 years of follow-up was to quantify the possible association between smoking, the use of snus and the risk of right- and left-sided colon cancer, rectal cancer and anal cancer in a large, well-defined cohort.

Key words: colorectal cancer, anal cancer, smoking, snus, incidence
DOI: 10.1002/ijc.25305
History: Received 19 Nov 2009; Accepted 15 Feb 2010; Online 5 Mar 2010
Correspondence to: Caroline Nordenvall, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Box 281, SE-171 77, Stockholm, Sweden, Tel.: +46-8-5248 2302, Fax: +46-8-31 49 75, E-mail: caroline.nordenvall@ki.se

Material 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 construction industry between 1969 and 1993. As previous papers on tobacco use and colorectal cancer

incidence have been limited by short follow-up,[15] we aimed to extend the follow-up time. A total of 361,280 construction workers in the cohort had at least 1 recorded visit between 1971 and 1992 and they were considered eligible for our study.

Exposure information

Cohort members included in 1971–1975 filled out a 200-item questionnaire with detailed questions about smoking and snus use. In connection with their personal visit at the clinic, answers were double-checked by attending staff. During this period, non-smokers were instructed to simply skip the questions regarding smoking habits and move to the snus questions. Non-response was coded as non-use. However, as non-response could be attributed not only to non-users but also to negligent smokers, of whom the latter are more likely to also inadequately skip the snus question, the paradoxical consequence could be that never-users of any tobacco might contain more smokers than the non-smoking snus user category.[16]

After a pause during 1976 through 1977, the collection of smoking and snus information was resumed in 1978 with a new form filled out directly by the staff. However, at repeated visits after the primary visit with the new form, the registration of tobacco use may be incorrect. If the tobacco habits were unchanged, the staff tended to leave the questions on tobacco habits unanswered. If so, the cohort member was incorrectly coded as non-user.

All data were compiled in a computerized central register. The number of visits for each cohort member ranged from 1 to 13. Because repeated visits were variable in number and timing, possibly linked to the probability of the studied outcome, and as the validity of exposure data was uncertain at repeat visits after 1978, we only used the exposure information recorded at the first registered visit, which was defined as 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, the total population, migration and causes of death. If a NRN could not be found in any of the latter 3 registers it was deemed to be incorrect and the record was excluded. The Swedish National Cancer Register, established in 1958 and shown to be 96–98% complete,[17,18] has coded malignant tumors according to the 7th revision of International Classification of Diseases (ICD7). The ICD7 code 153 was used for colon cancer, code 154.0 for rectal cancer and code 154.1 for anal cancer. Colon cancer was subdivided into right-sided (ICD 7 153.0–153.1) and left-sided (ICD7 153.2–153.3). 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, 2007, whichever came first. As we only considered first cancers, all cohort members recorded with a previous cancer at time of entry were excluded. Only clinically diagnosed colorectal or anal cancers were counted, and those identified incidentally during autopsy were not taken into account.

Statistical analysis

Cox proportional hazards regression models estimated hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) as measures of relative risk, using attained age (in years) as the time scale. In addition to the inherent adjustment for age, all models were adjusted for body mass index (BMI, kg/m^2) at entry categorized into quartiles (<25, 25–29.9, ≥ 30). Cigarette smoking was categorized into 5 classes (0, 1–4, 5–14, 15–24, ≥ 25 cigarettes/day) and cigar smoking into 3 classes (0, 1–7, ≥ 8 cigars/day); whereas, pipe smoking was divided into 4 classes (0, 1–29, 30–99, ≥ 100 g/week). The categorization was initially the same as in the previously mentioned paper from this cohort,[15] but the categorization of cigar smoking was reduced from 5 to 3 classes due to small numbers. The use of snus was only dichotomized (use *vs.* non-use).

We grouped tobacco-using cohort members into pure smokers, pure snus users, and combined smokers and snus users. Never-users of any tobacco were used as the reference group in all analyses. The assumption of proportional hazards for tobacco use and covariates was examined by the method of Shoenfeld's partial residuals; there was no indication of violation of this assumption for any of the variables in the regression models.[19]

At study entry, the participants reported the duration of tobacco use. Cigarette smoking duration was categorized into 1–14, 15–24 and ≥ 25 years, while duration of snus use was divided into 1–9, 10–24 and ≥ 25 years. As snus users were younger at study entry, we chose to use different categorizations for cigarette smokers and snus users. To better evaluate the importance of the total duration of tobacco use on the risk of colorectal and anal cancer, we estimated the total duration of cigarette smoking by adding follow-up time to self-reported duration of cigarette smoking at study entry assuming a continued use throughout the follow-up period. The estimated total duration of cigarette smoking was categorized into 1–29, 30–39, 40–49 and ≥ 50 years. Similarly, we categorized estimated total duration of snus use into 1–24, 25–34, 35–44 and ≥ 45 years. The hazard ratios related to the estimated durations were calculated using time-dependent models.

To estimate a possible "healthy workers effect," we computed the standardized incidence ratios (SIR) for colorectal cancer in the construction workers cohort. The number of expected events in the cohort was calculated by multiplying the age-, sex- and calendar year–specific incidence rate (expected rate) in the general population by the person-time accrued in corresponding strata in the cohort. The number of observed events was divided by the number of expected

Table 1. Characteristics of the male Swedish Construction Workers Cohort

Age at entry (yrs)	Number of men	Year of entry (%)			No. of tobacco users (%)				Person-years of follow-up
		1971–75	1978–84	1985–93	Never users	Snus users[1]	Smokers[2]	Both smokers and snus users	
<30	155,082	39,956 (26)	57,523 (37)	57,603 (37)	55,134 (36)	30,448 (20)	45,677 (29)	23,823 (15)	3,865,880
30–34	41,364	16,838 (41)	15,993 (39)	8,533 (21)	10,659 (26)	3,339 (8)	19,070 (46)	8,296 (20)	1,107,251
35–39	32,682	13,524 (41)	12,487 (38)	6,671 (20)	8,530 (26)	1,862 (6)	16,556 (51)	5,734 (18)	856,630
40–44	26,797	12,336 (46)	8,839 (33)	5,622 (21)	7,178 (27)	1,195 (4)	14,193 (53)	4,231 (16)	679,857
45–49	23,162	12,508 (54)	6,730 (29)	3,924 (17)	6,116 (26)	892 (4)	12,774 (55)	3,380 (15)	561,634
50–54	22,112	13,650 (62)	5,991 (27)	2,471 (11)	5,579 (25)	909 (4)	12,289 (56)	3,335 (15)	494,739
55–59	19,650	12,489 (64)	5,513 (28)	1,648 (8)	4,840 (25)	1,154 (6)	10,789 (55)	2,867 (15)	385,006
60–64	13,544	9,368 (69)	3,372 (25)	804 (6)	3,401 (25)	983 (7)	7,234 (53)	1,926 (14)	228,539
≥65	1,988	1,779 (89)	159 (8)	50 (3)	522 (26)	150 (8)	1,056 (53)	260 (13)	29,206
Overall	336,381	132,448 (39)	116,607 (35)	87,326 (26)	101,959 (30)	40,932 (12)	139,638 (42)	53,852 (16)	8,208,741

[1]Pure snus users (never smokers). [2]Pure smokers (never snus users).

events, producing a SIR with 95% CIs, assuming that the observed events followed a Poisson probability distribution.[20]

Sensitivity analysis

As previously mentioned, the questions about tobacco use were suboptimal in 1971–1975 because it was impossible to distinguish between non-use and non-response. As this could potentially bias the results, some studies using this cohort have chosen to only include recorded visits after 1977. However, given that previous papers on tobacco use and colorectal cancer incidence have been limited by short follow-up, we aimed to have as long follow-up time as possible and used data recorded in 1971–1975. In a sensitivity analysis, we included only cohort members with visits after 1977 and used the exposure information recorded at their first registered visit after this date.

SAS statistical software (release 9.2) was used in the analyses. The study was approved by the Stockholm Ethics Review Board.

Results

The analyses were restricted to men (n = 343,822), as less than 5% (n = 17,458) of the participants were women. Additionally, 7,441 men were excluded due to various reasons; incorrect NRN (n = 388), history of cancer (n = 1,229), death (n = 27) or emigration (n = 2,765) before entry or missing information regarding BMI (body mass index) (n = 3,032), leaving 336,381 male workers for our final analyses. The cohort was followed for up to 37 years (mean 24, quartile [Q] 1 = 19 years, median 25 years and Q3 = 29 years) corresponding to 8,208,741 person-years under observation. The mean age at entry was 35 years (range 15–82 years, Q1 = 24 years, median 31 years, and Q3 = 44 years). Table 1 shows characteristics of the cohort members by age categories. Overall, 42% of the workers were ever smokers at time of entry, 12% were only snus users, 16% were combined smokers and snus users and the rest never-users of tobacco. The prevalence of isolated snus use was higher among young workers at study inclusion.

A total of 2,552 cohort members were diagnosed with colon cancer during follow-up: 1,179 cancers were right-sided, 937 left-sided and 436 had no registered subsite (Table 2). SIR for colon cancer in the total cohort, compared to the general Swedish male population of the same ages and during the same calendar periods, was 0.95 (95% CI 0.92–0.99). A small risk elevation by 8% for colon cancer was observed among pure smokers, just short of being statistically significant (Table 2). The point estimate of the excess (8%) was of similar magnitude among snus users, but it was farther from reaching statistical significance. Division of total colon cancer into right- and left-sided revealed a general tendency toward somewhat higher relative risks for the latter. However, although a 30% excess of left-sided colon cancer among combined users of smoking and smokeless tobacco attained statistical significance, the differences between right- and left-sided colon cancers were non-significant. There were 1,863 cases of rectal cancer; SIR in the total cohort was 0.99 (95% CI 0.94–1.03). Among smokers the risk of rectal cancer was increased by a significant 16%, while the excess was only 5% (nonsignificant) among snus users. However, the difference between smokers and snus users was not statistically significant. Among 53 cases with anal cancer, 31 cases were pure smokers with a statistically significantly elevated HR of 2.4. There were no indications of any association between isolated snus use and risk of anal cancer but we only observed 1 exposed case.

Table 3 elaborates on the associations by types of smoking tobacco and duration of cigarette smoking. Overall, there was a tendency for dose-response in the association with colon

Table 2. Relative risks of colorectal and anal cancer, expressed as age- and BMI-adjusted hazard ratios (HR), in different groups of tobacco users

	All men at risk		Colon[1]		Right colon[1]		Left colon[1]		Rectum		Anus	
	N[2]	Person-years	*N*[3]	HR (95%CI)	*N*[3]	HR (95%CI)	*N*[3]	HR (95%CI)	*N*[3]	HR (95%CI)	*N*[3]	HR (95%CI)
Non-users of any tobacco	101,959	2,487,208	677	Ref.	324	Ref.	238	Ref.	467	Ref.	7	Ref.
Pure smokers	139,638	3,443,126	1,282	1.08 (0.99–1.19)	602	1.07 (0.93–1.22)	468	1.12 (0.95–1.30)	978	1.16 (1.04–1.30)	31	2.41 (1.06–5.48)
Pure snus users	40,932	910,145	153	1.08 (0.91–1.29)	59	0.86 (0.65–1.13)	60	1.28 (0.97–1.71)	99	1.05 (0.85–1.31)	1	0.61 (0.07–5.07)
Both smokers and snus users	53,852	1,368,261	440	1.17 (1.04–1.32)	194	1.09 (0.91–1.30)	171	1.30 (1.06–1.58)	319	1.21 (1.05–1.39)	14	3.48 (1.40–8.64)
All	336,381	8,208,741	2,552		1,179		937		1,863		53	

[1]The numbers in the right and left colon column do not add up to the numbers in the colon column since some colon cancers could not be classified as right or left. [2]All men in the cohort. [3]All cancer cases in the cohort for each site.

cancer, seemingly more evident for right-sided than for left-sided colon cancer. Even though significantly increased risks for rectal cancer were seen among cigarette and cigar smokers, this dose-response was less evident. The greatest risk increase for rectal cancer (71%) was seen among cigar users, based on 31 exposed cases. Smokers of cigarettes and pipes had substantially increased point estimates of relative risk for anal cancer, although based on few cases, and statistically nonsignificant for pipe smokers.

Table 4 shows associations between colorectal/anal cancer risk and snus use by self-reported duration at study entry and by estimated total duration. Although the highest relative risk estimates were seen for left-sided colon cancers, only one of the estimates attained statistical significance, and no clear dose-response patterns emerged.

Sensitivity analysis

In the sensitivity analysis that only considered exposure data collected at the first visit after 1997, 20,740 workers were excluded (14,982 women, 334 with incorrect NRN, 4,032 with cancer/death/emigration before entry and 1,392 with missing information on BMI), leaving 279,897 for the final analysis. For 203,933, the first visit after 1977 was also their first encounter with "Bygghälsan." The relative risk of colon cancer was 1.08 (95% CI 0.96–1.21) among smokers and 0.97 (95% CI 0.76–1.24) among snus users. The corresponding estimates for rectal cancer were 1.15 (95% CI 1.00–1.31) and 1.13 (95% CI 0.87–1.49), respectively. The relative risk of anal cancer among smokers was 2.4 (95% CI 0.96–5.78). The estimates in subanalyses were similar to those presented for the entire cohort (data not shown).

To get an approximation of possible misclassification of tobacco use, we compared exposure data in workers who had registered visits both before and after 1977. Among 39,234 workers who were classified as never smokers at their first visit in 1971–1975, 1,447 (3.7%) were coded as ex- or current smokers at their first visit after 1977. Among 101,215, initially categorized as never-users of snus 4,224 (4.2%) were subsequently classified as snus users. With a mean interval of 7.5 years, 5,312 (10.7%) out of 49,817 workers reporting current smoking at their first visit in 1971–1975 were classified as ex-smokers at the first visit after 1977.

Discussion

This large cohort study showed an unimpressive association of colon cancer with smoking, just short of being statistically significant overall but seemingly mainly confined to heavy and long-term smokers. We did not find persuasive evidence of differential relationships for right- and left-sided colon cancers. However, the association of smoking with rectal cancer was somewhat stronger than that with colon cancer but with less apparent dose-response in regard to amount and duration. While we were unable to statistically confirm a similar relationship of colon cancer with snus use, the risk of type II error must be kept in mind because the number of

Table 3. Relative risks of colorectal and anal cancer, expressed as age- and BMI-adjusted hazard ratios (HR), among pure smokers in the Swedish Construction Workers Cohort

		Colon		Right-sided colon		Left-sided colon		Rectum		Anus	
	All men at risk	N^1	HR (95%CI)	N^1	HR (95%CI)	N^1	HR (95%CI)	N^1	HR (95%CI)	N^1	HR (95%CI)
Non-users of any tobacco	**101,959**	677	Ref.	324	Ref.	238	Ref.	467	Ref.	7	Ref.
Amount of tobacco											
≤15g/day	86,749	777	1.04 (0.94–1.16)	359	1.01 (0.87–1.17)	280	1.05 (0.89–1.25)	610	1.16 (1.03–1.31)	18	2.26 (0.94–5.42)
>15g/day	47,135	452	1.17 (1.04–1.32)	219	1.20 (1.01–1.43)	165	1.19 (0.98–1.46)	335	1.20 (1.05–1.38)	12	2.89 (1.14–7.36)
Missing	5,754	53		24		23		33		1	
Mixed smoking[2]	**20,061**	440	1.04 (0.89–1.21)	194	1.04 (0.89–1.21)	171	1.07 (0.84–1.36)	319	1.15 (0.96–1.37)	14	2.15 (0.58–8.00)
Cigarette[3]	**98,183**	690	1.10 (0.99–1.22)	331	1.12 (0.96–1.31)	238	1.08 (0.90–1.29)	539	1.18 (1.04–1.34)	18	2.57 (1.07–6.17)
1–4 cigs/day	24,171	101	0.98 (0.79–1.21)	42	0.87 (0.63–1.20)	34	0.96 (0.67–1.37)	90	1.22 (0.97–1.52)	2	1.79 (0.37–8.63)
5–14 cigs/day	28,045	226	1.00 (0.86–1.16)	117	1.08 (0.87–1.34)	66	0.83 (0.63–1.09)	184	1.12 (0.94–1.33)	5	1.94 (0.61–6.12)
15–24 cigs/day	36,910	293	1.22 (1.06–1.40)	139	1.23 (1.01–1.51)	116	1.37 (1.10–1.71)	216	1.22 (1.03–1.43)	8	2.95 (1.06–8.20)
≥25 cigs/day	6,138	58	1.22 (0.94–1.60)	28	1.28 (0.87–1.88)	17	0.99 (0.61–1.62)	41	1.21 (0.88–1.66)	3	6.35 (1.63–24.71)
Missing	2,919	12		5		5		8		0	
Cigar[3]	**1,938**	24	0.89 (0.60–1.35)	12	0.94 (0.53–1.68)	10	1.01 (0.54–1.90)	31	1.71 (1.19–2.46)	0	–
1–7cigars/day	1,008	13	0.80 (0.46–1.38)	7	0.89 (0.42–1.88)	6	1.00 (0.44–2.25)	17	1.58 (0.97–2.56)	0	–
≥8 cigars/day	880	11	1.09 (0.60–1.97)	5	1.06 (0.44–2.56)	4	1.06 (0.39–2.85)	14	1.97 (1.15–3.35)	0	–
Missing	50	0		0		0		188	1.14 (0.96––1.35)	7	2.95 (0.99–8.80)
Pipe[3]	**16,988**	258	1.07 (0.92–1.24)	106	0.91 (0.73–1.14)	112	1.27 (1.01–1.59)	35	0.98 (0.69–1.38)	2	3.95 (0.80–19.56)
1–29 g/week	3,851	40	0.76 (0.55–1.04)	14	0.55 (0.32–0.94)	23	1.20 (0.78–1.84)	145	1.20 (0.99–1.44)	5	2.86 (0.87–9.41)
30–99 g/week	12,134	206	1.16 (0.99–1.36)	86	1.01 (0.79–1.28)	85	1.31 (1.02–1.69)	8	1.00 (0.50–2.01)	0	–
≥100 g/week	990	10	0.87 (0.46–1.62)	5	0.91 (0.38–2.20)	3	0.71 (0.23–2.22)	532		18	
Missing	13	2		1		1		149	1.30 (1.07–1.57)	5	2.60 (0.79–8.52)
Cigarette smoking duration[4,5]	**97,060**	684		331		232		153	1.08 (0.90–1.30)	5	2.29 (0.72–7.30)
1–14 years	49,527	166	1.06 (0.89–1.26)	75	1.01 (0.78–1.31)	55	1.10 (0.81–1.48)	230	1.18 (1.01–1.39)	8	2.84 (1.02–7.94)
15–24 years	27,562	210	1.12 (0.96–1.32)	103	1.19 (0.95–1.49)	68	1.03 (0.78–1.35)	7		0	
≥25 years	19,971	308	1.12 (0.98–1.28)	153	1.16 (0.96–1.41)	109	1.07 (0.85–1.35)	532		18	
Missing	1,123	6		0		6		89	1.15 (0.90–1.46)	2	1.33 (0.23–7.70)
Estimated total cigarette smoking duration[4,6]	**97,060**	684		331		232		147	1.17 (0.97–1.43)	5	2.98 (0.87–10.2)
1–29 years	17,086	114	0.98 (0.79–1.22)	49	0.85 (0.62–1.18)	39	1.17 (0.82–1.67)	181	1.23 (1.03–1.47)	9	4.58 (1.60–13.1)
30–39 years	31,067	162	1.02 (0.85–1.22)	80	1.13 (0.87–1.46)	53	0.94 (0.69–1.28)	115	1.14 (0.92–1.41)	2	1.26 (0.25––6.42)
40–49 years	32,050	217	1.14 (0.97–1.33)	101	1.19 (0.94–1.50)	73	1.01 (0.77–1.33)	7		0	
≥50 years	16,857	191	1.22 (1.03–1.45)	101	1.27 (1.01–1.60)	67	1.18 (0.89–1.56)				
Missing	1,123	6		0		6					

[1]All cancer cases in the cohort for each site. [2]Only pure smokers who combine the use of cigarettes, cigar and pipes. [3]Only pure smokers. [4]Only pure cigarette smoking. [5]Smoking duration at inclusion. [6]Estimated total duration = [Duration of tobacco use at inclusion] + [Time of follow-up].

Table 4. Relative risks of colorectal and anal cancer, expressed as age- and BMI-adjusted hazard ratios (HR), among pure snus users in the Swedish Construction Workers Cohort

	All men at risk	Colon		Right-sided colon		Left-sided colon		Rectum		Anus	
	N^3	N^3	HR (95%CI)	N^3	HR (95%CI)	N^3	HR (95%CI)	N^3	HR (95%CI)	N^3	HR (95%CI)
Non-users of any tobacco	101,959	677	Ref.	324	Ref.	238	Ref.	467	Ref.	7	Ref.
Duration of snus[1]	40,600	153		59		60		97		1	
1–9 years	26,124	39	1.33 (0.94–1.88)	16	1.09 (0.64–1.86)	11	1.55 (0.83–2.90)	15	0.71 (0.42–1.20)	0	–
10–24 years	11,407	43	1.02 (0.74–1.38)	17	0.84 (0.51–1.37)	19	1.35 (0.85–2.17)	33	1.07 (0.75–1.53)	0	–
≥25years	3,069	71	1.06 (0.83–1.36)	26	0.80 (0.53–1.19)	30	1.21 (0.82–1.78)	49	1.18 (0.88–1.60)	1	2.05 (0.23–18.1)
Missing	332	0		0		0		2		0	
Estimated total duration of snus use[2]	40,600	153		59		60		97		1	
1–24 years	10,555	27	1.15 (0.75–1.76)	13	1.07 (0.58–1.98)	5	1.09 (0.43–2.76)	12	0.81 (0.44–1.50)	0	–
25–34 years	17,932	27	0.97 (0.65–1.43)	12	0.92 (0.51–1.66)	11	1.19 (0.64–2.21)	17	0.78 (0.47–1.27)	0	–
35–44 years	8,388	33	1.01 (0.71–1.44)	9	0.63 (0.32–1.22)	20	1.66 (1.05–2.63)	27	1.10 (0.74–1.63)	0	–
≥45 years	3,725	66	1.16 (0.89–1.50)	25	0.87 (0.57–1.31)	24	1.19 (0.77–1.82)	41	1.27 (0.92–1.77)	1	2.88 (0.31–26.9)
Missing	332	0		0		0		2		0	

[1]Duration at inclusion. [2]Estimated total duration = [Duration of tobacco use at inclusion] + [Time of follow-up]. [3]All cancer cases in the cohort for each site.

pure users of snus was smaller. Generally, the point estimates of relative risk among snus users were not dramatically different from those observed among smokers. The difference between smoking and snus use was more persuasive (albeit not statistically confirmed) in regard to risks of rectal and anal cancer, the latter being a low-incidence type of cancer that is known to be associated with smoking and anatomically close to colon and rectum.[1,21–25] As expected, we found an increased risk among smokers but not among snus users. The relative risk estimate among snus users, however, was very imprecise.

During the last decades, several researchers have investigated the risk of colorectal cancer in relation to smoking. Contradictive results have been reported, but the data of adenoma and smoking have been fairly consistent. In a review in 2001, Giovannucci concluded that 21/22 studies described a 2- to 3-fold increased risk of colorectal adenoma associated with long-term heavy smoking.[26] This was verified by Botteri in 2008.[8] Before the 1980s, no clear association between smoking and colorectal cancer was shown, and, in 1986, the International Agency for Research on Cancer (IARC) concluded that, based on existing evidence, tobacco smoking was not a risk factor for colorectal cancer.[27] However, during the latest decade, accumulating evidence suggests that colorectal cancer is a tobacco-associated malignancy[28–36] and that the inability to confirm this association might be due to too short period of follow-up.[26] One study reported earlier onset of colorectal cancer among smokers and has initiated a discussion of smoking as a marker of high risk in screening programs.[37]

However, meta-analyses may be limited by publication bias, and we did not know whether the results were applicable to the Swedish population. Previously, no association with colon cancer, and a small excess risk of rectal cancer, was reported from the same cohort as in the present study, at that time based on 713 and 505 cases of colon and rectal cancer observed during a maximum of 20 years of follow-up (mean 17.6 years).[15] To gain sufficient follow-up time and increase statistical power, we undertook the present study, with an addition of 16 years of follow-up and inclusion of workers up through 1992. As we aimed to have as long follow-up as possible, we chose to use information from 1971 to 1975, despite possible misclassification of smoking status. However, a comparison of data collected before and after 1977 suggested that the importance of possible misclassification in 1971–1975 was small, and the sensitivity analysis, including only cohort members with visits after 1977, indicated that our main results were robust. Our outcome information was trustworthy because of the prospective design, precise record linkages using the NRNs as identifiers (and thus virtually complete follow-up), and the excellent accuracy of the Swedish cancer register.[17,18]

To our knowledge, this is the first cohort study that has investigated associations between smoking, snus use and the risk of colon cancer by subsite. Possible subsite-specific

associations with smoking have previously been addressed in 4 case-control studies,[38–41] but no subsite was significantly associated with smoking. Our study did not reveal any significant difference between right- and left-sided colon cancers, although point estimates of relative risk, both among smokers and snus users, tended to be higher for left-sided cancer. Moreover, a significant 30% risk elevation for left-sided cancer was observed among combined smokers and snus users. On the other hand, while a fairly convincing positive relationship between estimated total duration of habit and risk of left-sided, but not right-sided, colon cancer was noted among snus users, dose-response patterns among smokers tended to be clearer for right-sided than for left-sided cancers. Thus, our results do not provide any unequivocal support for differential relationships with right- and left-sided colon cancers among smokers, whereas preferential occurrence of colon cancer in the left part cannot be excluded in long-term snus users. However, the latter results were imprecise, and multiple significance testing may have generated borderline significant results by chance, though larger studies seem warranted.

The mechanisms behind a possible causal relationship between tobacco use and colorectal cancer development remain speculative. Smoking is associated with microsatellite instability (MSI),[33,42] but it has also been hypothesized that the association between smoking and colon cancer is independent of MSI status, explained by methylation of CpG islands and BRAF mutations.[43] Smokers have a longer colonic transit time than non-smokers,[44] and a longer exposure of carcinogenic substances in the stool might affect the risk of cancer. In a human colon cancer cell line, cigarette smoke extract has been shown to induce the release of factors capable of promoting angiogenesis, and proliferation of human umbilical vascular endothelial cells was also observed.[45] It has, further, been suggested that a possible carcinogenic effect of cigarette smoke is mediated by the systemic circulation and not a direct effect.[46] The mechanistic link with smokeless tobacco, if any, remains to be delineated.

It has been proposed that the induction and latency period for colorectal cancer after tobacco smoke exposure might be as long as 40 years.[26] We, therefore, estimated total smoking duration by adding years of follow-up to the smoking duration that was self-reported at entry into the cohort. Although this doubtlessly introduces some misclassification because many smokers may have changed their habit, the risk of colon cancer seemed to increase with estimated total smoking duration, whereas this pattern could not be confirmed for rectal cancer. Similarly, a relationship between reported number of cigarettes per day and risk was more apparent for colon cancer than for rectal cancer.

Overall, our results are mostly nonsignificant and the excesses so small that they could be explained by confounding from unmeasured factors. Although the restriction to male construction workers has reduced the scope for confounding by factors related to socioeconomic status and occupation, there were no data on other possible confounders such as *e.g.*, diet, alcohol intake and NSAID use. Physical activity is inversely associated with risk of colon cancer, but does not affect rectal cancer risk.[47] Large variations in physical activity are unlikely in this rather homogenous cohort of construction workers, but smokers are known to perform less physical activity than non-smokers.[48] Hence, changes in physical activity might be in the causal pathway. With SIRs of 0.95 and 0.99 for colorectal cancer in the entire Construction Worker cohort, there is no obvious healthy worker effect that needs to be considered when our results are to be generalized to wider populations.

The smoking prevalence among Swedish men has plunged in the last decades, and the incidence of voluntary smoking cessation has increased correspondingly. Unrecorded smoking cessation might partly explain our inability to find a clear association between smoking and colorectal cancer. However, heavy smokers are less likely to quit,[49–51] and our own data indicate that less than 11% of pure smokers in 1971–1975 quitted during a mean follow-up of 7.5 years. Anal cancer, for which there is an established association between smoking and its incidence, serves as a positive control, and the increased risk of anal cancer associated with smoking contradicts an important underestimation of the association between smoking and colorectal cancer.

IARC has classified snus as a class I carcinogenic substance mainly based on *in vitro* studies and animal models. So far, snus has been shown to accelerate the growth of gastric malignancies in mice,[52] and significantly increased risks have been seen for pancreatic cancer[53,54] and esophageal cancer.[16] This is the first study analyzing the association between Swedish snus and colorectal and anal cancer, and although the results were nonsignificant, the pattern of the point estimates for colon cancer was similar to the pattern among smokers.

Our results from a large and homogenous cohort of Swedish male construction workers with up to 37 years of follow-up do not convincingly support an important role of tobacco use in the etiology of colorectal cancer. As expected, an increased risk of anal cancer was associated with smoking.

References

1. Daling JR, Madeleine MM, Johnson LG, Schwartz SM, Shera KA, Wurscher MA, Carter JJ, Porter PL, Galloway DA, McDougall JK. Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. *Cancer* 2004;101: 270–80.
2. National Board of Health and Welfare. Causes of death, 2006. Stockholm: National Board of Health and Welfare, 2008.
3. National Board of Health and Welfare. Cancer incidence in Sweden, 2007. Stockholm: National Board of Health and Welfare, 2008.

4. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. *CA Cancer J Clin* 2007;57:43–66.
5. Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. *Ann Oncol* 2007;18:581–92.
6. Hemminki K, Lonnstedt I, Vaittinen P, Lichtenstein P. Estimation of genetic and environmental components in colorectal and lung cancer and melanoma. *Genet Epidemiol* 2001;20:107–16.
7. Terry MB, Neugut AI. Cigarette smoking and the colorectal adenoma-carcinoma sequence: a hypothesis to explain the paradox. *Am J Epidemiol* 1998;147:903–10.
8. Botteri E, Iodice S, Raimondi S, Maisonneuve P, Lowenfels AB. Cigarette smoking and adenomatous polyps: a meta-analysis. *Gastroenterology* 2008;134:388–95.
9. Peipins LA, Sandler RS. Epidemiology of colorectal adenomas. *Epidemiol Rev* 1994; 16:273–97.
10. Boutron MC, Faivre J, Dop MC, Quipourt V, Senesse P. Tobacco, alcohol, and colorectal tumors: a multistep process. *Am J Epidemiol* 1995;141:1038–46.
11. Boutron-Ruault MC. Re: "Cigarette smoking and the colorectal adenoma-carcinoma sequence: a hypothesis to explain the paradox" [comment]. *Am J Epidemiol* 1999;149:787–8.
12. Giovannucci E, Martinez ME. Tobacco, colorectal cancer, and adenomas: a review of the evidence. *J Natl Cancer Inst* 1996;88: 1717–30.
13. Folkhälsoinstitutet, Nationella folkhälsoenkäten. Statens folkhälsoinstitut, 2005.
14. Heineman EF, Zahm SH, McLaughlin JK, Vaught JB. Increased risk of colorectal cancer among smokers: results of a 26-year follow-up of US veterans and a review. *Int J Cancer* 1994;59:728–38.
15. Nyren O, Bergstrom R, Nystrom L, Engholm G, Ekbom A, Adami HO, Knutsson A, Stjernberg N. Smoking and colorectal cancer: a 20-year follow-up study of Swedish construction workers. *J Natl Cancer Inst* 1996;88:1302–7.
16. Zendehdel K, Nyren O, Luo J, Dickman PW, Boffetta P, Englund A, Ye W. Risk of gastroesophageal cancer among smokers and users of Scandinavian moist snuff. *Int J Cancer* 2008;122:1095–9.
17. Barlow L, Westergren K, Holmberg L, Talback M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. *Acta Oncol* 2009;48:27–33.
18. Mattsson B, Wallgren A. Completeness of the Swedish Cancer Register. Non-notified cancer cases recorded on death certificates in 1978. *Acta Radiol Oncol* 1984;23:305–13.
19. Shoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika* 1982;69:239–41.
20. Breslow NE, Day NE. Statistical methods in cancer research. Volume II–The design and analysis of cohort studies. *IARC Sci Publ* 1987:1–406.
21. Tseng HF, Morgenstern H, Mack TM, Peters RK. Risk factors for anal cancer: results of a population-based case–control study. *Cancer Causes Control* 2003;14: 837–46.
22. Daling JR, Sherman KJ, Hislop TG, Maden C, Mandelson MT, Beckmann AM, Weiss NS. Cigarette smoking and the risk of anogenital cancer. *Am J Epidemiol* 1992; 135:180–9.
23. Frisch M, Glimelius B, Wohlfahrt J, Adami HO, Melbye M. Tobacco smoking as a risk factor in anal carcinoma: an antiestrogenic mechanism? *J Natl Cancer Inst* 1999;91: 708–15.
24. Phillips DH, Hewer A, Scholefield JH, Skinner P. Smoking-related DNA adducts in anal epithelium. *Mutat Res* 2004;560: 167–72.
25. Moore TO, Moore AY, Carrasco D, Vander Straten M, Arany I, Au W, Tyring SK. Human papillomavirus, smoking, and cancer. *J Cutan Med Surg* 2001;5:323–8.
26. Giovannucci E. An updated review of the epidemiological evidence that cigarette smoking increases risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev* 2001;10: 725–31.
27. International Agency for Research of Cancer (IARC). IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, Vol 38. Tobacco smoking. Lyon, France: IARC, 1986.
28. Hannan LM, Jacobs EJ, Thun MJ. The association between cigarette smoking and risk of colorectal cancer in a large prospective cohort from the United States. *Cancer Epidemiol Biomarkers Prev* 2009;18: 3362–7.
29. Luchtenborg M, White KK, Wilkens L, Kolonel LN, Le Marchand L. Smoking and colorectal cancer: different effects by type of cigarettes? *Cancer Epidemiol Biomarkers Prev* 2007;16:1341–7.
30. Sturmer T, Glynn RJ, Lee IM, Christen WG, Hennekens CH. Lifetime cigarette smoking and colorectal cancer incidence in the Physicians' Health Study I. *J Natl Cancer Inst* 2000;92:1178–81.
31. Driver JA, Gaziano JM, Gelber RP, Lee IM, Buring JE, Kurth T. Development of a risk score for colorectal cancer in men. *Am J Med* 2007;120:257–63.
32. Minami Y, Tateno H. Associations between cigarette smoking and the risk of four leading cancers in Miyagi Prefecture. Japan: a multi-site case-control study. *Cancer Sci* 2003;94:540–7.
33. Chia VM, Newcomb PA, Bigler J, Morimoto LM, Thibodeau SN, Potter JD. Risk of microsatellite-unstable colorectal cancer is associated jointly with smoking and nonsteroidal anti-inflammatory drug use. *Cancer Res* 2006;66:6877–83.
34. Botteri E, Iodice S, Bagnardi V, Raimondi S, Lowenfels AB, Maisonneuve P. Smoking and colorectal cancer: a meta-analysis. *JAMA* 2008;300:2765–78.
35. Liang PS, Chen TY, Giovannucci E. Cigarette smoking and colorectal cancer incidence and mortality: systematic review and meta-analysis. *Int J Cancer* 2008.
36. Huxley RR, Ansary-Moghaddam A, Clifton P, Czernichow S, Parr CL, Woodward M. The impact of dietary and lifestyle risk factors on risk of colorectal cancer: A quantitative overview of the epidemiological evidence. *Int J Cancer* 2009.
37. Acott AA, Theus SA, Marchant-Miros KE, Mancino AT Association of tobacco and alcohol use with earlier development of colorectal cancer: should we modify screening guidelines? *Am J Surg* 2008;196: 915–8; discussion 8–9.
38. Hu J, Morrison H, Mery L, DesMeules M, Macleod M. Diet and vitamin or mineral supplementation and risk of colon cancer by subsite in Canada. *Eur J Cancer Prev* 2007;16:275–91.
39. Inoue M, Tajima K, Hirose K, Hamajima N, Takezaki T, Hirai T, Kato T, Ohno Y. Subsite-specific risk factors for colorectal cancer: a hospital-based case-control study in Japan. *Cancer Causes Control* 1995;6: 14–22.
40. Poynter JN, Haile RW, Siegmund KD, Campbell PT, Figueiredo JC, Limburg P, Young J, Le Marchand L, Potter JD, Cotterchio M, Casey G, Hopper JL, et al. Associations between smoking, alcohol consumption, and colorectal cancer, overall and by tumor microsatellite instability status. *Cancer Epidemiol Biomarkers Prev* 2009;18:2745–50.
41. Sharpe CR, Siemiatycki JA, Rachet BP. The effects of smoking on the risk of colorectal cancer. *Dis Colon Rectum* 2002;45:1041–50.
42. Slattery ML, Curtin K, Anderson K, Ma KN, Ballard L, Edwards S, Schaffer D, Potter J, Leppert M, Samowitz WS. Associations between cigarette smoking, lifestyle factors, and microsatellite instability in colon tumors. *J Natl Cancer Inst* 2000;92:1831–6.
43. Samowitz WS, Albertsen H, Sweeney C, Herrick J, Caan BJ, Anderson KE, Wolff RK, Slattery ML. Association of smoking. Cp. G island methylator phenotype, and V600E BRAF mutations in colon cancer. *J Natl Cancer Inst* 2006;98:1731–8.
44. Meier R, Beglinger C, Dederding JP, Meyer-Wyss B, Fumagalli M, Rowedder A,

Turberg Y, Brignoli R. Influence of age, gender, hormonal status and smoking habits on colonic transit time. *Neurogastroenterol Motil* 1995;7:235–8.
45. Ye YN, Wu WK, Shin VY, Cho CH. A mechanistic study of colon cancer growth promoted by cigarette smoke extract. *Eur J Pharmacol* 2005;519:52–7.
46. Abrams JA, Terry MB, Neugut AI. Cigarette smoking and the colorectal adenoma-carcinoma sequence. *Gastroenterology* 2008;134:617–9.
47. Samad AK, Taylor RS, Marshall T, Chapman MA. A meta-analysis of the association of physical activity with reduced risk of colorectal cancer. *Colorectal Dis* 2005;7:204–13.
48. Sneve M, Jorde R. Cross-sectional study on the relationship between body mass index and smoking, and longitudinal changes in body mass index in relation to change in smoking status: the Tromso Study. *Scand J Public Health* 2008;36: 397–407.
49. Hymowitz N, Cummings KM, Hyland A, Lynn WR, Pechacek TF, Hartwell TD. Predictors of smoking cessation in a cohort of adult smokers followed for five years. *Tob Control* 1997;6(Suppl 2):S57–62.
50. Holtrop JS, Stommel M, Corser W, Holmes-Rovner M. Predictors of smoking cessation and relapse after hospitalization for acute coronary syndrome. *J Hosp Med* 2009;4:E3–9.
51. Ong KC, Cheong GN, Prabhakaran L, Earnest A. Predictors of success in smoking cessation among hospitalized patients. *Respirology* 2005;10:63–9.
52. Stenstrom B, Zhao CM, Rogers AB, Nilsson HO, Sturegard E, Lundgren S, Fox JG, Wang TC, Wadstrom TM, Chen D. Swedish moist snuff accelerates gastric cancer development in *Helicobacter pylori*-infected wild-type and gastrin transgenic mice. *Carcinogenesis* 2007;28: 2041–6.
53. Boffetta P, Aagnes B, Weiderpass E, Andersen A. Smokeless tobacco use and risk of cancer of the pancreas and other organs. *Int J Cancer* 2005;114:992–5.
54. Luo J, Ye W, Zendehdel K, Adami J, Adami HO, Boffetta P, Nyren O. 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; 369:2015–20.