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TOBACCO, ALCOHOL AND THE RISK OF GASTRIC CANCER. A POPULATION-BASED CASE-CONTROL STUDY IN SWEDEN

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Previous studies have provided conflicting information on the role of tobacco and alcohol in gastric carcinogenesis. A population-based case-control study with 338 histologically confirmed gastric-cancer cases and 679 control subjects was conducted. Information relating to life-time tobacco consumption, alcohol intake and diet during adolescence and 20 years before interview, and to socio-economic conditions was obtained through face-to-face interviews. Current cigarette smokers were found to have a greater risk than non-users of tobacco. The duration of cigarette or pipe smoking was positively associated with gastric-cancer risk. There was significant interaction between tobacco use and fruit consumption. High fruit intake was more protective among users of tobacco than among non-users, and the risk estimates associated with cigarette smoking were higher among those with low fruit consumption than among frequent fruit-eaters. Likewise, though to a lesser extent, vegetable intake interacted with tobacco use. Snuff dipping and alcohol intake was not associated with gastric-cancer risk. However, high alcohol intake tended to increase the risk associated with tobacco use. This study adds further support to the role of tobacco smoking in gastric carcinogenesis, and demonstrates that high intake of fruits and vegetables may be particularly beneficial in smokers.

The importance of environmental factors as determinants of gastric-cancer risk is widely accepted (Howson *et al.*, 1986), yet the relationship between this cancer and the most well-established carcinogenic exposure-cigarette smoking-is not clear. Many epidemiological studies have reported a weak-to-moderate association of tobacco use with gastric cancer, but only a few have found a dose-response relationship (De Stefani *et al.*, 1990; Kato *et al.*, 1990; Kneller *et al.*, 1991; Wu-Williams *et al.*, 1990; You *et al.*, 1988; Yu and Hsieh, 1991). Because most of the case-control studies have been hospital-based (Correa *et al.*, 1985; De Stefani *et al.*, 1990; Hoshiyama and Sasaba, 1992; Kabat *et al.*, 1993; Kato *et al.*, 1990), the selection of controls may have affected the reported results. Also, although many previous investigators addressed possible confounding of the smoking-gastric cancer relationship by other factors (Correa *et al.*, 1985; De Stefani *et al.*, 1990; Hoshiyama and Sasaba, 1992; Kabat *et al.*, 1993; Kato *et al.*, 1990, 1992; Kono *et al.*, 1987; Risch *et al.*, 1985; Yu and Hsieh, 1991), no one has assessed the modification of the effect of tobacco use by factors other than alcohol (De Stefani *et al.*, 1990; Kabat *et al.*, 1993; Kono *et al.*, 1987). However, in the case of diet, such interactions are plausible: there are clear inverse associations between cigarette smoking and serum levels of vitamin C and beta-carotene (Schectman *et al.*, 1989; Stryker *et al.*, 1988), and smoking could have an impact on risk only among those with already marginal levels of these nutrients.

Since alcohol is strongly associated with esophageal cancer (Tuyns, 1983), one might also expect an association with cancer of the stomach, where contact with the alcohol is more prolonged. However, despite several studies on this topic (IARC, 1988) there are only sporadic reports of alcohol as a risk factor for gastric cancer (Correa *et al.*, 1985; De Stefani *et al.*, 1990). However, in many studies, control for confounding by dietary and socio-economic factors has been inadequate. Also, most previous studies have been performed in populations with a higher *per capita* intake of alcohol than that in Sweden, and it is possible that alcohol may have effects that depend on the pattern of its use.

To address these issues, we examined, in a population-based case-control study, the influence of tobacco and alcohol on the risk of gastric cancer, while controlling for SES and diet. We also evaluated the possible interactions between tobacco use and other factors possibly associated with gastric-cancer risk.

SUBJECTS AND METHODS

A detailed description of subjects and methods is presented elsewhere (Hansson *et al.*, 1993). In brief, this study was conducted in 3 counties in central Sweden (Uppsala, Västmanland and Södermanland) with an incidence rate of gastric cancer below the national average, and 2 counties in northern Sweden (Västerbotten and Norrbotten) with the country's highest incidence of gastric cancer. The study base consisted of all individuals 40–79 years, born in Sweden, and living in the above-mentioned counties from February 1989 through January 1992. All patients in the study base with a newly diagnosed, histologically confirmed, gastric cancer were eligible as cases. Approximately 2 controls per case were randomly selected from continuously updated population registers covering the entire population. The selection was stratified by age and gender according to the expected distribution among cases.

Face-to-face interviews were carried out by professional interviewers, using a structured questionnaire to cover consumption of various sorts of tobacco during the whole lifespan. Cigarette smokers were defined as those smoking one or more cigarettes a day for at least half a year, and pipe-smokers as those smoking at least one pipe a week for half a year or more. Since more cases than controls had stopped smoking during the year preceding the interview, possibly due to insidious cancer symptoms, current smokers were defined as those who were smoking 2 years before the interview. Intake of alcoholic beverages during adolescence and 20 years before interview was assessed with a frequency questionnaire, with answers categorized into 9 levels, ranging from "never" to "twice daily, or more". There were also supplementary questions on the average amount consumed each time, allowing us to express the consumption in ml/month. Total alcohol consumption was calculated taking into account separately wine, hard liquor, light beer (1.8 weight% alcohol), medium-strong beer (3.5 weight% alcohol), and strong beer (4.5 weight% alcohol). Further questions focused on dietary habits in 2 periods of life (adolescence and 20 years before interview), demographic and socio-economic conditions, occupational and medical histories. The interviewees were grouped into 5 socio-economic classes based on their entire occupational experience (Hansson *et al.*, 1993): unskilled manual workers, skilled manual

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workers, non-manual workers, self-employed persons, and farmers.

Of 456 eligible cases, 338 (74.1%) were included in the study. The reasons for non-participation were: patient refusal (15 cases; 3.3%), mental or physical illness (other than gastric cancer) (13 cases; 2.9%), and advanced malignant disease or early death (90 cases; 19.7%). The mean age of participating cases was 67.7 years (64.4% males), and among those non-participating 69.1 years (66.4% males). Of 880 selected control subjects, 132 (15.0%) refused to take part in the study, 59 (6.7%) were mentally or physically unfit for interview, and 10 (1.1%) could not be located. Eventually, 679 control subjects (77.3% of the original sample) were included in the study. The mean age among participating control subjects was 67 years.

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

Analysis

The logistic-regression model was used in univariate and multivariate analyses of the relationship between gastric-cancer risk and possible risk factors. Model parameters were estimated by the maximum likelihood method. From these, odds ratios (OR) and 95% confidence intervals (CI) were computed. Adjustment for the stratification variables age and gender was made in all analyses. In the modelling, continuous variables were considered in categorized form as well as in original continuous form. In addition to the basic models, various multivariate models were also fitted to obtain risk estimates of variables after adjustment for effects of certain other variables. To study interaction effects between variables such as smoking, alcohol intake, fruit and vegetable consumption, the following strategy was employed: for a formal test of the interaction effect, models with product terms directly included were formulated and fitted. To obtain more easily interpretable results, models were also fitted after stratification for variables of interest. When analyzing the effect of cigarette smoking, we adjusted for other tobacco use (smoking of cigars, and pipes, chewing snuff and tobacco). Similarly, when we analyzed the effect of other tobacco exposures, we adjusted in each instance for the complementary uses of tobacco, including cigarette smoking.

RESULTS

Tobacco

A total of 163 cases and 312 control subjects had ever smoked cigarettes, while 50 cases and 82 controls had used other kinds of tobacco but not cigarettes. There were 20 cases but only 6 control subjects who had stopped smoking cigarettes during the year of interview or the year before. Corresponding figures for pipe smokers were 9 cases and 3 controls. Table I shows the risk of gastric cancer associated with cigarette and pipe smoking. Current smokers of cigarettes had a 72% higher risk than subjects who did not use tobacco in any form. Ex-smokers had virtually no increased risk. Age at which

TABLE I - ODDS RATIOS ASSOCIATED WITH SMOKING OF CIGARETTES OR PIPES

Variable	Cigarette smoking			Pipe smoking		
	Cases	Controls	Multivariate analyses including age, gender, SES and other tobacco use OR (95% CI)	Cases	Controls	Multivariate analyses including age, gender SES and other tobacco use OR (95% CI)
Non-users of tobacco	120	281	Reference	120	281	Reference
Ex-smokers	85[1]	199[1]	1.09 (0.75–1.59)	93[2]	186[2]	1.33 (0.90–1.97)
Current smokers	78	113	1.72 (1.16–2.54)	33	37	2.24 (1.28–3.92)
Age at start						
≥ 21	36	79	1.17 (0.73–1.88)	35	69	1.46 (0.88–2.43)
16–20	86	165	1.35 (0.93–1.96)	62	116	1.38 (0.89–2.12)
≤ 15	41	69	1.52 (0.93–2.48)	23	34	1.60 (0.87–2.94)
			p value for trend = 0.38[3]			p value for trend = 0.85[3]
Duration (years)						
1–10	18	41	1.13 (0.60–2.11)	49	108	1.26 (0.80–1.98)
11–20	20	46	1.07 (0.58–1.97)			
21–30	25	74	0.83 (0.49–1.40)	35	69	1.31 (0.79–2.18)
31–40	42	58	1.84 (1.15–2.95)			
≥ 41	57	87	1.62 (1.05–2.49)	39	46	2.05 (1.21–3.49)
			p value for trend = 0.01			p value for trend = 0.01
Amount smoked (cig./day while being smoker)						
1–5	34	74	1.08 (0.68–1.73)			
6–10	51	93	1.38 (0.89–2.12)			
11–15	34	44	2.08 (1.22–3.52)			
≥ 16	44	101	1.17 (0.75–1.84)			
			p value for trend = 0.10			
Cessation (years before interview)						
≥ 31	18	48	0.92 (0.50–1.69)			
21–30	14	41	0.89 (0.46–1.73)			
11–20	28	59	1.22 (0.72–2.07)			
≤ 10	25	51	1.27 (0.73–2.20)			
Current smokers	78	113	1.72 (1.16–2.54)			
			p value for trend = 0.02			

[1]There were 50 cases and 82 controls who had never smoked cigarettes but who used other kinds of tobacco (not included in these figures).–[2]There were 87 cases and 172 controls who had never smoked a pipe but who used other kinds of tobacco (not included in this figure).–[3]This trend test does not include the reference group (non-users of tobacco).

smoking began tended to be inversely associated and amounts smoked tended to be positively associated with risk, but neither trend reached statistical significance. However, longer duration of cigarette smoking was more clearly associated with increasing gastric-cancer risk, and longer time since cessation conferred a decreasing relative risk, in both cases with statistically significant trends. Type of cigarettes (filter or not) and the habit of inhaling the smoke had no influence on the risk (data not shown). The risk estimates associated with cigarette smoking did not change substantially after further adjustment for the possible confounding effect of vegetable intake.

Current pipe smokers experienced a more-than-2-fold increase in gastric-cancer risk, which also increased steadily with longer duration of smoking (Table I). However, age at which pipe smoking began did not influence the risk substantially. There was no statistically significant association between cancer risk and snuff dipping (OR, 0.70; 95% CI, 0.47 to 1.06) or cigar smoking (OR, 1.00; 95% CI, 0.50 to 1.99) after adjustment for age, gender, SES, vegetable intake and other tobacco use. The number of tobacco chewers was too small to allow any reliable statistical analysis.

Table II summarizes the effect of vegetable or fruit intake on gastric-cancer risk among users and non-users of tobacco. There was a negative association between gastric-cancer risk and vegetable or fruit consumption which was more evident for users of tobacco than for non-users. This protective effect was particularly clear for fruit consumption. The interaction term for tobacco use (ever/never) and fruit intake (high/low) was statistically significant ($p = 0.048$), although this was not the case for vegetable intake (high/low) ($p = 0.25$).

Table III illustrates the joint smoking-diet effects from another perspective, by examining the effect of cigarette smoking in those with high and with low consumption of fruit. There were consistently higher risk estimates for cigarette smoking among those with low than among those with high fruit consumption. The differences in smoking-related relative risks between those with low (≤ 4 times/month) and high (high ≥ 4.1 times/month) consumption of vegetables were in general not as marked. However, the risk estimate for current cigarette smoking was higher among those with low vegetable intake (OR, 2.25; 95% CI, 1.03 to 4.92) than those with high intake (OR, 1.54; 95% CI, 0.96 to 2.46) (other data not shown). We found no similar pattern of effect modification between tobacco-use and other indices of gastric-cancer risk in this population (SES, refrigerator use, BMI, height or number of siblings) (Hansson *et al.*, 1993).

Alcohol

Alcohol intake 20 years before interview is shown in Table IV. No increased risk was noted for total alcohol consumption or for any type of alcoholic beverage. On the contrary, the highest intake category for wine tenced to be associated with decreased risk, although this association was erratic at different exposure levels. High intake of wine was correlated with

TABLE II – ODDS RATIOS ASSOCIATED WITH VEGETABLE OR FRUIT CONSUMPTION 20 YEARS BEFORE INTERVIEW AMONG USERS AND NON-USERS OF TOBACCO (ADJUSTED FOR AGE, GENDER AND SES)

Variable	Non-users of tobacco			Tobacco users		
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
Total vegetable consumption (times/month)						
≤ 4	33	56	Reference	73	94	Reference
4.1–12	32	90	0.57 (0.31–1.05)	54	94	0.73 (0.47–1.15)
13–26	35	80	0.76 (0.42–1.40)	57	115	0.68 (0.43–1.06)
≥ 30	16	53	0.59 (0.28–1.25)	26	87	0.42 (0.24–0.75)
			p value for trend = 0.30			p value for trend = 0.004
Total fruit consumption (times/month)						
≤ 8.6	31	68	Reference	78	100	Reference
8.7–21.8	30	69	0.93 (0.51–1.71)	69	99	0.91 (0.59–1.41)
21.9–41.0	23	65	0.74 (0.37–1.36)	37	95	0.52 (0.32–0.85)
≥ 41.1	29	70	0.91 (0.49–1.71)	27	97	0.38 (0.22–0.64)
			p value for trend = 0.62			p value for trend = 0.0001

TABLE III – ODDS RATIOS ASSOCIATED WITH CIGARETTE SMOKING AMONG THOSE WITH HIGH AND LOW CONSUMPTION OF FRUIT 20 YEARS BEFORE INTERVIEW

Smoking category	Cases	Controls	Low[1] fruit consumption OR (95% CI)	Cases	Controls	High[2] fruit consumption OR (95% CI)
Non-users of tobacco			Reference			Reference
Ex-smokers	60	96	1.35 (0.83–2.20)	25	103	0.80 (0.45–1.44)
Current smokers	54	59	1.77 (1.06–2.94)	24	54	1.55 (0.83–2.90)
Duration (years)						
1–30	44	70	1.20 (0.71–2.03)	19	91	0.73 (0.38–1.39)
≥ 31	69	82	1.79 (1.12–2.86)	30	63	1.48 (0.84–2.61)
			p value for trend = 0.02			p value for trend = 0.24
Amount smoked (cig./day while smoker)						
1–10	55	81	1.36 (0.84–2.23)	30	86	1.16 (0.66–2.05)
≥ 11	59	74	1.72 (1.03–2.86)	19	71	0.95 (0.50–1.82)
			p value for trend = 0.03			p value for trend = 0.97

[1] ≤ 21.8 times/month.–[2] ≥ 21.9 times/month.

TABLE IV - ODDS RATIOS ASSOCIATED WITH INTAKE OF ALCOHOLIC BEVERAGES 20 YEARS BEFORE INTERVIEW

Beverage	Cases	Controls	Multivariate analyses including: Age and gender OR (95% CI)	Age, gender and SES OR (95% CI)
Total alcohol consumption (ml 100% alcohol/month)				
Non-drinkers	83	160	Reference	Reference
1–35	95	165	1.12 (0.77–1.62)	1.17 (0.81–1.70)
36–160	87	167	1.01 (0.68–1.49)	1.11 (0.75–1.64)
> 160	73	179	0.79 (0.53–1.20)	0.92 (0.60–1.42)
			p value for trend = 0.22	p value for trend = 0.64
Light beer (ml/month)				
< 400	245	434	Reference	Reference
400–2300	42	111	0.66 (0.45–0.98)	0.69 (0.47–1.02)
≥ 2400	51	132	0.67 (0.46–0.97)	0.76 (0.51–1.13)
			p value for trend = 0.01	p value for trend = 0.08
Medium-strong beer (ml/month)				
< 400	273	535	Reference	Reference
≥ 400	65	143	0.92 (0.65–1.31)	0.96 (0.68–1.37)
Strong beer				
Non-drinkers	278	541	Reference	Reference
Drinkers	60	137	0.88 (0.62–1.25)	0.95 (0.67–1.35)
Wine (ml/month)				
Non-drinkers	154	297	Reference	Reference
1–59	86	127	1.31 (0.94–1.83)	1.35 (0.97–1.88)
60–199	31	88	0.69 (0.43–1.11)	0.70 (0.44–1.13)
200–599	51	94	1.05 (0.71–1.56)	1.21 (0.80–1.83)
≥ 600	16	71	0.44 (0.24–0.79)	0.57 (0.31–1.04)
			p value for trend = 0.04	p value for trend = 0.33
Hard liquor (ml/month)				
Non-drinkers	123	250	Reference	Reference
1–79	98	174	1.19 (0.85–1.65)	1.23 (0.87–1.76)
80–319	57	140	0.87 (0.59–1.29)	0.91 (0.61–1.38)
≥ 320	60	111	1.16 (0.77–1.75)	1.27 (0.83–1.96)
			p value for trend = 0.87	p value for trend = 0.61

higher SES, and adjustment for SES moved the OR towards unity for the highest consumption of wine. Very few subjects were drinking alcoholic beverages during adolescence, excluding any meaningful statistical analysis of the early intake of alcohol.

In a multiplicative model, we examined the joint effects of tobacco use (ever/never) and alcohol consumption [drinker/non-drinker (0 g alcohol/month)], adjusted for age, gender and SES. Among non-drinkers the OR of tobacco use was 0.53 (95% CI, 0.25 to 1.12), but among drinkers it was 1.77 (95% CI, 1.22 to 2.57). The product term in the corresponding logistic model was statistically significant ($p = 0.0073$).

DISCUSSION

This population-based study found a significantly increased risk of gastric cancer among current cigarette or pipe smokers as compared with non-users of tobacco. There was also a dose-response relationship between risk and duration of cigarette and pipe smoking. However, the effect of tobacco use seemed to differ with dietary intake of fruit and vegetables. The risk estimates associated with cigarette smoking were higher among those with low fruit consumption than among those with high consumption. Also, the protective effect of vegetables and fruit was stronger among tobacco users than among non-users of tobacco. We found no association between snuff dipping or alcohol consumption and gastric cancer.

The majority of previous cohort studies reported an increased risk of gastric cancer (or gastric-cancer death) among cigarette smokers (Hammond, 1966; Hirayama, 1990; Kahn, 1966; Kato *et al.*, 1992: Kneller *et al.*, 1991; Kono *et al.*, 1987; Nomura *et al.*, 1990), but only one discerned a dose-response relationship with respect to number of cigarettes smoked/day (Kneller *et al.*, 1991). The results of previous case-control studies are more contradictory, some disclosing a positive association (Correa *et al.*, 1985; De Stefani *et al.*, 1990; Kato *et al.*, 1990; Risch *et al.*, 1985; Wu-Williams *et al.*, 1990; You *et al.*, 1988; Yu and Hsieh, 1991) and others not (Boeing *et al.*, 1991; Buiatti *et al.*, 1989; Graham *et al.*, 1990; Jedrychowski *et al.*, 1986). Only a minority of the positive studies revealed a dose-response relationship with respect to duration (De Stefani *et al.*, 1990) or intensity (De Stefani *et al.*, 1990; Wu-Williams *et al.*, 1990; You *et al.*, 1988; Yu and Hsieh, 1991). Our findings suggest that the variation in smoking-related findings may be due in part to modification of the effects by diet (or other risk factors) in the populations studied. We noted different rates of quitting smoking among cases and controls in the year preceeding the interview. This discrepancy would lead to underestimation of the risk associated with current smoking. In our study, the OR for current smoking would have decreased from 1.72 to 1.34 had we not defined current smoking as smoking 2 years before interview. Several previous studies have not paid attention to this question, and this may explain why some studies have even reported risk estimates below unity for current smoking (Boeing *et al.*, 1991; Jedrychowski *et al.*, 1986).

A few studies have reported increased risk associated with pipe smoking (Kneller *et al.*, 1991; Correa *et al.*, 1985), in line with our findings. The prevalence of snuff dipping is comparatively high among Swedish males (13%) (Österdahl and Slorach, 1988), but in contrast to a US cohort study (Kneller *et al.*, 1991) we found no increased risk associated with snuff dipping.

The importance of current smoking status for gastric-cancer risk in the present study may indicate that the later rather than

the early stages of gastric carcinogenesis are influenced. In a study from China (Kneller *et al.*, 1992), cigarette smoking was found to double the risk of transition from chronic atrophic gastritis to dysplasia. Also, recent findings of significantly greater adduct levels in the tumor-tissue DNA of male cigarette smokers than in that of non-smokers with gastric cancer adds some biochemical evidence concerning the role of smoking in gastric carcinogenesis (Dyke *et al.*, 1992).

There are several mechanisms by which tobacco use might increase gastric-cancer risk. Indeed, tobacco smoke contain numerous carcinogenic substances, or compounds which may metabolize to carcinogens. Nitrogen oxides in tobacco smoke may promote the formation of endogenous *N*-nitroso compounds (Hoffmann and Hecht, 1985). Also, cigarette smoke contains large amounts of free radicals, which may induce oxidant stress in smokers. Decreased vitamin C and beta-carotene concentrations in plasma have been reported in smokers even after adjustment for reported intake (Comstock *et al.*, 1987; Schectman *et al.*, 1989; Stryker *et al.*, 1988). At least for vitamin C, this probably reflects increased turnover in response to the oxidant load. Our finding of a more pronounced protective effect of vegetables and fruits (rich in vitamin C, beta-carotene and other anti-oxidants) among smokers than among non-smokers may reflect the relative deficit of these nutrients in smokers and hence a more marked risk-reducing effect of increased intake among them (Hornig and Glatthaar, 1985). It may be the case that tobacco use can affect gastric-cancer risk only if anti-oxidant defenses are weak.

In our data, intake of alcoholic beverages was not associated with any increased risk of gastric cancer, in line with a recent Swedish cohort study in alcoholics that showed no excess risk (Adami *et al.*, 1992). Previous case-control studies have been inconsistent, but no cohort study has showed any excess risk for gastric cancer (IARC, 1988). Overall, a causal role of alcoholic beverages in gastric carcinogenesis is unlikely. However, alcohol may operate as a co-factor for carcinogens in cigarette smoke, conceivably through breaking protective barriers, or acting as a vehicle for carcinogens (IARC, 1988). Supporting this, we found a joint effect of tobacco use and alcohol intake, corroborating findings from another study (De Stefani *et al.*, 1990).

Cigarette smoking is generally accurately recalled, suggesting that response bias is unlikely to have affected our results regarding smoking. The proportion who correctly recall smoking status 20 and 32 years before inquiry has been reported to be 90% and 86%, respectively; the accurate recall of smoking dose was 74% after 20 years and 57% after 32 years (Krall *et al.*, 1989). However, recalled alcohol consumption after 18 years tends to be over-estimated (Simpura and Poikolainen, 1983). The number of reports of high alcohol intake was small among our subjects compared with that in most other investigations (De Stefani *et al.*, 1990). Although the average alcohol consumption is low in Sweden [the *per capita* annual sale of alcohol in Sweden was 5.5 liters ethanol in 1986, as compared with 13.0 liters in France (CAN, 1988)], a certain degree of under-reporting cannot be ruled out.

To conclude, cigarette and pipe smoking moderately increase the risk of gastric cancer, and duration seems to be more important than the intensity of the habit. Intake of vegetables, fruit and alcohol interact with the risk-increasing effect of cigarette smoking. Our study provides further evidence of a possible causal relationship between cigarette smoking and gastric-cancer risk, especially among tobacco users with diets that already place them at high risk.

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