Int. J. Cancer: 85, 340–346 (2000)

Publication of the International Union Against Cancer

THE ROLE OF TOBACCO, SNUFF AND ALCOHOL USE IN THE AETIOLOGY OF CANCER OF THE OESOPHAGUS AND GASTRIC CARDIA

Jesper LAGERGREN[1,2]*, Reinhold BERGSTRÖM[1,3], Anders LINDGREN[4] and Olof NYRÉN[1]

[1]*Department of Medical Epidemiology, Karolinska Institutet, Stockholm, Sweden*
[2]*Division of Surgery, Karolinska Institutet Danderyd Hospital, Stockholm, Sweden*
[3]*Department of Statistics, Uppsala University, Uppsala, Sweden*
[4]*Department of Pathology, Falu Hospital, Falun, Sweden*

While tobacco and alcohol are established risk factors for oesophageal squamous-cell carcinoma, their roles in the aetiology of the increasingly common oesophageal adenocarcinoma remains uncertain. We tested the association between tobacco, snuff and alcohol use and the risk of oesophageal and cardia cancer in a nationwide, population-based case-control study in Sweden. Face-to-face interviews were conducted with 618 (81% of all eligible) patients (189 oesophageal adenocarcinoma, 262 cardia adenocarcinoma and 167 oesophageal squamous-cell carcinoma) and 820 control subjects. Odds ratios (OR) were calculated by logistic regression with multivariate adjustments for potential confounding. The risk of oesophageal adenocarcinoma was not associated with snuff or alcohol use, and the association with smoking was weak or absent. Gastric cardia adenocarcinoma was dose-dependently associated with smoking (OR=4.2, 95% CI=2.5–7.0 among heavy smokers compared with never-smokers), but not with alcohol or snuff use. Oesophageal squamous-cell carcinoma was strongly associated with tobacco, moderately with alcohol, but not with snuff use; combined use of tobacco and alcohol entailed a strongly increased risk (OR=23.1, 95% CI=9.6–56.0 among heavy users compared with never-users). We conclude that tobacco smoking, a strong risk factor for oesophageal squamous-cell carcinoma and cardia adenocarcinoma, does not play an important role in the aetiology of oesophageal adenocarcinoma. None of the studied exposures can explain the increasing incidence of oesophageal adenocarcinoma. *Int. J. Cancer* 85:340–346, 2000.
© *2000 Wiley-Liss, Inc.*

Cancer of the oesophagus is one of the most lethal forms of cancer (Boring *et al.*, 1993). Attempts to improve the prognosis have been discouraging (Farrow and Vaughan, 1996), and primary prevention is therefore a desirable goal. The steeply rising incidence of oesophageal adenocarcinoma (Blot *et al.*, 1991; Powell and McConkey, 1992; Hansson *et al.*, 1993; Hansen *et al.*, 1997) indicates that external, and possibly preventable, risk factors are responsible.

Tobacco and alcohol are established main risk factors for oesophageal squamous-cell carcinoma (Muir and MacKinney, 1992). Tobacco also is claimed to be a major risk factor for adenocarcinoma of the oesophagus and gastric cardia and an important reason for the increasing incidence (Gammon *et al.*, 1997). The few studies that have addressed this association showed, however, relative risk estimates that were considerably less extreme than those pertaining to squamous-cell carcinoma (Kim *et al.*, 1997). The lack of parallelism between secular trends for tobacco smoking and incidence of oesophageal adenocarcinoma is not consistent with a major role for smoking in the aetiology of this cancer.

In an attempt to resolve this ambiguity, we have investigated the role of tobacco smoking, snuff dipping and alcohol drinking in a nationwide case-control study of oesophageal and cardia cancer.

MATERIAL AND METHODS

Design

The design of our population-based case-control study has been described in detail (Lagergren *et al.*, 1999). Briefly, the study base comprised the whole population of Sweden in 1995 through 1997, except for persons aged 80 years or older and individuals born abroad. All patients with a new diagnosis of adenocarcinoma of the oesophagus or gastric cardia and half of the patients with oesophageal squamous-cell carcinoma (born on even dates) occurring in the study base were eligible as cases. A nationwide organisation for rapid case ascertainment, including all Swedish hospital departments involved in the diagnosis and/or treatment of gastro-oesophageal cancers, and all local tumour registries enabled us to conduct face-to-face interviews with all cases shortly after diagnosis and to obtain a correct denominator in the calculation of participation rates.

Uniform routines for documentation and prospective reporting of the tumour site were adopted by endoscopists, surgeons and pathologists. Moreover, 97% of the biopsies and/or surgical specimens were re-examined by one pathologist. A cancer of the gastric cardia had to have its centre within 2 cm proximal or 3 cm distal to the gastro-oesophageal junction, which is defined as the point where the proximal longitudinal mucosal folds begin in the stomach. If Barrett's oesophagus, a columnar metaplasia of the distal oesophagus replacing the native squamous-cell mucosa (Spechler and Goyal, 1986), was detected adjacent to the tumour, it was classified as oesophageal irrespective of its location. Squamous-cell carcinomas were always classified as oesophageal.

Subjects

Out of 216 eligible case subjects of oesophageal adenocarcinoma, we interviewed 189 (87%). Non-participation was due to physical or mental impediments (including advanced cancer) in 25 (12%) cases, and unwillingness in 2 (1%). Interviewed were also 262 of the 313 (83%) eligible case subjects of gastric cardia adenocarcinoma. Cardia cancer represented 13% of all stomach cancer in Sweden during the study period. The reasons for non-participation were physical or mental impediments in 41 (13%) patients, and unwillingness in 10 (3%). There were 228 eligible case subjects with squamous-cell carcinoma, of whom 167 (73%) were interviewed. Physical or mental impediments were the reason for non-participation in 50 patients (22%) in this case group, while 11 (5%) refused interview. In the groups with oesophageal adenocarcinoma, cardia adenocarcinoma and oesophageal squamous-cell carcinoma, the median ages at diagnosis were 69, 66 and 67 years, respectively, and men constituted 87%, 85% and 72%.

Control subjects were randomly selected from age and sex strata in the study base to resemble the age and sex distributions among the oesophageal adenocarcinoma cases (frequency matching). The

Grant sponsor: NCI; Grant number: R01 CA57947–03; Grant sponsor: Swedish Cancer Society (JL and ON).

*Correspondence to: Department of Medical Epidemiology, Karolinska Institutet, Box 281, S-171 77 Stockholm, Sweden. Fax: +46 8 31 49 57. E-mail: Jesper.Lagergren@mep.ki.se

Received 6 June 1999; Revised 4 August 1999

TABLE 1 - ODDS RATIOS (OR) AND 95% CONFIDENCE INTERVALS (CI) FOR THE RISK OF DEVELOPING OESOPHAGEAL ADENOCARCINOMA, GASTRIC CARDIA ADENOCARCINOMA OR OESOPHAGEAL SQUAMOUS-CELL CARCINOMA ASSOCIATED WITH VARIOUS ASPECTS OF TOBACCO SMOKING

		Oesophageal adenocarcinoma			Gastric cardia adenocarcinoma			Oesophageal squamous- cell carcinoma		
	Number of controls (percent)	Number of cases (percent)	Age- and gender-adjusted OR (95% CI)	Multivariately[1] adjusted OR (95% CI)	Number of cases (percent)	Age- and gender-adjusted OR (95% CI)	Multivariately[1] adjusted OR (95% CI)	Number of cases (percent)	Age- and gender-adjusted OR (95% CI)	Multivariately[1] adjusted OR (95% CI)
Smoking status of cigarettes, cigars or pipe										
Never[2]	325 (40%)	57 (30%)	1.0 (referent)	1.0 (referent)	43 (16%)	1.0 (referent)	1.0 (referent)	22 (13%)	1.0 (referent)	1.0 (referent)
Previous	314 (38%)	89 (47%)	1.5 (1.1–2.2)	1.9 (1.2–2.9)	124 (47%)	3.1 (2.1–4.5)	3.4 (2.2–5.2)	44 (26%)	2.7 (1.5–4.7)	2.5 (1.4–4.7)
Current	181 (22%)	43 (23%)	1.3 (0.8–2.0)	1.6 (0.9–2.7)	95 (36%)	3.9 (2.6–5.8)	4.5 (2.9–7.1)	101 (60%)	10.6 (6.2–18.1)	9.3 (5.1–17.0)
Duration of smoking of cigarettes, cigars or pipe										
1–20 years	155 (19%)	42 (22%)	1.5 (1.0–2.4)	1.8 (1.1–3.1)	38 (15%)	1.8 (1.1–2.9)	2.1 (1.2–3.4)	21 (13%)	2.4 (1.3–4.7)	2.3 (1.1–4.6)
21–35 years	156 (19%)	37 (20%)	1.3 (0.8–2.1)	1.5 (0.9–2.6)	77 (29%)	3.6 (2.3–5.5)	3.9 (2.4–6.2)	27 (16%)	3.2 (1.7–6.0)	2.9 (1.5–5.8)
>35 years	184 (22%)	53 (28%)	1.5 (1.0–2.3)	2.0 (1.2–3.3)	104 (40%)	4.6 (3.0–6.9)	5.7 (3.6–9.1)	97 (58%)	10.4 (6.1–17.9)	8.8 (4.9–16.1)
Dose—cigarette smoking (cigarettes per day)										
1–9	138 (17%)	32 (17%)	1.2 (0.7–1.9)	1.2 (0.7–2.2)[3]	46 (18%)	2.2 (1.4–3.4)	2.3 (1.4–3.7)[3]	28 (17%)	3.1 (1.7–5.4)	2.8 (1.5–5.2)[3]
10–19	156 (19%)	46 (24%)	1.5 (1.0–2.3)	1.7 (1.0–2.9)[3]	73 (28%)	3.0 (2.0–4.5)	3.1 (2.0–4.9)[3]	54 (32%)	5.0 (3.0–8.3)	3.9 (2.2–6.9)[3]
>19	158 (19%)	41 (22%)	1.3 (0.8–2.0)	1.1 (0.6–2.0)[3]	86 (33%)	3.5 (2.3–5.2)	3.6 (2.3–5.7)[3]	7 (34%)	6.4 (3.7–10.8)	4.9 (2.7–9.0)[3]
Dose—pipe smoking (number of pipes per week)										
1–15	97 (12%)	28 (15%)	1.4 (0.8–2.2)	1.3 (0.7–2.4)[3]	51 (19%)	2.1 (1.4–3.1)	1.4 (0.9–2.2)[3]	22 (13%)	1.9 (1.1–3.4)	1.2 (0.6–2.2)[3]
16–30	105 (13%)	29 (15%)	1.3 (0.8–2.1)	1.3 (0.7–2.4)[3]	39 (15%)	1.5 (0.9–2.2)	1.0 (0.6–1.6)[3]	26 (16%)	1.2 (1.2–3.5)	1.1 (0.6–2.1)[3]
>30	97 (12%)	29 (15%)	1.4 (0.9–2.3)	1.8 (1.0–3.4)[3]	36 (14%)	1.5 (1.0–2.3)	1.0 (0.6–1.7)[3]	29 (17%)	2.5 (1.5–4.3)	1.3 (0.7–2.3)[3]
Years since cigarette smoking cessation										
0–2	152 (19%)	40 (21%)	1.5 (0.9–2.3)	1.7 (1.0–3.0)	87 (33%)	4.2 (2.8–6.4)	5.0 (3.2–8.0)	93 (56%)	11.5 (6.7–19.8)	10.3 (5.6–19.1)
3–10	62 (8%)	20 (11%)	1.8 (1.0–3.3)	2.4 (1.2–4.8)	35 (13%)	4.1 (2.4–7.0)	4.9 (2.8–8.7)	18 (11%)	5.9 (2.9–12.1)	5.2 (2.4–11.3)
11–25	112 (14%)	29 (15%)	1.4 (0.9–2.4)	1.6 (0.9–2.5)	53 (20%)	3.7 (2.3–5.8)	4.2 (2.6–7.0)	15 (9%)	2.4 (1.2–4.9)	2.1 (1.0–4.7)
>25	126 (15%)	30 (16%)	1.2 (0.8–2.1)	1.6 (0.9–2.8) $p = 0.02$	30 (11%)	1.9 (1.1–3.1)	2.1 (1.2–3.6) $p < 0.0001$	13 (8%)	1.9 (0.9–3.9)	1.9 (0.8–4.0) $p < 0.0001$

[1]Adjustments were made for age, gender, alcohol use, educational level, body mass index, reflux symptoms, intake of fruit and vegetables, energy intake and physical activity.–[2]Never-smoker of any tobacco type was the reference group in all analyses.–[3]The multivariate adjustments also included mutual adjustments for cigarette smoking, pipe smoking and snuff use.

participation rate among the control subjects was 73%, leaving 820 control subjects with completed interviews. The main reason for non-participation in the control group was unwillingness, which was noted in 210 (19%), while in 70 controls (6%) the reasons were physical or mental impediments. Further, 28 (2%) of the selected control subjects could not be traced. The median age was 68 years, and men constituted 83% of the control subjects.

Exposure data

We did not accept substitute responders, and the face-to-face interviews were carried out by professional interviewers from Statistics Sweden. The interviewers could not be blinded to the case/control status of the interviewees, but they were unaware of the study hypotheses and were trained to deal with the cases and controls in a strictly equal manner. They inquired about the lifetime smoking history of cigarettes, cigars and pipes. Tobacco users were defined as individuals smoking regularly (at least 1 cigarette per day or at least 1 cigar or pipe per week) or taking a quid of snuff at least once a week for 6 months or more. Tobacco usage 2 years before the interview determined the user status. Those who smoked at that time were referred to as current smokers, while ex-smoker status (previous smokers) was reserved for those who had stopped 2 or more years before the interview. Alcohol intake was assessed with separate questions about beer, wine and liquor consumption 20 years before the interview. The average frequency and amount of alcohol use was converted to total consumption of pure alcohol in grams per week. We also collected detailed information about exposure to several potential confounding factors, as specified below.

Statistical analyses

Logistic regression was used in all analyses. The model parameters were estimated by the maximum likelihood method (Breslow and Day, 1980). Odds ratios (OR) with 95% confidence intervals (CI) estimated relative risks. The cases in each cancer category were compared with all controls. In the baseline model, adjustments were made for age (in 5-year classes) and sex, since the frequency distributions of these factors could differ between the studied groups. In the multivariate analyses, we further adjusted for socioeconomic status, reflected by number of years of formal education (in 4 classes), intake of fruit and vegetables (in 4 classes), energy intake (in 3 classes), gastro-oesophageal reflux symptoms (heartburn and/or regurgitation occurring at least once a week), body mass index (BMI)(quartiles) and physical activity (in 4 levels, including usual activities such as standing, walking and climbing stairs, physical exercises during leisure time and physical exertion at work). In the analyses of tobacco smoking, we adjusted for alcohol use (grams of pure alcohol in 4 classes), and when analysing effects of alcohol, we adjusted for tobacco smoking (never-, ex- and current smokers). In the analyses of snuff dipping, we adjusted for both tobacco smoking and alcohol use. In analyses of beverage-specific associations, mutual adjustments were made for the different types of alcoholic beverages, and similarly in the analyses of different tobacco types, we performed mutual adjustments for these. Wald and likelihood ratio tests were used. Variables were considered in both categorised and continuous form.

Ethics

The study was approved by all regional ethics committees in Sweden, and individual informed consent was obtained from all subjects.

RESULTS

Tobacco smoking

Oesophageal adenocarcinoma. The association between tobacco smoking and the risk of oesophageal adenocarcinoma was weak or absent, most ORs being statistically non-significant (Table I). Although the point estimates among smokers were consistently above unity, there were no dose-risk or duration-risk trends. Among current smokers, OR was 1.6 (95% CI=0.9–2.7) compared with never-smokers, while a significant 2-fold increase in risk was found among previous smokers and among persons who had been smoking for more than 35 years. OR was 1.1 (95% CI=0.6–2.2) among persons who had smoked more than 20 cigarettes daily for more than 35 years compared with never-smokers. Among frequent pipe smokers, OR was 1.8 (95% CI=1.0–3.4) compared with never-smokers. Cigar smoking was not associated with the risk (data not shown). There was a declining risk with time since cessation of smoking (p for trend=0.02).

Gastric cardia adenocarcinoma. Smoking was significantly associated with the risk of gastric cardia adenocarcinoma (Table I). The OR was 4.5 (95% CI=2.9–7.1) among current smokers compared with never-smokers. The dose-risk and duration-risk trends were both significant, but a combination of high dose and long duration did not increase the risk further (OR=4.2; 95% CI=2.5–7.0 among long-term and high-dose smokers compared with never-smokers). After multiple adjustments, pipe smoking was unrelated to the risk. The risk decreased significantly with time since cessation of smoking (p for trend<0.0001).

Oesophageal squamous-cell carcinoma. The association between tobacco smoking and risk of oesophageal squamous-cell carcinoma was strong and depended both on dose and duration (Table I). Among persons who had smoked more than 20 cigarettes daily for more than 35 years, OR was 10.4 (95% CI=5.6–19.4). The risk decreased significantly with time since cessation of smoking. After adjustment for cigarette smoking, no significant excess risk was found in association with pipe (Table I) or cigar smoking (data not shown).

Comparison of the risk effects of dose and duration of cigarette smoking. By including both dose and duration in the same logistic-regression models, we investigated which of these aspects of smoking was more important for the risk of oesophageal squamous-cell carcinoma and cardia adenocarcinoma. In Table II, the smoking variables are presented in continuous form with

TABLE II – COMPARISON OF THE EFFECTS OF CIGARETTE SMOKING DOSE (NUMBER OF CIGARETTES PER DAY) AND DURATION (IN YEARS) ON THE RISK FOR OESOPHAGEAL SQUAMOUS-CELLCARCINOMA AND GASTRIC CARDIA ADENOCARCINOMA

	Oesophageal squamous- cell carcinoma			Gastric cardia adenocarcinoma		
	OR	95% CI	Chi-square statistic	OR	95% CI	Chi-square statistic
Not mutually adjusted						
Dose	1.070	1.050–1.090	52.02	1.048	1.033–1.064	40.29
Duration	1.048	1.037–1.058	87.59	1.028	1.020–1.036	49.84
Mutually adjusted						
Dose	1.025	1.003–1.048	4.69	1.025	1.006–1.043	6.68
Duration	1.044	1.029–1.053	44.87	1.020	1.010–1.030	9.61

The variables are in continuous form. Age- and sex-adjusted odds ratios (OR) and 95% confidence intervals (CI) per unit of the explanatory variable.

TABLE III - ODDS RATIOS (OR) AND 95% CONFIDENCE INTERVALS (CI) FOR THE RISK OF DEVELOPING OESOPHAGEAL ADENOCARCINOMA, GASTRIC CARDIA ADENOCARCINOMA OR OESOPHAGEAL SQUAMOUS-CELL CARCINOMA ASSOCIATED WITH VARIOUS ASPECTS OF SNUFF USE

	Number of controls (percent)	Oesophageal adenocarcinoma			Gastric cardia adenocarcinoma			Oesophageal squamous- cell carcinoma		
		Number of cases (percent)	Age- and gender-adjusted OR (95% CI)	Multivariately[1] adjusted OR (95% CI)	Number of cases (percent)	Age- and gender-adjusted OR (95% CI)	Multivariately[1] adjusted OR (95% CI)	Number of cases (percent)	Age- and gender-adjusted OR (95% CI)	Multivariately[1] adjusted OR (95% CI)
Snuff use status										
Never[2]	694 (85%)	154 (81%)	1.0 (referent)	1.0 (referent)	209 (80%)	1.0 (referent)	1.0 (referent)	134 (80%)	1.0 (referent)	1.0 (referent)
Ever	126 (15%)	35 (19%)	1.2 (0.8–1.9)	1.2 (0.7–2.0)	53 (20%)	1.3 (0.9–1.9)	1.2 (0.8–1.8)	33 (20%)	1.7 (1.1–2.7)	1.4 (0.9–2.3)
Duration of snuff use										
1–10 years	44 (5%)	10 (5%)	1.0 (0.5–2.1)	0.9 (0.4–2.2)	18 (7%)	1.2 (0.7–2.2)	1.0 (0.5–1.8)	11 (7%)	1.6 (0.8–3.2)	1.2 (0.5–2.5)
11–25 years	45 (5%)	10 (5%)	1.0 (0.5–2.0)	0.8 (0.3–1.8)	19 (7%)	1.3 (0.7–2.3)	1.1 (0.6–2.0)	8 (5%)	1.2 (0.5–2.6)	0.9 (0.4–2.1)
>25 years	37 (5%)	15 (8%)	1.7 (0.9–3.3)	1.9 (0.9–4.0)	15 (6%)	1.4 (0.7–2.6)	1.1 (0.6–2.2)	14 (8%)	2.8 (1.4–5.4)	2.0 (0.9–4.1)
				$p = 0.31$			$p = 0.45$			$p = 0.18$
Intensity of snuff use (number of quids used per week)										
1–14	45 (6%)	11 (6%)	1.0 (0.5–2.1)	1.0 (0.4–2.3)	19 (7%)	1.3 (0.8–2.3)	1.2 (0.6–2.1)	10 (6%)	1.4 (0.7–2.9)	1.2 (0.5–2.5)
15–35	34 (4%)	17 (9%)	2.2 (1.2–4.1)	2.0 (1.0–4.3)	15 (6%)	1.5 (0.8–2.8)	1.3 (0.7–2.5)	15 (9%)	2.8 (1.5–5.5)	2.1 (1.0–4.4)
>35	45 (6%)	7 (4%)	0.7 (0.3–1.6)	0.8 (0.3–2.0)	18 (7%)	1.2 (0.7–2.1)	1.3 (0.7–2.4)	7 (4%)	1.1 (0.5–2.6)	1.0 (0.4–2.4)
				$p = 0.53$			$p = 0.30$			$p = 0.27$

[1]Adjustments were made for age, gender, tobacco smoking, alcohol use, educational level, body mass index, reflux symptoms, intake of fruit and vegetables, energy intake and physical activity.–[2]Never-user of snuff was the reference category in all analyses.

adjustment for age and gender. The full model rendered similar results (data not shown). For both tumours, the duration of smoking was more important than the dose, according to likelihood ratio tests and Wald statistics, but the difference was more distinct for squamous-cell carcinoma. After mutual adjustment, the effects of both duration and dose remained significant.

Snuff dipping

Oesophageal adenocarcinoma. Snuff users had an OR of 1.2 (95% CI=0.8–1.9) for oesophageal adenocarcinoma compared with never-users (Table III). The duration-risk relation was non-linear and non-significant (p for trend=0.31), but there was an almost statistically significant 90% excess risk among persons who had used snuff for more than 25 years. Similarly, those using 15–35 quids per week showed a statistically significant 2-fold increase in the risk compared with never-users. A higher consumption was associated with a low risk (but this was based on few observations).

Gastric cardia adenocarcinoma. Snuff dipping was not significantly associated with the risk of cardia adenocarcinoma (Table III). OR among ever-users was 1.2 (95% CI=0.8–1.8).

Oesophageal squamous-cell carcinoma. The association between snuff dipping and oesophageal squamous-cell carcinoma was attenuated after adjustment for smoking, but a statistically non-significant 40% excess risk remained. There was no apparent dose-response relation, but point estimates of borderline significance were observed in single high-dose or long-duration categories (Table III).

Alcohol use

Oesophageal adenocarcinoma. Never-users of alcohol had a higher risk of oesophageal adenocarcinoma compared with ever-users. Beer and wine consumption were not associated with a risk of oesophageal adenocarcinoma, but users of hard liquor ran a low risk. This negative association, however, was not dose-dependent (Table IV).

Gastric cardia adenocarcinoma. Our data gave no indication that the risk of cardia adenocarcinoma was linked to any type of alcoholic consumption (Table IV).

Oesophageal squamous-cell carcinoma. Although high consumption of alcohol, particularly hard liquor, was associated with a significantly increased risk of oesophageal squamous-cell carcinoma, there was no clear trend across a wide range of dose levels (Table IV). The dose-response curve, although statistically significant (p for trend <0.0001), seemed to be flat up to the upper 2 deciles of alcohol consumption, regardless of type.

The combined effect of tobacco smoking and alcohol drinking

OR for oesophageal squamous-cell carcinoma among persons who were both long-term smokers (>35 years) and heavy alcohol users (>70 g/week) was 23.1 (95% CI=9.6–56.0) compared with never-users. The corresponding ORs for oesophageal and cardia adenocarcinoma were 2.3 (95% CI=0.9–5.7) and 5.1 (95% CI=2.5–10.5), respectively.

DISCUSSION

In agreement with others (Muir and MacKinney, 1992), we found a strong relation between combined tobacco and alcohol use and oesophageal squamous-cell carcinoma. Also in conformity with most previous reports (Gammon *et al.*, 1997; Li *et al.*, 1989; Wu-Williams *et al.*, 1990; Kabat *et al.*, 1993; Brown *et al.*, 1994; Gonzalez *et al.*, 1994; Vaughan *et al.*, 1995; Zhang *et al.*, 1996) was our finding of a moderately strong association between smoking and risk of gastric cardia adenocarcinoma. More controversial was the absence of important links between smoking and risk of oesophageal adenocarcinoma. Although all our point estimates were above unity, they were mostly statistically non-significant and showed no dose-response trends. We found no strong association

TABLE IV – ODDS RATIOS (OR) AND 95% CONFIDENCE INTERVALS (CI) FOR THE RISK OF DEVELOPING OESOPHAGEAL ADENOCARCINOMA, GASTRIC CARDIA ADENOCARCINOMA OR OESOPHAGEAL SQUAMOUS-CELL CARCINOMA ASSOCIATED WITH VARIOUS ASPECTS OF ALCOHOL CONSUMPTION

		Oesophageal adenocarcinoma			Gastric cardia adenocarcinoma			Oesophageal squamous- cell carcinoma		
	Number of controls (percent)	Number of cases (percent)	Age- and gender-adjusted OR (95% CI)	Multivariately[1] adjusted OR (95% CI)	Number of cases (percent)	Age- and gender-adjusted OR (95% CI)	Multivariately[1] adjusted OR (95% CI)	Number of cases (percent)	Age- and gender-adjusted OR (95% CI)	Multivariately[1] adjusted OR (95% CI)
Any alcohol										
Never	132 (16%)	41 (22%)	1.0 (referent)	1.0 (referent)	34 (13%)	1.0 (referent)	1.0 (referent)	16 (10%)	1.0 (referent)	1.0 (referent)
Ever	688 (84%)	148 (78%)	0.7 (0.4–1.0)	0.5 (0.3–0.9)	228 (87%)	1.2 (0.8–1.8)	0.8 (0.5–1.2)	151 (90%)	2.0 (1.1–3.5)	1.1 (0.6–2.1)
Grams of ethanol per week[2]										
1–15	221 (27%)	54 (29%)	0.8 (0.5–1.2)	0.6 (0.4–1.1)	73 (28%)	1.2 (0.8–2.0)	0.9 (0.5–1.5)	34 (20%)	1.3 (0.7–2.5)	0.9 (0.4–1.8)
16–70	289 (35%)	51 (27%)	0.5 (0.3–0.9)	0.4 (0.2–0.7)	79 (30%)	1.0 (0.6–1.6)	0.6 (0.4–1.1)	39 (23%)	1.5 (0.8–2.8)	0.8 (0.4–1.8)
>70	178 (22%)	43 (23%)	0.7 (0.4–1.2)	0.6 (0.3–1.1)	76 (29%)	1.5 (0.9–2.4)	0.9 (0.5–1.5)	78 (47%)	5.6 (2.9–10.7)	3.1 (1.4–6.7)
Strong beer[3]										
Never	553 (67%)	127 (67%)	1.0 (referent)	1.0 (referent)	173 (66%)	1.0 (referent)	1.0 (referent)	103 (62%)	1.0 (referent)	1.0 (referent)
Ever	267 (33%)	62 (33%)	1.0 (0.7–1.5)	1.2 (0.8–1.8)	89 (34%)	1.0 (0.7–1.3)	0.9 (0.7–1.3)	64 (38%)	1.6 (1.1–2.3)	1.3 (0.9–2.0)
Grams of ethanol per week										
1–5	90 (11%)	22 (12%)	1.1 (0.6–1.8)	1.3 (0.7–2.5)	25 (10%)	0.9 (0.5–1.4)	0.8 (0.5–1.4)	21 (13%)	1.4 (0.8–2.4)	1.3 (0.7–2.3)
6–25	103 (13%)	22 (12%)	0.9 (0.6–1.5)	1.6 (0.9–3.0)	28 (11%)	0.8 (0.5–1.3)	0.9 (0.5–1.5)	21 (13%)	1.3 (0.8–2.2)	1.0 (0.6–1.9)
>25	74 (9%)	18 (10%)	1.1 (0.6–2.0)	1.4 (0.6–2.9)	36 (14%)	1.4 (0.9–2.2)	1.4 (0.8–2.4)	22 (13%)	2.3 (1.3–4.0)	1.2 (0.6–2.3)
Wine[4]										
Never	320 (39%)	91 (48%)	1.0 (referent)	1.0 (referent)	114 (44%)	1.0 (referent)	1.0 (referent)	68 (41%)	1.0 (referent)	1.0 (referent)
Ever	500 (61%)	98 (52%)	0.7 (0.5–1.0)	0.9 (0.6–1.4)	148 (56%)	0.8 (0.6–1.1)	0.9 (0.6–1.2)	99 (59%)	0.9 (0.6–1.2)	0.9 (0.6–1.4)
Grams of ethanol per week										
1–5	164 (20%)	45 (24%)	1.0 (0.6–1.5)	1.2 (0.7–1.9)	56 (21%)	1.0 (0.7–1.4)	1.0 (0.7–1.5)	26 (16%)	0.7 (0.4–1.1)	0.8 (0.5–1.5)
6–25	174 (21%)	29 (15%)	0.6 (0.4–1.0)	1.0 (0.6–1.8)	48 (18%)	0.8 (0.5–1.1)	0.9 (0.6–1.5)	29 (17%)	0.7 (0.5–1.2)	0.9 (0.5–1.7)
>25	162 (20%)	24 (13%)	0.5 (0.3–0.9)	0.9 (0.5–1.8)	44 (17%)	0.7 (0.5–1.1)	0.8 (0.5–1.2)	44 (26%)	1.2 (0.8–1.9)	1.2 (0.7–2.1)
Hard liquor[5]										
Never	175 (21%)	56 (30%)	1.0 (referent)	1.0 (referent)	44 (17%)	1.0 (referent)	1.0 (referent)	26 (16%)	1.0 (referent)	1.0 (referent)
Ever	645 (79%)	133 (70%)	0.6 (0.4–0.9)	0.5 (0.3–0.9)	218 (83%)	1.3 (0.9–1.8)	0.9 (0.6–1.4)	141 (84%)	1.8 (1.1–2.9)	1.0 (0.6–1.8)
Grams of ethanol per week										
1–7	229 (28%)	41 (22%)	0.6 (0.4–0.9)	0.5 (0.3–0.9)	79 (30%)	1.3 (0.9–2.0)	1.1 (0.7–1.8)	26 (16%)	0.8 (0.5–1.5)	0.6 (0.3–1.2)
8–30	237 (29%)	40 (21%)	0.5 (0.3–0.8)	0.4 (0.2–0.8)	63 (24%)	1.0 (0.6–1.6)	0.8 (0.4–1.3)	39 (23%)	1.9 (1.1–3.5)	1.1 (0.5–2.2)
>30	179 (22%)	52 (28%)	0.8 (0.5–1.3)	0.5 (0.3–0.9)	76 (29%)	1.5 (1.0–2.4)	0.9 (0.5–1.6)	76 (46%)	5.0 (2.8–9.0)	2.3 (1.1–4.7)

[1]Adjustments were made for age, gender, tobacco smoking, educational level, body mass index, reflux symptoms, intake of fruit and vegetables, energy intake and physical activity.–[2]All beverages converted to grams of absolute alcohol.–[3]In the multivariate model, additional adjustments were made for wine and hard liquor consumption.–[4]In the multivariate model, additional adjustments were made for strong beer and hard liquor consumption.–[5]In the multivariate model, additional adjustments were made for strong beer and wine consumption.

between snuff dipping and any of the 3 cancer types. Alcohol use was not related to an increased risk of oesophageal or cardia adenocarcinoma.

Significant associations between cigarette smoking and oesophageal and/or gastric cardia adenocarcinoma have been reported from 7 previous case-control studies, with ORs of generally about 1.5–2.5 (Gammon *et al.*, 1997; Li *et al.*, 1989; Wu-Williams *et al.*, 1990; Kabat *et al.*, 1993; Brown *et al.*, 1994; Gonzalez *et al.*, 1994; Vaughan *et al.*, 1995; Zhang *et al.*,1996). In 2 studies of oesophageal adenocarcinoma, however, no association was found (Levi *et al.*, 1990; Gao *et al.*, 1994).

In our study, the association of smoking with cardia adenocarcinoma was stronger and the association with oesophageal adenocarcinoma weaker than in most previous studies. Some features of our study may explain these discrepancies. First, owing to the favorable conditions for population-based studies in Sweden, with complete and continuously updated population registers, identifiability of all residents through their national registration numbers, and the homogeneous and entirely public in-hospital services, combined with our comprehensive organization for case ascertainment, we were able to identify virtually all cases occurring in the study base and select controls representative of the study base. Second, 87% of the cases were interviewed face-to-face shortly after diagnosis, which obviated the need for substitute responders. The risk of differential exposure misclassification among cases and controls is probably higher if substitute responders are interviewed. Third, standardised measurements for specification of the tumour site by clinicians and pathologists and re-examination of all tissue specimens minimised misclassification of squamous-cell carcinoma or cardia adenocarcinoma as oesophageal adenocarcinoma. Admixture of such cases to the oesophageal adenocarcinoma category might otherwise have resulted in a spurious association with smoking.

The strength of the association between smoking, particularly in combination with heavy alcohol use, and squamous-cell carcinoma, well in line with the accumulated results, indicates good validity and sensitivity of our study. Hence, it is unlikely that differential or non-differential exposure misclassification or biased selection of cases or controls led to concealment of any important association between smoking and risk of oesophageal adenocarcinoma. If smoking is associated with poor survival, a deficit of smokers among participating cases may result in a spuriously weak association. Our rapid case ascertainment, however, minimised such potential selection bias. Furthermore, since losses to interview were higher among the squamous-cell carcinoma patients, underestimation of the association would have affected this category more.

Non-participation among controls could not explain our weak association between smoking and risk of oesophageal adenocarcinoma. Participants are generally more likely to be non-smokers. This would inflate the association. But an analysis of 24 controls who first refused the interview revealed that their smoking and alcohol habits were strikingly similar to those of the participants (data not shown). Since insidious tumour symptoms might lead to cessation of smoking, we closed our time window for exposure assessment 2 years before the interview. The strong association between smoking and risk of squamous-cell carcinoma seemed to confirm that bias due to such reversed causality did not play an important role. Confounding that would cancel a true positive association between smoking and risk of oesophageal adenocarcinoma is also unlikely, particularly in light of our multiple adjustments. With a power of 90% and a=0.05 (two-sided test), we could not statistically exclude excess risks for oesophageal adenocarcinoma lower than 170% among current smokers. Further, a tendency toward higher risks in some exposure strata indicates that smoking cannot be definitely ruled out as a possible risk factor. After adjustment for confounding variables, significant associations (about 2-fold increased risks) were found among previous smokers and among persons who had been smoking for more than 35 years. Hence, the duration of smoking might be of some importance for the risk of oesophageal adenocarcinoma. When we added high dosage of smoking to long duration, the risk was back to unity, however. Also, ecological observations are consistent with a weak and unimportant effect. While smoking has declined considerably among men, as reflected by the falling incidence of lung cancer (Cancer Registry, 1997), the increasing incidence of oesophageal adenocarcinoma is particularly marked in men (Blot *et al.*, 1991; Hansson *et al.*, 1993).

The absence of positive associations between alcohol use and risk of oesophageal and cardia adenocarcinoma is consistent with the findings in 7 previous case-control studies (Gammon *et al.*, 1997; Li *et al.*, 1989; Zhang *et al.*, 1996; Levi *et al.*, 1990; Gao *et al.*, 1994; Palli *et al.*, 1992), but not in 6 others (Wu-Williams *et al.*, 1990; Kabat *et al.*, 1993; Brown *et al.*, 1994; Gonzalez *et al.*, 1994; Vaughan *et al.*, 1995; Jedrychowski *et al.*, 1993). The apparent negative association between liquor consumption and risk of oesophageal adenocarcinoma in our study has no support in the previous results and might be a chance finding, particularly since there was no dose-response trend among the users.

Tobacco and alcohol use have long (Young and Russel, 1926) been known as strong risk factors for oesophageal squamous-cell carcinoma (Muir and MacKinney, 1992). In our study, smoking duration was a more important determinant of the risk than amount smoked per day. Although a suggested (Gammon *et al.*, 1997; Gronbaek *et al.*, 1998) protective action of wine could not be verified, our data indicate that wine consumption may not be harmful.

We found no statistically significant association between snuff dipping and risk of any of the studied tumours. This is in agreement with the results of the few studies in which snuff and oesophageal cancer have specifically been investigated (Pottern *et al.*, 1981; Lewin *et al.*, 1998) but in conflict with some reports on predominantly non-snuff smokeless tobacco (Jussawalla and Deshpande, 1971; Jayant *et al.*, 1977; Bjelke *et al.*, 1982; Sankaranarayanan *et al.*, 1991). In Sweden, snuff is produced by heat processing instead of fermentation, and as the latter may increase the concentration of tobacco-specific carcinogens, our results may not be generalizable to all types of snuff or other smokeless tobacco.

Our multiple statistical testing increases the risk of type-I error. Such error could not explain our negative results but must be considered for the positive associations. The association between smoking and cardia adenocarcinoma, in particular, is stronger than expected, and influence of chance cannot be excluded.

In conclusion, the results of our nationwide case-control study challenge the recently proposed (Gammon *et al.*, 1997) major role of smoking in the aetiology of oesophageal adenocarcinoma. If smoking is a risk factor at all, the association is probably weak and not responsible for the dramatically rising incidence in men. Gastric cardia adenocarcinoma, on the other hand, seemed to be more clearly related to smoking, indicating differential aetiologies for these 2 cancers. Our results provide no evidence that alcohol is importantly involved in the aetiology of any of the adenocarcinomas.

ACKNOWLEDGEMENTS

We express our gratitude to Mrs. L. Nyrén for her invaluable coordination of the field work and to Dr. W. Kraaz for expert pathology guidance in the planning of the study and during the field work. Further, we are grateful to all of the 227 doctors who acted as contact persons at the participating departments and provided invaluable input during the planning of this study.

REFERENCES

BJELKE, E. and SCHUMAN, L.M., Chewing of tobacco and use of snuff. Relationship to cancer of pancreas and other sites in two prospective studies. *In: Proceedings of the 13th International Cancer Congress, Seattle,* p. 207 (1982).

BLOT, W.J., DEVESA, S.S., KNELLER, R.W. and FRAUMENI, J.F., Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *J. amer. med. Assoc.*, **265,** 1287–1289 (1991).

BORING, C.C., SQUIRES, T.S. and TONG, T., Cancer statistics, 1993. *Cancer J. Clin.*, **43,** 7–26 (1993).

BRESLOW, N.E. and DAY, N.E., Statistical methods in cancer research. Vol. I. The analysis of case-control studies. *IARC Sci. Publ.*, **32,** 5–338 (1980).

BROWN, L.M., SILVERMAN, D.T., POTTERN, L.M., SCHOENBERG, J.B., GREENBERG, R.S., SWANSON, G.M., LIFF, J.M., SCHWARTZ, A.G., HAYES, R.B., BLOT, W.J. and HOOVER, R.N., Adenocarcinoma of the esophagus and esophagogastric junction in white men in the United States: alcohol, tobacco, and socioeconomic factors. *Cancer Causes Control,* **5,** 333–340 (1994).

CANCER REGISTRY. *Cancer incidence in Sweden 1994.* National Board of Health and Welfare, Stockholm (1997).

FARROW, D.C. and VAUGHAN, T.L., Determinants of survival following the diagnosis of esophageal adenocarcinoma (United States). *Cancer Causes Control,* **7,** 322–327 (1996).

GAMMON, M.D. and 14 OTHERS, Tobacco, alcohol, and socioeconomic status and adenocarcinomas of the esophagus and gastric cardia. *J. nat. Cancer Inst.*, **89,** 1277–1284 (1997).

GAO, Y.T., MCLAUGHLIN, J.K., BLOT, W.J., JI, B.T., BENICHOU, J., DAI, Q. and FRAUMENI, J.F. JR., Risk factors for esophageal cancer in Shanghai, China. Role of cigarette smoking and alcohol drinking. *Int. J. Cancer,* **58,** 192–196 (1994).

GONZALEZ, C.A., AGUDO, A., MONTES, J., RIBOLI, E. and SANZ, J.M., Tobacco and alcohol intake in relation to adenocarcinoma of the gastric cardia in Spain. *Cancer Causes Control,* **5,** 88–89 (1994).

GRONBAEK, M., BECKER, U., JOHANSEN, D., TONNESEN, H., JENSEN, G. and SORENSEN, T.I., Population based cohort study of the association between alcohol intake and cancer of the upper digestive tract. *Brit. med. J.,* **317,** 844–847 (1998).

HANSEN, S., WIIG, J.N., GIERCKSKY, K.E. and TRETLI, S., Esophageal and gastric carcinoma in Norway 1958–1992: incidence time trend variability according to morphological subtypes and organ subsites. *Int. J. Cancer,* **71,** 340–344 (1997).

HANSSON, L.E., SPARÉN, P. and NYRÉN, O., Increasing incidence in both histological types of esophageal carcinomas among men in Sweden. *Int. J. Cancer,* **54,** 402–407 (1993).

JAYANT, K., BALAKRISHNAN, V., SANGHVI, L.D. and JUSSAWALLA, D.J., Quantification of the role of smoking and chewing tobacco in oral, pharyngeal, and oesophageal cancers. *Brit. J. Cancer,* **35,** 232–235 (1977).

JEDRYCHOWSKI, W., BOEING, H., WAHRENDORF, J., POPIELA, T., TOBIASZ-ADAMCZYK, B. and KULIG, J., Vodka consumption, tobacco smoking and risk of gastric cancer in Poland. *Int. J. Epidemiol.*, **22,** 606–613 (1993).

JUSSAWALLA, D.J. and DESHPANDE, V.A., Evaluation of cancer risk in tobacco chewers and smokers: an epidemiologic assessment. *Cancer,* **28,** 244–252 (1971).

KABAT, G.C., NG, S.K. and WYNDER, E.L., Tobacco, alcohol intake, and diet in relation to adenocarcinoma of the esophagus and gastric cardia. *Cancer Causes Control,* **4,** 123–132 (1993).

KIM, R., WEISSFELD, J.L., REYNOLDS, J.C. and KULLER, L.H., Etiology of Barrett's esophagus and esophageal adenocarcinoma. *Cancer Epidemiol. Biomark. Prev.*, **6,** 369–377 (1997).

LAGERGREN, J., BERGSTRÖM, R., LINDGREN, A. and NYRÉN, O., Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N. Engl. J. Med.*, **340,** 825–831 (1999).

LEVI, F., OLLYO, J.B., LA VECCHIA, C., BOYLE, P., MONNIER, P. and SAVARY, M., The consumption of tobacco, alcohol and the risk of adenocarcinoma in Barrett's esophagus. *Int. J. Cancer,* **45,** 852–854 (1990).

LEWIN, F., NORELL, S.E., JOHANSSON, H., GUSTAVSSON, P., WENNERBERG, J., BIORKLUND, A. and RUTQVIST, L.E., Smoking tobacco, oral snuff, and alcohol in the etiology of squamous-cell carcinoma of the head and neck: a population-based case-referent study in Sweden. *Cancer,* **82,** 1367–1375 (1998).

LI, J.Y., ERSHOW, A.G., CHEN, Z.J., WACHOLDER, S., LI, G.Y., GUO, W., LI, B. and BLOT, W.J., A case-control study of cancer of the esophagus and gastric cardia in Linxian. *Int. J. Cancer,* **43,** 755–761 (1989).

MUIR, C.S. and MACKINNEY, P.A., Cancer of the esophagus: a global overview. *Europ. J. Cancer Prev.*, **1,** 259–264 (1992).

PALLI, D. and 12 OTHERS, A case-control study of cancers of the gastric cardia in Italy. *Int. J. Cancer,* **65,** 263–266 (1992).

POTTERN, L.M., MORRIS, L.E., BLOT, W.J., ZIEGLER, R.G. and FRAUMENI, J.F. JR., Esophageal cancer among black men in Washington, D.C. I. Alcohol, tobacco, and other risk factors. *J. nat. Cancer Inst.*, **67,** 777–783 (1981).

POWELL, J. and MCCONKEY, C.C., The rising trend in esophageal adenocarcinoma and gastric cardia. *Europ. J. Cancer Prev.*, **1,** 265–269 (1992).

SANKARANARAYANAN, R., DUFFY, S.W., PADMAKUMARY, G., NAIR, S.M., DAY, N.E. and PADMANABHAN, T.K., Risk factors for cancer of the oesophagus in Kerala, India. *Int. J. Cancer,* **49,** 485–489 (1991).

SPECHLER, S.J. and GOYAL, R.K., Barrett's esophagus. *N. Engl. J. Med.*, **316,** 362–371 (1986).

VAUGHAN, T.L., DAVIS, S., KRISTAL, A. and THOMAS, D.B., Obesity, alcohol, and tobacco as risk factors for cancers of the esophagus and gastric cardia: adenocarcinoma versus squamous-cell carcinoma. *Cancer Epidemiol. Biomark. Prev.*, **4,** 85–92 (1995).

WU-WILLIAMS, A.H., YU, M.C. and MACK, T.M., Life-style, workplace, and stomach cancer by subsite in young men of Los Angeles county. *Cancer Res.*, **50,** 2569–2576 (1990).

YOUNG, M. and RUSSEL, W.T., An investigation into the statistics of cancer in different trades and professions. *Medical Research Council, Special Report Series 99.* HMSO, London (1926).

ZHANG, Z.F., KURTZ, R.C., SUN, M., KARPEH, M. JR., YU, G.P., GARGON, N., FEIN, G.S., GEORGOPOULOS, S.K. and HARLAP, S., Adenocarcinomas of the esophagus and gastric cardia: Medical conditions, tobacco, alcohol, and socioeconomic factors. *Cancer Epidemiol. Biomark. Prev.*, **5,** 761–768 (1996).