Int. J. Cancer: **83**, 223–229 (1999)

Publication of the International Union Against Cancer
Publication de l'Union Internationale Contre le Cancer

TOBACCO, ALCOHOL AND THE RISK OF GASTRIC CANCER BY SUB-SITE AND HISTOLOGIC TYPE

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Few studies have provided information on the role of smoking and alcohol in the carcinogenesis of gastric cancer by sub-site and histologic type. The relationship of snuff dipping with risk of gastric cancer has also been rarely studied. In a population-based case-control study conducted in 5 counties of Sweden from February 1989 to January 1995, a total of 90 cases of gastric cardia cancer, 260 and 164 cases of distal gastric cancer of intestinal and diffuse types, respectively, and 1164 frequency-matched control subjects were personally interviewed about life-time smoking, use of smokeless tobacco and use of alcohol 20 years ago. Current smokers had a higher risk than never-smokers for all 3 kinds of gastric adenocarcinoma [odds ratio (OR) 1.7, 95% confidence interval (CI) 1.0–3.1 for gastric cardia adenocarcinoma; OR 1.8, 95% CI 1.2–2.7 for distal gastric cancer of intestinal type; and OR 2.2, 95% CI 1.4–3.5 for distal gastric cancer of diffuse type], and the risk rose with increasing dose and duration of smoking among current smokers. However, no elevated risk was observed for ex-smokers. Neither intake of alcoholic beverages nor snuff dipping was associated with an increased risk of any type of cardia or gastric cancer. Our study did not support the hypothesis that the role of tobacco differs by sub-site and histologic sub-type of gastric cancer. *Int. J. Cancer* 83:223-229, 1999.
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Over the years, tobacco and alcohol have attracted considerable attention as possible causes of gastric cancer. A meta-analysis has suggested a 50 to 60% increase in risk of gastric cancer among smokers compared with non-smokers (Trédaniel *et al.*, 1997), while most earlier studies failed to find a positive association between alcohol intake and the risk of gastric cancer (Neugut *et al.*, 1996). Users of smokeless tobacco ingest much more carcinogenic nitrosamines than do smokers (IARC, 1985), reflected by higher levels of hemoglobin adducts of some tobacco-specific nitrosamines among the former (Carmella *et al.*, 1990). Therefore, a role of smokeless tobacco in the carcinogenesis of gastric cancer seems plausible, but the data on the use of smokeless tobacco and the risk of gastric cancer are scanty and contradictory.

It has become increasingly apparent that gastric cancer may consist of more than one disease entity, based on anatomic and histopathologic subdivisions. The incidence of cancer of the gastric cardia appears to be increasing rapidly in the US and Europe, in contrast to the steady decrease of distal gastric cancer (Neugut *et al.*, 1996). Gastric cancer can also be divided into 2 main histologic types, diffuse and intestinal, according to Lauren's classification (Neugut *et al.*, 1996). Based on the different patterns of occurrence, the intestinal type of gastric cancer is thought to be more environmentally related than the diffuse type, a hypothesis not yet well verified. The majority of studies did not consider these subdivisions, and the possibility of differential etiologies. We hypothesized that alcohol and tobacco may be differentially associated with risk of cardia and distal gastric cancer and with cancer of intestinal and diffuse histologic sub-types. To test this hypothesis, we analyzed the effects of smoking, use of smokeless tobacco, alcohol intake and the risk of gastric cancer by sub-site and histology in a large population-based case-control study.

MATERIAL AND METHODS

Study area and subjects

The study base of our case-control study consisted of all individuals between 40 and 79 years of age, born in Sweden, and living in one of 5 counties (with differing incidence rates of gastric cancer) in northern and central Sweden from February 1989 through January 1995. Eligible as cases were all persons with a new, histologically confirmed gastric cancer. Case ascertainment via contact persons at all departments of surgery and pathology, supplemented by linkages to regional and national cancer registries, ensured that all cases, even those treated outside the study area, or reported with long delays, were identified (Ekström *et al.*, 1999). Using information from special report forms prospectively filled out by clinicians, review of the clinical records, and re-evaluation of all histological material by one pathologist, all tumours were classified into cancers in the cardia with its center within 1 cm proximal and 2 cm distal to the gastroesophageal junction (Ekström *et al.*, 1999) or in the distal stomach (in the following referred to as "cardia cancer" and "gastric cancer" respectively) and into histologic type (diffuse, intestinal, mixed and indeterminate type). Approximately 2 controls per case were randomly selected from continuously updated population registers covering the entire study base. The selection was stratified by age and gender according to the expected distribution among all cases (frequency matching).

Face-to-face interviews were performed with 567 of 908 eligible cases. The primary reasons for non-participation were: early death or advanced disease (n = 270); mental or physical illness other than gastric cancer (40); refusal (28); and failure to locate the patient for interview (3); 6 cases for which we lacked information on tobacco use were further deleted from analysis. Among the remaining 561 cases, 90 had cardia cancer and 466 gastric cancer, while 5 had cancers that could not be classified with regard to site of origin. Of the gastric cancers, 260 were of the intestinal type, 164 diffuse type, 33 mixed type and 9 of indeterminate type. Analyses were restricted to cardia cancer, intestinal-type gastric cancer, and diffuse-type gastric cancer. Of 1534 randomly selected controls, 245 refused to participate, 90 could not be interviewed due to mental or physical illness (other than gastric cancer), and 34 could not be located. Consequently, 1165 controls were recruited, among whom one subject was deleted due to missing information on tobacco use.

Collection of exposure data

Interviews were carried out by specially trained professional interviewers from Statistics Sweden. It was impossible to blind them to the case/control status of the interviewees, but they were

Grant sponsor: National Cancer Institute; Grant number: R01 CA50959.

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Received 13 March 1999; Revised 26 April 1999

unaware of the study hypotheses and instructed to treat cases and controls in a strictly equal manner. We inquired about lifetime tobacco smoking (cigarettes, cigars or pipe). Cigarette smokers were defined as those smoking one cigarette or more per day for at least half a year, and pipe-smokers or cigar-smokers as those smoking at least one pipe or one cigar per week for half a year or more. Users of smokeless tobacco, including chewing tobacco and snuff, were defined as those practising the habit at least once a week for 6 months or more. To avoid reversed causality, tobacco-user status was determined 2 years prior to the interview; those having the habit at that point in time were referred to as current smokers (or smokeless-tobacco users), while ex-smoker (ex-user) status was reserved for those who had stopped 2 or more years before the interview. Alcohol intake was assessed with separate questions about light beer, medium-strong beer, strong beer, wine and hard-liquor consumption 20 years before interview. Answers were categorized into 9 levels, ranging from "never" to "twice daily or more". With supplementary questions about the average amount consumed each time, we transformed the data to milliliters per month. Total alcohol consumption was calculated by multiplying the latter figures by beverage-specific alcohol concentrations.

On the basis of lifetime occupational experience, the study subjects were grouped into 5 classes of socio-economic status (SES): unskilled manual workers, skilled manual workers, non-manual workers, self-employed persons, and farmers (Hansson, 1993). From 45 food-frequency questions, total consumption of fresh vegetables 20 years prior to interview was estimated by summing up the intake of specified vegetables. Similarly, total consumption of fruits was estimated by summing up the amounts of different fresh fruits and fruit juice. The quartiles of total fresh vegetable and fruit consumption were then given a score from 1 to 4. A sum of scores, ranging from 2 to 8, served as our index of total consumption of fresh vegetables and fruits (2–4, low; ≥5, high consumption). After transforming the information about food frequencies into quantitative data by using standard, item-specific portion sizes and the Swedish food composition database system KOST, an index of intake of anti-oxidants, ascorbic acid and beta-carotene, was also created (Hansson, 1993).

During the last part of our study period, we collected blood samples from interviewed cases (n = 298, among which 3 cases were further deleted from analysis, due to incomplete information on tobacco use) and controls (n = 245, participating rate = 70.5% of those asked to provide a blood sample). After centrifugation, sera were stored at −70°C until assayed for anti-*Helicobacter pylori* IgG antibodies, using a commercial ELISA kit (HM-CAP, Enteric Products, Westbury, NY). The sensitivity and specificity of this assay were 98% and 96% respectively (Marchildon *et al.*, 1996).

Statistical methods

Unconditional logistic regression was applied to estimate OR and corresponding 95% CI. All models included as co-variates age (entered as a continuous variable), gender, area of current residence (north *vs.* south), body-mass index (BMI) 20 years before interview (weight in kilograms divided by the square of height in meters, entered as a continuous variable) and SES (5 categories, entered as an indicator variable). When adjusting for smoking, we used a 3-level indicator variable (never/ex/current), and for use of smokeless tobacco a dichotomous term (never/ever). To adjust for possible confounding effects of beer, wine and hard liquor, each factor was entered as a dichotomous variable (ever/never). Tests for trend were done by logistic models based on semi-continuous variables. Potential interaction effects between smoking, alcohol use, intake of fresh vegetables and fruits and other factors were tested by using a multiplicative model with cross-product terms representing the interaction between the 2 variables.

The study was approved by the ethics committee at Uppsala University Hospital in Sweden, and all cases and controls gave informed consent to interview.

RESULTS

The distribution of 3 types of gastric cancer across age groups, gender and socio-economic strata is shown in Table I. The male/female ratios were 3.7, 2.7 and 1.1 for cardia, intestinal-type, and diffuse-type gastric cancer respectively. Within the age limit of the study base (40–79 years), the age distributions among cases of cardia and diffuse gastric cancer were similar, with mean ages 64.9 and 65.0 respectively. However, intestinal gastric cancer was more common in old age groups, with a mean age of 70.2. The mean age of control subjects was 67.0.

Table II shows the risk of gastric cancer in relation to smoking of any kind of tobacco products, *i.e.*, cigarette, pipe and cigar. In comparison with non-smokers, elevated risks were observed among current smokers for all 3 kinds of carcinoma after adjustments for age, gender, residence area, BMI, SES, use of smokeless tobacco and alcoholic beverages, though the 70% excess for cardia cancer was only marginally statistically significant. The excess was greatest (120%) for gastric cancer of the diffuse type. The risk among ex-smokers was not statistically different from that in non-smokers, and there was no clear trend associated with recency of cessation. Ex-smokers had a significantly lower risk of cardia cancer and diffuse-type stomach cancer when compared with current smokers ($p < 0.05$). When limited to cigarette smoking, a significant dose-risk relationship was observed for number of cigarettes smoked and duration of the habit among current smok-

TABLE I – DISTRIBUTION OF CASES AND CONTROLS ACROSS AGE GROUPS, GENDER AND SOCIO-ECONOMIC STRATA

	Cardia cancer		Distal stomach cancer				Control	
	All histologic types		Intestinal type		Diffuse type			
	n	%[1]	n	%[2]	n	%[3]	n	%[4]
Age at interview (years)								
40–49	11	12.2	2	0.8	17	10.4	105	9.0
50–59	18	20.0	24	9.2	28	17.1	97	8.3
60–69	26	28.9	73	28.1	54	32.9	370	31.8
70–79	35	38.9	161	61.9	65	39.6	592	50.9
Gender								
Male	71	78.9	190	73.1	87	53.0	779	66.9
Female	19	21.1	70	26.9	77	47.0	385	33.1
Socio-economic status								
Unskilled manual workers	35	38.9	115	44.2	90	54.9	446	38.3
Skilled manual workers	25	27.8	64	24.6	35	21.3	263	22.6
Non-manual workers	19	21.1	48	18.5	27	16.5	303	26.0
Self-employed persons	5	5.6	14	5.4	3	1.8	57	4.9
Farmers	6	6.7	19	7.3	9	5.5	95	8.2

[1]Percentage among a total of 90 cases.–[2]Percentage among a total of 260 cases.–[3]Percentage among a total of 164 cases.–[4]Percentage among a total of 1164 controls.

TABLE II – ADJUSTED OR AND 95% CI IN RELATION TO SMOKING BY SUB-SITE AND LAURÉN'S CLASSIFICATION[1]

Exposure	Controls	Cardia cancer		Distal stomach cancer			
		All histologic types		Intestinal type		Diffuse type	
		Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)
Smoking status[2]							
Never-smokers[3]	512	34	Reference	92	Reference	61	Reference
Ex-smokers	415	25	0.9 (0.5–1.6)	101	1.4 (1.0–2.0)	46	1.3 (0.8–2.0)
Current smokers	237	31	1.7 (1.0–3.1)	67	1.8 (1.2–2.7)	57	2.2 (1.4–3.5)
Cessation (years since quitting)							
≥21	161	9	0.7 (0.3–1.6)	43	1.4 (0.9–2.2)	12	0.9 (0.5–1.9)
11–20	134	8	0.6 (0.2–1.5)	30	1.4 (0.8–2.3)	21	1.8 (1.0–3.3)
≤10	120	8	0.9 (0.4–2.2)	28	1.4 (0.8–2.3)	13	1.1 (0.5–2.2)
		p value for trend = 0.59		p value for trend = 0.15		p value for trend = 0.32	
Cigarette smoking							
Ex-smokers	366	20	0.8 (0.4–1.5)	84	1.4 (0.9–2.0)	40	1.2 (0.8–2.0)
Current smokers							
1–10 cigarettes/day	87	9	1.7 (0.7–3.8)	21	1.6 (0.9–2.8)	21	1.9 (1.0–3.4)
11–15 cigarettes/day	44	4	1.2 (0.4–3.8)	12	1.8 (0.9–3.7)	11	2.5 (1.2–5.5)
≥16 cigarettes/day	64	13	2.2 (1.0–4.8)	17	2.0 (1.1–3.9)	19	2.7 (1.4–5.1)
		p value for trend = 0.04		p value for trend = 0.005		p value for trend = 0.0004	
Duration (years)							
1–30	69	8	1.3 (0.5–3.6)	8	1.2 (0.5–2.9)	18	1.9 (0.9–3.8)
≥31	128	18	2.2 (1.1–4.3)	42	2.1 (1.3–3.4)	33	2.6 (1.5–4.5)
		p value for trend = 0.03		p value for trend = 0.002		p value for trend = 0.0003	

[1]OR adjusted for age, gender, residence area, body-mass index, socio-economic status, use of smokeless tobacco, and use of beer, wine and liquor.–[2]Including cigarette smoking, pipe smoking or cigar smoking.–[3]Reference category for all estimates in this table is "Never-smokers".

TABLE III – RISK OF STOMACH CANCER BY SUB-SITE AND LAURÉN'S CLASSIFICATION ACCORDING TO COMBINED EFFECTS OF SMOKING AND CONSUMPTION OF FRESH VEGETABLES AND FRUITS

Type of habit[1]	Controls	Cardia cancer		Distal stomach cancer			
		All histologic types		Intestinal type		Diffuse type	
		Cases	OR (95% CI)[2]	Cases	OR (95% CI)[2]	Cases	OR (95% CI)[2]
Smoke(−) and index(high)	324	20	Reference	52	Reference	38	Reference
Smoke(−) and index(low)	188	14	1.1 (0.5–2.3)	40	1.3 (0.8–2.0)	23	0.9 (0.5–1.7)
Smoke(+) and index(high)	411	22	0.8 (0.4–1.6)	80	1.4 (0.9–2.1)	54	1.3 (0.8–2.2)
Smoke(+) and index(low)	241	34	2.0 (1.0–3.9)	88	2.2 (1.4–3.4)	49	2.2 (1.3–3.7)

[1]Smoke(+): ever-smoker; smoke(−): never-smoker, index(low): low consumption of fresh vegetables and fruits (see text); index(high): high consumption of fresh vegetables and fruits.–[2]OR estimated by adjusting for age, gender, residence area, body-mass index, socio-economic status, use of smokeless tobacco and use of beer, wine and hard liquor.

ers. For current smokers who smoked more than 15 cigarettes a day, the risk was 2-fold or more for all 3 types of gastric cancer. When analyses were stratified by age (<70 *vs.* ≥70 years), the estimated OR for smoking were similar for 2 strata in cardia cancer and diffuse-type gastric cancer. For intestinal-type gastric cancer, however, the association with smoking was seen only among people below the age of 70 years (OR 3.1, 95% CI 1.6–6.1 for ex-smokers; OR 3.6, 95% CI 1.8–7.0 for current smokers in the younger stratum; OR 1.0, 95% CI 0.6–1.5 for ex-smokers; OR 1.1, 95% CI 0.7–2.0 for current smokers in the older stratum) (data not shown).

The joint effects of smoking and consumption of fresh vegetables and fruits are shown in Table III. With adjustment for age, gender, residence area, BMI, SES, use of smokeless tobacco and alcoholic beverages, compared with never-smokers with high consumption of fresh vegetables and fruits, the risk for all 3 kinds of carcinoma was doubled for ever-smokers with low consumption index, while OR for ever-smokers with a high consumption of vegetables and fruits were near unity. However, the interaction terms were not statistically significant (data not shown). The interaction of smoking and the intake of anti-oxidants (ascorbic acid and beta-carotene) was also non-significant, with adjustment for age, gender, residence area, BMI, SES, total energy intake and vitamin supplement (data not shown). The results were similar when using an additive model to test interaction effects.

Among the 295 cases and 245 controls tested for antibodies against *H. pylori*, the OR for all cardia and gastric cancer among ex- and current smokers, compared with never-smokers, were 1.1 and 2.5 respectively, after adjustment for age, gender, residence area, BMI, SES, use of smokeless tobacco and alcoholic beverages. Further control for *H. pylori* seropositivity had little influence on the estimates, the corresponding OR being 1.0 and 2.4 respectively. We also introduced into the models proxy-variables for the risk of having been infected by *H. pylori* at young age, such as number of siblings and SES during childhood (subject's father's occupation). However, the smoking results did not change substantially. It thus appeared that *H. pylori* infection was not an important confounding factor for the association between smoking and the risk of gastric cancer.

Table IV shows the OR for alcohol intake. Neither beer nor hard liquor consumption, or total alcohol intake, was associated with the risk of any of the 3 kinds of adenocarcinoma, after adjustments for age, gender, residence area, BMI, SES, smoking, use of smokeless tobacco and use of other alcoholic beverages. However, wine drinking was inversely and dose-dependently associated with risk for cardia cancer, and to a lesser extent for intestinal gastric cancer, but not for diffuse gastric cancer. For cardia cancer, this seemingly protective effect remained after adjustment for vegetable and fruit consumption, number of siblings, age at first access to refrigerator and education (data not shown), while for the intestinal type, further control for confounders led the OR towards unity (data not

TABLE IV – ADJUSTED OR AND 95% CI IN RELATION TO ALCOHOL BY SUB-SITE AND LAURÉN'S CLASSIFICATION[1]

Exposure	Controls	Cardia cancer		Distal stomach cancer			
		All histologic types		Intestinal type		Diffuse type	
		Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)
Total alcohol consumption (ml 100% alcohol/month)							
Non-drinkers	265	18	Reference	52	Reference	36	Reference
1–35	260	20	0.9 (0.4–1.9)	64	1.2 (0.8–1.9)	50	1.3 (0.8–2.1)
36–160	312	27	0.8 (0.4–1.7)	73	1.2 (0.8–1.9)	42	1.0 (0.6–1.7)
>160	294	22	0.7 (0.3–1.5)	66	1.2 (0.7–1.9)	34	1.0 (0.5–1.8)
		p value for trend = 0.30		p value for trend = 0.56		p value for trend = 0.73	
Light beer (ml/month)							
<400	738	58	Reference	172	Reference	118	Reference
400–2399	205	14	1.0 (0.5–1.9)	35	0.8 (0.5–1.2)	24	0.9 (0.5–1.4)
≥2400	221	18	1.2 (0.7–2.3)	53	1.0 (0.7–1.5)	22	0.9 (0.5–1.5)
		p value for trend = 0.54		p value for trend = 0.87		p value for trend = 0.60	
Medium-strong beer (ml/month)							
<400	911	70	Reference	210	Reference	131	Reference
≥400	253	20	0.8 (0.5–1.5)	50	0.9 (0.6–1.3)	33	1.0 (0.6–1.6)
Strong beer							
Non-drinkers	911	69	Reference	207	Reference	133	Reference
Drinkers	253	21	0.8 (0.4–1.5)	53	1.1 (0.7–1.6)	31	0.9 (0.5–1.4)
Wine (ml/month)							
Non-drinkers	483	44	Reference	110	Reference	65	Reference
1–59	209	18	1.0 (0.5–1.8)	71	1.4 (1.0–2.1)	43	1.6 (1.0–2.6)
60–199	157	11	0.5 (0.2–1.1)	27	0.8 (0.5–1.3)	15	0.6 (0.3–1.2)
200–599	172	8	0.5 (0.2–1.2)	36	1.0 (0.6–1.6)	25	1.3 (0.7–2.4)
≥600	126	6	0.4 (0.2–1.1)	14	0.5 (0.3–1.0)	15	1.1 (0.6–2.3)
		p value for trend = 0.03		p value for trend = 0.08		p value for trend = 0.90	
Hard liquor (ml/month)							
Non-drinkers	405	24	Reference	83	Reference	58	Reference
1–79	281	27	1.5 (0.7–3.0)	61	1.0 (0.7–1.6)	41	0.9 (0.5–1.5)
80–319	279	19	0.9 (0.4–2.1)	58	1.1 (0.7–1.7)	32	0.8 (0.5–1.5)
≥320	189	17	1.2 (0.5–2.8)	54	1.5 (0.9–2.5)	32	1.4 (0.7–2.8)
		p value for trend = 0.91		p value for trend = 0.17		p value for trend = 0.42	

[1]OR adjusted for age, gender, residence area, body-mass index, socio-economic status, smoking, use of smokeless tobacco and use of different kinds of alcoholic beverages.

shown). Adjustment for *H. pylori* seropositivity among 540 cases and controls did not change our alcohol results materially (data not shown). We found no significant interactions between smoking and alcohol consumption (data not shown).

Only 8 cases and 14 controls reported having ever chewed tobacco, and none of the female study subjects had ever used moist snuff. Therefore, analyses of the effects of smokeless tobacco were restricted to snuff use among males. Table V shows the distribution of never-users and ever-users of snuff among male cases and controls by age, SES and smoking status. The overall exposure prevalence of snuff dipping was 22% and 25% among cases and controls respectively.

Table VI shows the associations between snuff dipping and the 3 kinds of gastric adenocarcinoma after adjustment for age, residence area, BMI, SES and smoking status. No increased risk was observed for ever-users. Examination of risks by age at start, duration and daily frequency revealed no conspicuous excesses in risk in any of the strata, and no clear trends. Due to the small number of exposed cases for each sub-type, however, the precision of our estimates was poor.

Users of snuff were over-represented among ever-smokers, particularly among ex-smokers. To explore any possible interaction between smoking and snuff dipping, and to further rule out that the low risk estimates among snuff users only reflected their propensity for giving up smoking, we estimated snuff-user-specific OR for total gastric and cardia cancer by smoking status (Table VII). After adjusting for age, residence area, BMI, SES and use of alcoholic beverages, a statistically significant 2-fold excess risk was noted for current smokers without any experience of snuff dipping. In contrast, current smokers who ever used snuff had an OR of 1.0, significantly smaller than that for those who did not use snuff ($p < 0.05$). But the former usually smoked less and for a shorter duration than smokers who did not use snuff.

TABLE V – DISTRIBUTION OF SNUFF USERS ACROSS AGE GROUPS, SOCIO-ECONOMIC STRATA AND SMOKING CATEGORIES IN MALES

	Cases	Controls
	Ever-users/total cases (%)	Ever-users/total controls (%)
Age at interview (years)		
40–49	7/22 (31.8)	32/68 (47.1)
50–59	11/50 (22.0)	20/70 (28.6)
60–69	21/116 (18.1)	45/260 (17.3)
70–79	44/187 (23.5)	95/381 (24.9)
Socio-economic status		
Unskilled manual workers	34/136 (25.0)	72/246 (29.3)
Skilled manual workers	24/109 (22.0)	61/211 (28.9)
Non-manual workers	12/80 (15.0)	37/219 (16.9)
Self-employed persons	3/22 (13.6)	6/46 (13.0)
Farmers	10/28 (35.7)	16/57 (28.1)
Smoking status		
Never-smokers	11/91 (12.1)	36/253 (14.2)
Ex-smokers	56/167 (33.5)	114/349 (32.7)
Current smokers	16/117 (13.7)	42/177 (23.7)

DISCUSSION

In this large population-based case-control study, smoking was positively and dose-dependently associated with both major histologic types of gastric carcinoma, and to a similar degree with cancer of the gastric cardia. Alcohol intake was not associated with

TABLE VI – ADJUSTED OR AND 95% CI IN RELATION TO SNUFF DIPPING BY SUB-SITE AND LAURÉN'S CLASSIFICATION IN MALES[1]

Snuff dipping	Controls	Cardia cancer		Distal stomach cancer			
		All histologic types		Intestinal type		Diffuse type	
		Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)
Never-users	587	56	Reference	146	Reference	68	Reference
Ex-users	74	6	0.8 (0.3–1.9)	18	0.9 (0.5–1.6)	8	0.7 (0.3–1.6)
Current users	118	9	0.5 (0.2–1.1)	26	0.8 (0.5–1.3)	11	0.6 (0.3–1.2)
Ever-users	192	15	0.6 (0.3–1.2)	44	0.8 (0.5–1.2)	19	0.7 (0.4–1.2)
Age at start (years)							
≥21	114	6	0.4 (0.1–1.0)	23	0.7 (0.4–1.2)	13	0.8 (0.4–1.5)
16–20	77	9	1.0 (0.4–2.0)	21	1.0 (0.6–1.7)	6	0.5 (0.2–1.1)
		p value for trend = 0.45		p value for trend = 0.62		p value for trend = 0.12	
Duration (years)							
1–10	60	6	0.9 (0.3–2.2)	11	0.7 (0.3–1.3)	5	0.6 (0.2–1.3)
11–30	65	6	0.7 (0.2–1.7)	9	0.5 (0.2–1.1)	11	1.1 (0.5–2.2)
≥31	66	3	0.3 (0.0–1.1)	24	1.2 (0.7–2.0)	3	0.4 (0.1–1.0)
		p value for trend = 0.09		p value for trend = 0.80		p value for trend = 0.17	
Times/day							
≤5	113	7	0.5 (0.2–1.2)	26	0.8 (0.5–1.3)	7	0.4 (0.2–0.9)
>5	78	8	0.8 (0.3–1.8)	18	0.9 (0.5–1.6)	12	1.0 (0.5–2.0)
		p value for trend = 0.30		p value for trend = 0.46		p value for trend = 0.50	

[1]OR adjusted for age, residence area, body-mass index, socio-economic status and smoking.

TABLE VII – ADJUSTED OR AND 95% CI FOR THE JOINT EFFECTS OF DIFFERENT COMBINATIONS OF SMOKING AND SNUFF DIPPING IN MALES[1]

Smoking	Snuff use	Cases	Controls	OR (95% CI)
Never-smokers	Never-users	80	217	Reference
	Ever-users	11	36	0.5 (0.2–1.2)
Ex-smokers	Never-users	111	235	1.2 (0.9–1.8)
	Ever-users	56	114	1.2 (0.8–1.9)
Current smokers	Never-users	101	135	2.0 (1.3–2.9)
	Ever-users	16	42	1.0 (0.5–1.8)

[1]OR adjusted for age, residence area, body-mass index, socio-economic status and use of beer, wine and hard liquor.

any excess risk. We found no indication that snuff dipping increases the risk of gastric cancer.

Our finding of an elevated risk for gastric cardia cancer among current smokers was in line with some earlier studies (Gammon *et al.*, 1997; Inoue *et al.*, 1994; Kabat *et al.*, 1993; Vaughan *et al.*, 1995; Wu-Williams *et al.*, 1990), but not all (Ji *et al.*, 1996; Palli *et al.*, 1992). In contrast to reports indicating limited benefits of smoking cessation (Gammon *et al.*, 1997; Inoue *et al.*, 1994; Kabat *et al.*, 1993; Vaughan *et al.*, 1995), we found that the OR for cardia cancer among ex-smokers was close to unity and significantly lower than in current smokers. This finding is supported by only one other study (Wu-Williams *et al.*, 1990). We were unable to confirm that smoking was more strongly associated with cardia cancer than with distal gastric cancer (Gammon *et al.*, 1997; Inoue *et al.*, 1994; Kabat *et al.*, 1993; De Stefani *et al.*, 1998). In fact, we found the opposite, as did some other investigators (Ji *et al.*, 1996; Wu-Williams *et al.*, 1990). If intestinal-type gastric cancer truly is more influenced by environmental factors than is the diffuse type, smoking may well be more closely linked to the former. However, our finding did not support this hypothesis, nor did a study in Poland (Jedrychowski *et al.*, 1993). A Japanese study (Kato *et al.*, 1990), however, found a smoking-associated risk increase isolated to the intestinal type, but only among women. Our study did not reveal any obvious gender difference in stratified analyses, but the statistical power was limited due to few cases in the female stratum, as noted also in the Japanese study. The smoking-associated risk in our study was, however, apparently modified by age, but only for intestinal-type gastric cancer. The biological plausibility of this finding is uncertain. Therefore, the observed modification of effect may be a chance finding.

The mechanism for tobacco-related gastric-cancer risk is not well understood. However, tobacco-specific nitrosamines and other nitroso-compounds, plus other carcinogens contained in tobacco and tobacco smoke, are swallowed and may thus be involved in the process of gastric carcinogenesis (Hecht and Hoffmann, 1989). Among gastric-cancer cases, smoking-related DNA-adduct levels were higher in smokers than in non-smokers (Dyke *et al.*, 1992), and a study in China found smoking to be a risk factor for intestinal metaplasia and gastric dysplasia arising from chronic atrophic gastritis (Kneller *et al.*, 1992).

The repeatedly observed inverse relationship between intake of fresh vegetables, fruits, and gastric-cancer risk is thought to be mediated by anti-oxidants such as ascorbic acid and carotenoids (Neugut *et al.*, 1996). Cigarette smoke contains oxidants and free radicals that may consume the protective anti-oxidants. Accordingly, smokers have lower plasma levels of some anti-oxidants, as compared with non-smokers (Buiatti *et al.*, 1996). Hence, it is conceivable that the effects of smoking on cancer risk are modified by dietary anti-oxidant intake. Indeed, significant interaction between tobacco use and fruit/vegetable consumption on gastric-cancer risk has been observed (Hansson, 1993). The point estimate in our study indicates that such modification might exist, and when all gastric cancer cases were included the interaction term was almost statistically significant ($p = 0.06$). After the material was broken down by sub-site and histologic type, however, no interaction term remained statistically significant, but the power to detect important interactions in the small strata was limited.

Little has been known about the effects of alcohol on risk of specific sub-types of gastric cancer. While some studies showed an association with alcohol confined to gastric-cardia carcinoma (Inoue *et al.*, 1994; Kabat *et al.*, 1993; Wu-Williams *et al.*, 1990), others did not (Ji *et al.*, 1996; De Stefani *et al.*, 1998). One study (Kato *et al.*, 1990) found no association of alcohol intake with either the intestinal or the diffuse type of gastric cancer, whereas another study (Jedrychowski *et al.*, 1993) revealed elevated risks for both types among vodka drinkers. In agreement with Gammon *et al.* (1997), we found no excess risk associated with beer, hard-liquor or total alcohol consumption, but a reduced risk of gastric-cardia cancer associated with wine drinking. The possible anti-cancer substance found only in wine, resveratrol, may account for this reduction of risk (Jang *et al.*, 1997). However, in Sweden, wine drinking is linked with high SES. Therefore, although adjustments for SES, education, age at first access to refrigerator and intake of fresh vegetables and fruits did not change our estimates substantially, the possibility of residual confounding by SES, and a generally healthier life-style, could not be completely excluded. In Italy (Palli *et al.*, 1992) and in the United States (Kabat *et al.*, 1993), no association was observed between high

intake of wine and cancer of the gastric cardia. Moreover, 3 case-control studies reported an elevated risk among wine drinkers, though these studies did not discriminate between anatomic or histologic sub-types (Falcao *et al.*, 1994). The association between wine drinking and gastric cancer by sub-site and histologic type should therefore be examined further in future studies.

Our study explores a possible relationship between the use of Swedish moist snuff and gastric-cancer risk by anatomic and histologic sub-types. Our results did not support any association with gastric-cardia cancer or with distal gastric cancer, of either the intestinal or the diffuse type, and are thus concordant with 2 American studies (IARC, 1985; Weinberg *et al.*, 1985). However, follow-up in the United States of a cohort of mainly Scandinavian and German descent revealed a 130% increase of gastric-cancer risk among ever-users of smokeless tobacco (Kneller *et al.*, 1991). When restricted to non-smokers, the estimated OR went up to 3.8 with a lower 95% CI of 1.0 (Kneller *et al.*, 1991). It should be noted that this result was based on only 3 cases, and that tobacco chewing and snuff dipping were not analyzed separately. There are possibly some differences in composition and in biologic effect of these 2 tobacco products (IARC, 1985), or the amount of carcinogens in Swedish snuff may be less than that in the United States. In fact, in the United States, moist snuff is produced through fermentation, while Swedish snuff is not (IARC, 1985). The failure of 2 case-control studies to find a positive association between Swedish moist-snuff use and the risk of oral or head-and-neck cancers (Schildt *et al.*, 1998) may indicate that Swedish moist snuff is less harmful than its international counterparts. We noted that current smokers without a history of snuff use had an elevated risk, whereas snuff-dipping current smokers had relative risks close to unity. The latter category tended to smoke less, but even after restriction to cigarette smokers and stratification by pack-years the results were the same. This result should be interpreted cautiously, due to the small number of cases, and more studies are warranted.

The accuracy of retrospective reports of habits in the distant past, essential to the interpretation of the study results, is relatively high as far as smoking is concerned (Hansson, 1993); and in a reliability study among controls from the early part of this study, the Pearson's-correlation coefficients between data obtained in the interview and those given in a mailed questionnaire 9 to 12 months later ranged from 0.52 to 0.78 for the 5 kinds of alcoholic beverages (Wolk *et al.*, 1997). Therefore, non-differential misclassification of these exposures due to imperfect recollection, typically biasing the effects towards null, is not likely to have had any decisive influence on our study results.

Despite the obvious methodological strengths of our study, some limitations should also be mentioned. First, the relatively small number of cardia-cancer cases (90) limited the statistical precision and prevented us from further dividing these cases into histologic sub-types. Second, of the eligible cases, 30% died or rapidly became too ill to be interviewed. If smoking and alcohol intake were associated with the prognosis of gastric cancer, the deficit of smoking/drinking cases thus created would bias the results towards null. It should be noted, though, that our comprehensive organization for case ascertainment, yielding a higher degree of completeness than the Swedish Cancer Registry (Ekström *et al.*, 1999), is likely to have inflated the denominator, resulting in a seemingly lower participation rates as compared with other studies. Moreover, 28 (3.1%) of cases and 245 (16%) of controls refused to participate. Since their smoking and drinking habits may differ from the average, this may have introduced bias, albeit of unknown direction. Third, differential recall among cases and controls is a concern in case-control studies of exposures for which preconceptions exist as to the unhealthy effects. The negative finding for snuff dipping and alcohol use should, to some extent, allay these concerns.

To conclude, smoking, but not the oral use of tobacco in the form of moist snuff, is positively associated with risk of gastric cancer. If the relationship is causal, the carcinogenic action possibly occurs at a fairly late stage. Alcoholic beverages do not seem to increase risk of any type of cardia or gastric cancer. Our study did not support the hypothesis that the role of smoking and alcohol intake, possibly with the exception of wine, differs between gastric cancer of different anatomic and histologic sub-divisions.

ACKNOWLEDGEMENTS

W.Y. was supported in part by an ICRETT fellowship from UICC and O.N. received support from the Swedish Cancer Society. We express our sincere appreciation for the outstanding support from the staff at the medical and pathology centers for case recruitment. We are indebted to Dr. B. Andersson (Sala Hospital, Sala), Dr. L. Athlin (University Hospital, Umeå), Dr. G. Dafnis (Kullbergska Hospital, Katrineholm), Dr. M. Egenvall (Eskilstuna Hospital, Eskilstuna), Dr. B.-Å. Elfberg (Sammariterhemmet Hospital, Uppsala), Dr. M. Eriksson (University Hospital, Umeå), Dr. B. Fornander (Nyköping Hospital, Nyköping), Dr. H. Fröberg (Lycksele Hospital, Lycksele), Dr. G. Gustafsson (University Hospital, Uppsala), Dr. L. Hardell (University Hospital, Umeå), Dr. U. Hyvönen (Kalix Hospital, Kalix), Dr. F. Jaska (Köping Hospital, Köping), Dr. V. Knezevic (Fagersta Hospital, Fagersta), Dr. P.-H. Liljeholm (Enköping Hospital, Enköping), Dr. A. Lundberg (Gällivare Hospital, Gällivare), Dr. L.-O. Lundström (Skellefteå Hospital, Skellefteå), Dr. M. Lyreskog (Piteå Hospital, Piteå), Dr. E. Nilsson (Luleå-Boden Hospital, Luleå), Dr. S. Taksdal (Kiruna Hospital, Kiruna) and Dr. P. Tracz (Västerås Hospital, Västerås), as well as the assistant staff members at the pathology clinics of Västerås Hospital, Umeå Hospital, Boden Hospital, Eskilstuna Hospital and Uppsala Academic Hospital for their help in the search for histologic slides.

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