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Tobacco, alcohol intake, and diet in relation to adenocarcinoma of the esophagus and gastric cardia

Geoffrey C. Kabat, Stephen K. C. Ng, and Ernst L. Wynder

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Little is known about the etiology of adenocarcinoma of the distal esophagus/cardia, a cancer which has increased in incidence in the United States over the last two decades. We analyzed data on smoking, alcohol use, dietary intake, and other factors obtained from 173 hospitalized males with adenocarcinoma of the distal esophagus/cardia (cases) and 4,544 hospitalized males with diseases not related to smoking and of other organ systems than the gastrointestinal tract (controls). Cases of squamous cell carcinoma of the esophagus (n = 136) and adenocarcinoma of the distal stomach (n = 122) were included as separate case groups. All subjects were interviewed in 28 hospitals in eight cities in the US between 1981 and 1990. After adjustment for covariates, the odds ratio (OR) for adenocarcinoma of the distal esophagus/cardia for current smokers was 2.3 (95 percent confidence interval [CI] = 1.4-3.9) and that for ex-smokers was 1.9 (CI = 1.2-3.0) relative to never-smokers. The OR for drinkers of four or more ounces of whiskey-equivalents of alcohol per day (relative to those consuming less than one drink per week) was 2.3 (CI = 1.3-4.3). Intakes of total fat and vitamin A from animal sources were significant risk factors and fiber intake was associated inversely with adenocarcinoma of the distal esophagus/cardia. Although the number of female cases of adenocarcinoma of the distal esophagus/cardia was small (n = 21), significant associations were observed for smoking and alcohol.

Key words: Alcohol, body mass index, dietary factors, esophageal cancer, gastric cancer, smoking, United States.

Introduction

The age-adjusted incidence of adenocarcinoma of the distal esophagus and cardia has been increasing steadily in the United States since at least the mid-1970s in contrast to the incidence of squamous cell carcinoma of the esophagus, which has been stable.[1,2] The annual rate of increase among men from 1976 to 1987 was between four percent and 10 percent, surpassing that of all other cancers. Adenocarcinoma of the esophagus and cardia (AEC) occurred predominantly among White men, whereas squamous cell carcinoma occurred predominantly among Blacks.[1,3-5] An increase in the incidence of adenocarcinoma of the distal esophagus and cardia has been noted also in the United Kingdom and Denmark.[6,7]

Little is known about risk factors for AEC. A number of studies have compared clinical characteristics and potential risk factors among cases with cancer of specific subsites within the esophagus and stomach.[8-11]

Dr Kabat is in the Department of Epidemiology and Social Medicine, Albert Einstein College of Medicine, Bronx, NY, USA. At the time of this work he was with the Division of Epidemiology, American Health Foundation, New York, NY. Drs Ng and Wynder are with the Division of Epidemiology, American Health Foundation. Address correspondence to Dr Kabat, Department of Epidemiology and Social Medicine, Albert Einstein College of Medicine, Belfer Bldg, Rm 1302, 1300 Morris Park Avenue, Bronx, NY 10461, USA. *Supported by National Cancer Institute Program Project grant CA32617 and Center grant CA17613.*

In addition, several case-control studies have examined risk factors for adenocarcinoma of the esophagus and/or gastric cardia.[12-16]

Using data from a hospital-based case-control study of tobacco-related cancers carried out between 1981 and 1990,[17] we analyzed data on smoking, alcohol, diet, and other risk factors in relation to: (i) squamous cell carcinoma of the esophagus; (ii) adenocarcinoma of the distal esophagus, gastro-esophageal junction, or cardia; and (iii) adenocarcinoma of the distal stomach.

Materials and methods

In the original study, newly diagnosed, histologically confirmed, primary cases of tobacco-related cancers (lung, larynx, oral cavity, bladder, kidney, pancreas and squamous cell carcinoma of the esophagus) were interviewed in 28 hospitals in eight US cities (NYC, NY; Birmingham, AL; Chicago, IL; Detroit, MI; Philadelphia, PA; Pittsburgh, PA; San Francisco, CA; Atlanta, GA).[17] For each case, a control patient with an admitting diagnosis of a condition not known to be associated with tobacco use was selected and interviewed within two months of the case interview. Controls were matched to cases on age (± 5 years), sex, race, and hospital. Control diagnoses included non-tobacco related cancers (stomach; colorectum; breast; prostate; endometrium; ovary; leukemia; lymphoma; sarcomas; central nervous system tumors, etc.), as well as non-cancer diagnoses (acute infections; fractures; spinal disc problems; other trauma; arthritis; and ophthalmological conditions).

Adenocarcinoma of the esophagus *or* cardia were both acceptable controls according to the study protocol and were coded as "stomach cancer". For the purposes of the present analysis, all diagnoses of both esophageal (among cases and controls) and stomach cancer (among controls) were reviewed and reclassified, using information recorded by the interviewer on the face sheet of the questionnaire—which included subsite and cell type—into three groups, according to the *International Classification of Diseases, Ninth Revision*[18] (ICD-9): (i) squamous cell carcinoma of the esophagus (ICD-9 code 150); (ii) adenocarcinoma of the distal esophagus, gastro-esophageal junction, or cardia (151.0); and (iii) adenocarcinoma of the distal stomach (151.1-151.9).

No attempt was made to separate adenocarcinoma of the distal esophagus or gastro-esophageal junction from adenocarcinoma of the cardia. The majority of cases had "gastro-esophageal junction" as the specified subsite, and we henceforth will refer globally to adenocarcinoma of the esophagus/cardia (AEC). Out of 587 cancers of the esophagus or stomach, 26 (4.4 percent) were excluded for the following reasons: uncertain cell type or subsite ($n = 9$); non-carcinomas (carcinoid, lymphoma, leiomyosarcoma) ($n = 15$); adenocarcinoma located in the middle third of the esophagus ($n = 2$).

For the present analysis, all digestive tract cancers (mainly of the colon and rectum) were excluded from the control group. The distribution of the remaining diagnoses among the controls was as follows: in males, 38 percent cancers (including, in declining order of frequency, prostate, skin, lymphoma, sarcoma, and leukemia) and 62 percent non-cancers (including fractures, disc problems, trauma, hernias, benign prostatic hypertrophy, eye problems, and acute infections); in females, 54 percent cancers (breast, ovary, endometrium, skin, leukemia, lymphoma, and sarcoma) and 46 percent non-cancers (including arthritis, fractures, disc problems, eye problems, acute infections and trauma).

Since there was only a small number of non-White cases, the analysis was limited to Whites.

All subjects were interviewed in the hospital by trained interviewers using a questionnaire covering the following content areas: demographics; occupation and occupational exposures; detailed smoking history; alcohol use; medical history; vitamin and mineral supplements; height; and weight five years prior to diagnosis.

For the period 1985-90, a brief food-frequency questionnaire including 30 specific food items or classes of foods was used, as previously described.[19] These foods were judged to account for approximately 80 percent of the average American intake of dietary fat and vitamin A from plant and animal sources. Subjects were asked for their usual adult intake prior to the onset of the current illness. Portion sizes were not asked, except in the case of eggs and milk. For the remaining foods, a standard portion size was assigned to each food item. Nutrient scores other than fiber were computed using the USDA's food composition tables.[20] Fiber values were taken from Anderson.[21] Computation of nutrient scores involved summing, for each subject, the amount of each nutrient derived from each of the food items contributing to that nutrient. The sex-specific quartile distributions of the dietary scores and of body mass index (BMI, weight [kg]/height [m]^2) were used to compute odds ratios (OR).

The percentage of total subjects interviewed between 1985 and 1990 and on whom we had dietary data was 50 percent in males and 53 percent in females. For AEC cases, however, the percentage was higher (77 percent in males and 76 percent in females due to the increasing frequency of this cancer over the study period (Figure 1).

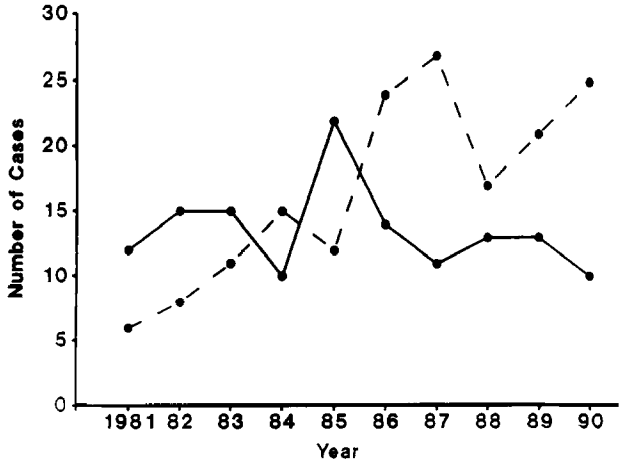

Figure 1. Number of male cases of squamous cell carcinoma of the esophagus (SCCE, —) and of adenocarcinoma of the esophagus/cardia (AEC, - - -) enrolled per year in the present study, 1981-90.

Smoking was examined in terms of smoking status (never-smoker, current smoker of cigarettes, ex-smoker of cigarettes, pipe/cigar only); amount smoked; and years since quitting. A never-smoker was someone who throughout life had not smoked on a regular basis (defined as smoking at least one cigarette per day for at least one year). An ex-smoker was a regular smoker who had quit at least one year prior to diagnosis. Alcohol was analyzed as number of drinks per day (in ounces of whiskey-equivalents) from beer, wine, and hard liquor combined, relative to those consuming less than one drink per week ('nondrinkers'). Those drinking at least one drink per week but less than one per day were termed 'occasional drinkers'. The effect of individual beverages was also examined.

Subjects were asked whether they had ever used vitamin and/or mineral supplements at least three times per week for at least six months. For each type of supplement, the age at first use, average number per month, and number of years of use were obtained. Because of the low frequency of use in the age groups in this study, vitamin use was analyzed in terms of ever/never use of any vitamin supplement and ever/never use of vitamin A and C supplements, separately.

More than 40 self-reported occupational and environmental exposures were grouped into six categories: dusts; emissions/exhausts; fumes; chemicals and solvents; metals; and ionizing radiation. Exposure was examined as a dichotomous variable (yes/no) for each of the six classes.

Results are presented for squamous cell carcinoma of the esophagus (SCCE), adenocarcinoma of the esophagus/cardia (AEC), and adenocarcinoma of the distal stomach (ADS) compared with controls. In order to compare male-to-female ratios for the three sites, the ratios for AEC and ADS (which were control diagnoses in the original study and therefore selected as matches for cases) were adjusted for the 2.1-fold greater number of male than female cases. This was done by dividing the crude male:female ratios for AEC and ADS by 2.1. Since SCCE was a case in the original study, it required no adjustment. Odds ratios (OR) and 95 percent confidence intervals (CI) were calculated from unconditional logistic regression models, including age, education, and other risk factors as covariates.[22] ORs for levels of intake of dietary factors were computed from models which included the remaining dietary variables entered as continuous variables.

Results

Figure 1 shows the numbers of cases of SCCE and AEC interviewed in each year of the study. In contrast to the generally stable numbers of SCCE, there is a marked rise in the numbers of AEC over the study period in conformity with what is seen in the Surveillance, Epidemiology and End Results (SEER) data.[1] The male-to-female ratio was 1.7 for SCCE, 3.7 for AEC, and 1.9 for ADS.

Descriptive variables among cases and controls are presented in Table 1. In males, the frequency of ever-smoking was highest in SCCE (89 percent), followed by AEC (86 percent), ADS (81 percent), and controls (77 percent). The highest proportion of drinkers of one drink or more per week was seen in SCCE (95 percent), followed by AEC (90 percent), controls (80 percent), and ADS (76 percent). In females, the proportion of ever-smokers was highest in SCCE (79 percent), followed by ADS and AEC (68 and 67 percent, respectively), and controls (48 percent). Only SCCE had an elevated proportion of drinkers of one drink or more per week (79 percent) compared with controls (54 percent).

The association of smoking variables, adjusted for covariates (not including dietary factors), is presented for males in Table 2. For SCCE, the association with current smoking was significant (OR = 4.5, CI = 2.5-8.1) but that with ex-smoking was not. In ever-smokers there was an increase in the OR from the lowest level of smoking to the intermediate level but no further increase from intermediate to highest level of smoking. A highly significant reduction in the OR with increasing years since quitting was evident. For AEC, both current and ex-smokers had significantly elevated OR (OR = 2.3, CI = 1.4-3.9, and OR = 1.9, CI = 1.2-3.0, respectively). Among ever-smokers, there was a gradient in the OR with increasing amount

Table 1. Distribution of descriptive variables (%) in three digestive tract cancers,[a] cases and controls, by sex

	Males				Females			
	SCCE (No. = 136)	AEC (No. = 173)	ADS (No. = 122)	Controls (No. = 4,544)	SCCE (No. = 78)	AEC (No. = 21)	ADS (No. = 31)	Controls (No. = 2,228)
Age (yrs)								
< 60	43.0	40.8	37.7	48.9	29.5	23.8	38.7	46.9
60-69	40.7	46.2	45.1	38.6	50.0	47.6	48.4	36.9
70 +	16.3	13.0	17.2	12.5	20.5	28.6	12.9	16.2
Education (yrs)								
< 13	49.2	39.0	53.8	49.9	61.5	52.4	48.4	59.7
13-15	18.7	21.9	10.7	19.0	21.8	14.3	29.0	21.0
16 +	32.1	39.1	35.5	31.1	16.7	33.3	22.6	19.3
Occupational level								
Professional	39.3	40.8	35.3	36.8	15.4	23.8	25.8	21.6
Skilled	37.8	43.2	43.4	42.2	48.7	38.1	35.4	41.4
Semi-skilled	14.8	12.4	13.9	13.1	3.8	0.0	6.5	6.6
Unskilled	8.1	3.6	7.4	7.9	2.6	9.5	9.7	6.0
Housewife	—	—	—	—	29.5	28.6	22.6	24.8
Religion								
Protestant	24.4	29.6	16.4	29.2	29.5	38.1	9.7	28.0
Catholic	66.7	50.9	54.1	48.6	57.7	38.1	74.2	49.2
Jewish	5.2	17.2	23.8	17.7	11.5	23.8	12.9	20.2
Other	3.7	2.3	5.7	4.5	1.3	0.0	3.2	2.6
Place of birth								
US	88.7	90.6	83.3	90.2	89.7	100.0	90.3	89.7
Other	11.3	9.4	16.7	9.8	10.3	0.0	9.7	10.3
Smoking status								
Never smoked	11.1	14.2	18.9	23.2	20.5	33.3	33.3	51.8
Current smoker	49.6	29.0	26.2	27.1	52.6	42.9	33.4	22.1
Ex-smoker	31.1	51.5	48.4	42.4	26.9	23.8	33.3	26.1
Pipe/cigar only	8.2	5.3	6.5	7.3				
Alcohol intake								
Nondrinker[b]	5.4	9.5	24.2	20.0	20.5	47.6	54.9	46.2
Occasional[c]	11.5	31.6	38.3	30.4	21.8	23.8	29.0	37.0
1-3.9 oz/d[d]	20.0	35.1	20.8	28.5	32.1	14.3	12.9	13.7
4-6.9 oz/d[d]	15.4	9.5	6.7	8.9	11.5	4.8	0.0	1.9
7 + oz/d	47.7	14.3	10.0	12.2	14.1	9.5	3.2	1.2

[a] SCCE = squamous cell carcinoma of the esophagus; AEC = adenocarcinoma of the esophagus or cardia; ADS = adenocarcinoma of the distal stomach.
[b] Less than 1 drink per week.
[c] ≥ 1 drink per week but less than 1 drink per day.
[d] Ounces of whiskey-equivalents per day.

smoked. In ex-smokers, there was no trend with years since quitting, however the OR was significantly reduced in ex-smokers of 21 + years. For ADS, none of the associations reached statistical significance, but there was a suggestion of an association with smoking.

Current smoking was significantly associated with cancer of all three sites in women, with the strongest association seen for SCCE, followed by AEC and ADS (Table 3). The ORs for ever-smokers of 21 + cigarettes per day were similar for all three sites (between 4.0 and 5.0). The ORs for SCCE decreased with increasing years since quitting. There was also a suggestion that women who quit 11 or more years ago are at reduced risk of AEC.

In both sexes, alcohol consumption was associated strongly with SCCE, showing a dose-response relationship, and less strongly with AEC but not with ADS (Table 4). In those consuming four or more ounces of whiskey-equivalents per day (w-e/d), the adjusted OR for SCCE was 10.9 in males and 13.2 in females. In contrast, there was a shallow gradient in the OR for AEC in males with increasing alcohol intake. The OR for drinkers of four or more ounces of w-e/d was 2.3. In females, the OR for AEC was elevated only

Table 2. Association[a] of smoking with three types of digestive tract cancer (males)[b]

	SCCE (No. = 134)		AEC (No. = 169)		ADS (No. = 121)	
	OR[c]	(CI)[d]	OR[c]	(CI)	OR[c]	(CI)
Never smoked	1.0	—	1.0	—	1.0	—
Current smoker	4.5	(2.5-8.1)	2.3	(1.4-3.9)	1.7	(1.0-3.0)
Ex-smoker	1.3	(0.7-2.4)	1.9	(1.2-3.0)	1.4	(0.9-2.4)
Pipe/cigar only	1.8	(0.8-4.1)	1.1	(0.5-2.3)	1.0	(0.4-2.2)
Ever-smoked (cigarettes per day)[e]						
1-20	1.9	(1.1-3.5)	1.8	(1.1-2.9)	1.7	(1.0-2.8)
21-30	2.7	(1.3-5.4)	2.1	(1.1-3.9)	0.8	(0.3-1.8)
31 +	2.7	(1.5-5.0)	2.4	(1.5-4.0)	1.6	(0.9-2.9)
Years since quitting[f]						
1-5	0.5	(0.3-1.0)	0.5	(0.2-1.1)	1.0	(0.5-2.0)
6-10	0.4	(0.2-0.8)	1.1	(0.6-1.9)	1.1	(0.6-2.4)
11-20	0.3	(0.2-0.6)	1.2	(0.8-1.9)	1.1	(0.6-1.9)
21 +	0.2	(0.1-0.3)	0.5	(0.3-0.9)	0.6	(0.3-1.2)

[a] Adjusted for age (continuous), education (continuous), alcohol (nondrinker, ≥ 1 drink per week), hospital (cancer center, other), and time period (1981-84, 1985-90). SCGE = squamous cell carcinoma of the esophagus; AEC = adenocarcinoma of the esophagus or cardia; ADS = adenocarcinoma of the distal stomach.
[b] Slight discrepancies between these numbers and those in Table 1 are due to missing values. No. of controls = 4,540.
[c] OR = odds ratio.
[d] CI = 95% confidence interval.
[e] Relative to never smoked.
[f] Relative to current smoker.

Table 3. Association[a] of smoking with three types of digestive tract cancer (females)[b]

	SCCE (No. = 78)		AEC (No. = 21)		ADS (No. = 31)	
	OR[c]	(CI)[d]	OR[c]	(CI)[d]	OR[c]	(CI)[d]
Never smoked	1.0	—	1.0	—	1.0	—
Current smoker	6.8	(3.7-12.1)	4.8	(1.7-14.0)	3.2	(1.3-7.7)
Ex-smoker	2.2	(1.1-4.3)	1.4	(0.4-4.4)	2.0	(0.8-4.9)
Ever-smoked (cigarettes per day)[e]						
1-20	3.7	(2.0-6.7)	1.9	(0.7-5.4)	1.6	(0.6-3.8)
21 +	4.8	(2.4-9.5)	4.5	(1.4-14.2)	4.8	(1.9-11.9)
Years since quitting[f]						
1-10	0.4	(0.2-0.9)	0.3	(0.1-1.7)	0.7	(0.2-2.2)
11 +	0.3	(0.1-0.5)	0.3	(0.1-1.1)	0.7	(0.2-2.1)

[a] Adjusted for age (continuous), education (continuous), alcohol (nondrinker, ≥ 1 drink per week), hospital (cancer center, other), and time period (1981-84, 1985-90). SCCE = squamous cell carcinoma of the esophagus; AEC = adenocarcinoma of the esophagus or cardia; ADS = adenocarcinoma of the distal stomach.
[b] No missing values among females. No. of controls = 2,228.
[c] OR = odds ratio.
[d] CI = 95% confidence interval.
[e] Relative to never smoked.
[f] Relative to current smoker.

for the highest drinking category and did not reach statistical significance (OR = 3.8, CI = 0.9-16.6).

When individual alcoholic beverages were examined, in males, daily drinkers of hard liquor, but not of beer or wine, had a significantly increased risk of SCCE relative to nondrinkers (OR adjusted for age, education, and smoking = 6.7, CI = 4.1-11.1). In females, daily drinkers of all three beverages were at increased risk for SCCE (for beer, OR = 7.2, CI = 3.5-14.6; for wine, OR = 5.3, CI = 2.9-9.5; for hard liquor, OR = 5.2, CI = 3.0-9.2). Only hard liquor intake was associated with AEC in males (for occasional drinkers, OR = 1.8, CI = 1.2-2.7; for daily drinkers, OR = 2.0, CI = 1.3-3.0); only daily beer intake was associated

Table 4. Association[a] of alcohol intake with three types of digestive tract cancer, by sex[b]

	SCCE		AEC		ADS	
	OR[c]	(CI)[d]	(OR)[c]	(CI)[d]	OR[c]	(CI)[d]
Males						
Nondrinker[e]	1.0	—	1.0	—	1.0	—
Occasional[f]	1.4	(0.6-3.5)	2.0	(1.1-3.5)	1.0	(0.6-1.7)
1-3.9 oz w-e/d[g]	2.3	(1.0-5.4)	2.1	(1.2-3.6)	0.5	(0.3-0.9)
4 + oz w-e/d[g]	10.9	(4.9-24.4)	2.3	(1.3-4.3)	0.7	(0.4-1.3)
Females						
Nondrinker[e]	1.0	—	1.0	—	1.0	—
Occasional[f]	1.4	(0.7-2.9)	0.6	(0.2-1.9)	0.6	(0.3-1.4)
1-3.9 oz w-e/d[g]	4.4	(2.2-8.7)	0.9	(0.2-3.5)	0.6	(0.2-1.8)
4 + oz w-e/d[g]	13.2	(6.1-28.8)	3.8	(0.9-16.6)	0.9	(0.3-3.1)

[a] Adjusted for age (continuous), education (continuous), smoking (never, ever 1-20 cpd, ever 21 + cpd), hospital (cancer center, other), and time period (1981-84, 1985-90). SCCE = squamous cell carcinoma of the esophagus; AEC = adenocarcinoma of the esophagus or cardia; ADS = adenocarcinoma of the distal stomach.

[b] Numbers included in analysis: *males*: SCCE 122; AEC 160; ADS 113; *male controls* 4,162; *females*: SCCE 78; AEC 21; ADS 30; *Female controls* 2,222. Numbers are reduced mainly due to exclusion of pipe/cigar smokers in males.

[c] OR = odds ratio.

[d] CI = 95% confidence interval.

[e] Less than 1 drink per week.

[f] ≥ 1 drink per week but less than 1 drink per day.

[g] w-e/d = whiskey-equivalent per day.

Table 5. Joint effect of smoking and drinking for three digestive tract cancers (males)[a]

Smoking	Drinking	SCCE		AEC		ADS	
		OR[b]	(CI)[c]	(OR)[b]	(CI)[c]	OR[b]	(CI)[c]
Never	Nondrinker/occasional	1.0	—	1.0	—	1.0	—
Never	≥ oz w-e/d[d]	4.3	(1.4-12.5)	1.5	(0.7-3.5)	0.6	(0.2-1.6)
Ever	Nondrinker/occasional	1.5	(0.5-4.2)	2.0	(1.1-3.7)	1.5	(0.9-2.7)
Ever	≥ 1 oz w-e/d[d]	7.6[e]	(3.1-18.6)	2.4[f]	(1.3-4.2)	0.9	(0.5-1.5)

[a] Numbers included in analysis: 124 SCCE, 160 AEC, 113 ADS, and 4,213 controls. SCCE = squamous cell carcinoma of the esophagus; AEC = adenocarcinoma of the esophagus or cardia; ADS = adenocarcinoma of the distal stomach.

[b] OR = odds ratio.

[c] CI = 95% confidence interval.

[d] W-e/d = ounces of whiskey-equivalents per day.

[e] Expected joint effect (multiplicative model): 6.3.

[f] Expected joint effect (additive model): 2.5.

with AEC in females (OR = 4.9, CI = 1.1-22.8).

Table 5 examines the joint effects of smoking (ever/never) and alcohol (one ounce or more of w-e/d, nondrinker/occasional) for the three cancer sites in males. For SCCE, there was evidence of a greater than multiplicative effect; for AEC, the data were consistent with an additive effect; while for ADS, there was no suggestion of any joint effect. It should be noted that, due to small numbers, it was not possible to discriminate between 'nondrinkers' and 'occasional drinkers'. The small number of female cases precluded examination of joint effects.

BMI based on self-reported weight five years prior to diagnosis showed an inverse association with SCCE in males (OR for leanest quartile = 6.3, CI = 2.8-14.0) but not with AEC or ADS (Table 6). Total fat intake was associated with AEC and showed an increasing trend with increasing level of intake (P-value for trend < 0.001). For SCCE, the OR for the third quartile of fat intake was significantly elevated, but there was less of a gradient (P-value for trend < 0.05), and there was little association of fat intake with ADS. The OR for SCCE and AEC, but not for ADS, increased with increasing intake of vitamin A from animal sources (P-value for trend < 0.01 for both sites). Fiber intake was associated inversely with AEC (P-value for trend < 0.01) but not with SCCE or ADS, whereas intake of vitamin A derived from plant sources and vitamin C intake both

Table 6. Adjusted odds ratios[a] (OR) for body mass index and dietary factors with three types of digestive tract cancer[b] (males)

	SCCE (No. = 75)		AEC (No. = 121)		ADS (No. = 69)	
	OR	(CI)[c]	OR	(CI)[c]	OR	(CI)[c]
Body mass index						
≥28	1.0	—	1.0	—	1.0	—
25-27.9	1.3	(0.6-2.6)	0.7	(0.4-1.1)	1.5	(0.8-3.0)
22-24.9	2.2	(1.1-4.4)	0.7	(0.4-1.2)	1.7	(0.8-3.5)
<22	6.3[d]	(2.8-14.0)	1.2	(0.6-2.4)	0.8	(0.2-3.7)
Total fat intake						
1 (lowest quartile)	1.0	—	1.0	—	1.0	—
2	1.2	(0.6-2.4)	1.8	(1.1-3.2)	1.8	(0.9-3.4)
3	2.2	(1.1-4.2)	2.2	(1.2-3.9)	1.2	(0.5-2.5)
4	2.0[g]	(0.9-4.4)	2.9[e]	(1.5-5.6)	2.0	(0.8-4.8)
Vitamin A from animal sources						
1 (lowest quartile)	1.0	—	1.0	—	1.0	—
2	1.2	(0.6-2.7)	1.7	(0.9-3.2)	0.9	(0.4-1.8)
3	1.7	(0.8-3.7)	1.7	(0.9-3.2)	0.6	(0.3-1.4)
4	2.6[f]	(1.2-5.6)	2.4[f]	(1.3-4.6)	0.9	(0.4-2.0)
Vitamin A from plant sources						
1 (highest quartile)	1.0	—	1.0	—	1.0	—
2	1.3	(0.6-2.8)	1.2	(0.7-2.1)	0.7	(0.3-1.5)
3	1.6	(0.7-3.4)	0.9	(0.5-1.7)	0.7	(0.3-1.6)
4	2.1[h]	(0.9-5.0)	1.0	(0.5-2.0)	1.8	(0.8-4.2)
Vitamin C intake						
1 (highest quartile)	1.0	—	1.0	—	1.0	—
2	0.9	(0.4-2.0)	1.1	(0.6-1.9)	0.9	(0.5-1.7)
3	2.0	(0.9-4.3)	0.8	(0.4-1.5)	0.6	(0.3-1.3)
4	1.9[g]	(0.8-4.5)	0.9	(0.5-1.7)	0.6	(0.3-1.5)
Fiber intake						
1 (highest quartile)	1.0	—	1.0	—	1.0	—
2	0.5	(0.2-1.1)	1.6	(0.8-3.0)	1.0	(0.5-2.2)
3	0.8	(0.4-1.8)	2.0	(1.0-4.0)	1.2	(0.5-2.7)
4	1.3	(0.5-3.1)	3.2[f]	(1.5-7.0)	1.1	(0.4-3.1)

[a] Adjusted for smoking (never, ever 1-20 cpd, ever 21+ cpd), alcohol (nondrinker, ≥1 drink per week), age (continuous), education (continuous), hospital (cancer center, other), and remaining dietary factors (continuous).

[b] SCCE = squamous cell carcinoma of the esophagus; AEC = adenocarcinoma of the esophagus or cardia; ADS = adenocarcinoma of the distal stomach. Numbers omit 6 SCCE, 8 AEC, 8 ADS, and 159 controls with missing information.

[c] CI = 95% confidence interval.

[d] *P*-value for trend = 0.0001.

[e] *P*-value for trend < 0.001.

[f] *P*-value for trend < 0.01.

[g] *P*-value for trend < 0.05.

[h] *P*-value for trend < 0.10.

showed an inverse relationship to SCCE (*P*-value for trend <0.1 and <0.05, respectively), but not to the other sites.

Adjustment for dietary factors did not affect materially the associations of alcohol with SCCE or of smoking and alcohol with AEC. The OR for current smoking with SCCE was reduced from 4.5 (CI = 2.5-8.1) to 2.5 (CI = 1.2-5.1).

In females, leanness was also a risk factor for SCCE (adjusted OR for BMI <25 relative to BMI ≥25 = 3.1, CI = 1.7-5.6) but not for AEC or ADS. Due to small numbers of female cases and the fact that dietary information was available only for a subset of the study population, it was not possible to evaluate dietary risk factors in females.

Use of vitamin/mineral supplements was not associated with cancer of any of the three sites in either sex (data not shown), however the numbers did not permit analysis by type of supplement, other than A and C, or duration of use. Use of smokeless tobacco and self-reported occupational and environmental exposures were not related to the risk of any of the three sites.

Discussion

Although AEC has been described by clinicians, interest in the epidemiology of this disease has been kindled by several recent reports indicating that the incidence of this cancer has been increasing and that its distribution by sex and race differs from that of squamous cell carcinoma of the esophagus.[1-7] To date, few case-control studies have examined risk factors for adenocarcinoma of the esophagus/cardia.[12-16]

Several features of our study population are consistent with data from the SEER registry. First, the increasing number of cases per year of AEC in males over the period 1981-90 in our study reflects the rising incidence rates observed in the SEER data.[1] Second, the male-to-female ratio for AEC (3.7) was considerably higher than that for SCCE (1.7) or ADS (1.9), similar to what is seen in the SEER data.[1]

Consistent with previous reports, smoking and drinking were both associated with SCCE.[23,24] Smoking showed a significant, dose-related relationship with AEC in both sexes. Alcohol intake was also associated significantly with AEC but with little evidence of a dose-response relationship. The associations of smoking and alcohol with AEC were not affected by adjustment for dietary factors or other covariates. The association of smoking, but without evidence of a trend with amount smoked, and the lack of association of alcohol with ADS are in accord with the majority of prior studies.

The limited available evidence on the relationship of smoking and alcohol to AEC is inconsistent. In a case-control study conducted in Linxian, China, smoking was associated weakly with AEC in low-risk southern communes but not in high-risk communes.[13] In a report from Japan, smoking was associated with stomach cancer overall in males and particularly strongly with cancer of the cardia, whereas alcohol showed no association.[16] In a study of stomach cancer occurring in young males in Los Angeles (CA),[14] smokers had a significantly increased relative-risk for cancer of the cardia as well as other subsites, with evidence of a dose-response among current smokers, while alcohol was most strongly associated with the cardia. A study from Italy[15] yielded no suggestion of a relationship between cancer of the cardia and smoking or drinking. Of two reports comparing patients with adenocarcinoma of the esophagus and concomitant Barrett's esophagus and patients with benign Barrett's esophagus, one[25] showed that smoking was associated with malignancy, whereas the other indicated no role of smoking or drinking.[12]

Of two studies which used adenocarcinoma of the distal stomach as a control, one[10] reported an elevated OR for AEC associated with smoking and drinking (no confidence intervals are given), whereas the other[26] found no differences in smoking or drinking habits between AEC and adenocarcinoma of the distal stomach. Since smoking has been noted to be a risk factor for stomach cancer in a number of studies,[27-30] clearly this is not a desirable control group. If AEC cases had been compared with ADS cases in our study, the association with smoking would not have been detected.

Of the dietary factors, total fat intake and vitamin A from animal sources showed positive, dose-related associations with SCCE and AEC. In addition, fiber intake was associated inversely with AEC. No consistent trends were seen for dietary factors in relation to ADS.

Numerous studies have reported associations between dietary factors and cancer of the esophagus, most commonly an inverse association with intake of fruits and vegetables.[23,31-34,36] In addition, three studies have noted a positive relationship between retinol intake and esophageal cancer.[34-36] Graham *et al*[34] found that the initial association between fat intake and esophageal cancer was no longer significant when retinol was included in the model. In our data, total fat intake showed a significant, although weaker, relationship to SCCE than did intake of animal-derived vitamin A. Each nutrient remained significantly associated with AEC, after adjustment for the other. Two previous studies of cancer of the cardia indicate that beef[14] or meat, protein, and cholesterol[15] are risk factors and that fresh fruits and vegetables are potential protective factors.[14,15]

The finding that BMI is associated inversely with risk of SCCE in both males and females agrees with the results of a previous report,[23] although another study[34] found no association. Use of self-reported weight five years prior to diagnosis to compute BMI makes it unlikely that this association is due to weight loss secondary to dysphagia. A similar inverse association with cancer of the lung after adjustment for smoking has been noted by us and by others.[17]

Several limitations of our study should be pointed out. Since adenocarcinoma of the esophagus and stomach were control diagnoses in the original study, no attempt was made to enroll all such patients. This contrasts with squamous cell carcinoma of the esophagus, which was a case diagnosis in the original study. The most obvious factors contributing to possible selection bias in the controls are the matching factors: age, sex, and race. However, comparison of our enrolled AEC and ADS cases to those reported in unselected series indicates that both groups have similar age, sex, and race distributions.[4,5,9,10,25,26] We did not attempt to distinguish among adenocarcinomas of the

distal third of the esophagus, gastroesophageal junction, and cardia, because of the likelihood of misclassification between these subsites. The majority of cases were of the gastroesophageal junction. Furthermore, the majority of cases classified as ADS were described only as 'stomach cancer'.

Our dietary questions were limited to 30 items which were selected to provide an estimate of intake of dietary fat and vitamin A from animal and plant sources. Thus other components of diet, such as sodium, starches, and total calories, were not addressed. In addition, dietary data were collected only on a subset of the total study population. For these reasons, the dietary findings in this study need to be interpreted cautiously.

We did not have information on prior history of hiatal hernia, duodenal ulcer, esophageal reflux, or on family history of esophageal or stomach cancer, factors which have been found to differ between gastrointestinal tract subsites or between cases and controls.[9,10,14,15,25] Another potential risk factor is use of antacids and other medications for ulcers.

Our results suggest that smoking, alcohol consumption and, possibly, dietary factors play a role in the etiology of AEC, as well as confirming associations of smoking, alcohol, and dietary factors with SCCE. Smoking showed an inconsistent, borderline association with ADS, whereas alcohol showed no association. Compared with their role in SCCE, smoking and drinking appear to be, at most, relatively weak risk factors for AEC. This is consistent with the epidemiology of this disease in contrast to that of known tobacco and alcohol related cancers, including SCCE. More work is needed to clarify the role of environmental factors (including medication for ulcers) and antecedent conditions (including gastroesophageal reflux and Barrett's esophagus) in the development of AEC.

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References

1. Blot WJ, Devesa SS, Kneller RW, Fraumeni JF. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA* 1991; **265:** 1287-9.
2. Zheng T, Mayne ST, Holford TR, *et al.* Time trend and age-period-cohort effects on incidence of esophageal cancer in Connecticut, 1935-89. *Cancer Causes Control* 1992; **3:** 481-92.
3. Yang PC, Davis S. Incidence of cancer of the esophagus in the US by histologic type. *Cancer* 1988; **61:** 612-7.
4. Hesketh PJ, Clapp RW, Doos WG, Spechler SJ. The increasing frequency adenocarcinoma of the esophagus. *Cancer* 1989; **64:** 526-30.
5. Harvey JC, Kagan R, Ahn C, Frankl H, Davidson W. Adenocarcinoma of the esophagus: a survival study. *J Surg Oncol* 1990; **45:** 29-32.
6. Powell J, McConkey CC. Increasing incidence of adenocarcinoma of the gastric cardia and adjacent sites. *Br J Cancer* 1990; **62:** 440-3.
7. Moller H, Jensen OM. Trends in incidence of esophagus, cardia, and stomach cancer in Denmark, 1943-1982. In: *The Sixth Annual ECP Symposium, International Symposium on Gastric Carcinogenesis*, 6th ed. London, 1988.
8. MacDonald WC. Clinical and pathologic features of adenocarcinoma of the gastric cardia. *Cancer* 1972; **29:** 724-32.
9. MacDonald WC, MacDonald JB. Adenocarcinoma of the esophagus and/or gastric cardia. *Cancer* 1987; **60:** 1094-8.
10. Wang HH, Antonioli DA, Goldman H. Comparative features of esophageal and gastric adenocarcinomas: Recent changes in type and frequency. *Hum Path* 1986; **17:** 482-7.
11. Yang PC, Davis S. Epidemiological characteristics of adenocarcinoma of the gastric cardia and distal stomach in the United States, 1973-1982. *Int J Epidemiol* 1988; **17:** 293-7.
12. Levi F, Ollyo JB, La Vecchia C, Boyle P, Monnier P, Savary M. The consumption of tobacco, alcohol and the risk of adenocarcinoma in Barrett's oesophagus. *Int J Cancer* 1990; **45:** 852-4.
13. Li JY, Ershow AG, Chen ZJ, *et al.* A case-control study

of cancer of the esophagus and gastric cardia in Linxian. *Int J Cancer* 1989; **43:** 755-61.
14. Wu-Williams AH, Yu MC, Mack TM. Life-style, workplace, and stomach cancer by subsite in young men of Los Angeles County. *Cancer Res* 1990; **50:** 2569-76.
15. Palli D, Bianchi S, Decarli A, *et al.* A case-control study of cancers of the gastric cardia in Italy. *Br J Cancer* 1992; **65:** 263-6.
16. Unakami M, Hara M, Fukuchi S, *et al.* Cancer of the gastric cardia and the habit of smoking. *Acta Pathol Japonica* 1989; **39:** 420-4.
17. Kabat GC, Wynder EL. Body mass index and lung cancer risk. *Am J Epidemiol* 1992; **135:** 769-74.
18. World Health Organization. *International Classification of Diseases, Ninth Revision.* Geneva: WHO, 1977.
19. Hebert JR, Kabat GC. Differences in dietary intake associated with smoking status. *Eur J Clin Nutr* 1990; **44:** 185-93.
20. United States Department of Agriculture. *Composition of Foods, Handbook No. 8.* Washington, DC: US Government Printing Office, 1976.
21. Anderson JW, Chen WL, Sieling B. *Plant Fiber in Foods.* Lexington, KY: HCF Diabetes Research Foundation, Inc., 1980.
22. SAS Institute Inc. *SAS/STAT User's Guide, Version 6, 4th ed.*, Cary, NC: SAS Institute Inc., 1990.
23. Pottern LM, Morris LE, Blot WJ, Ziegler RG, Fraumeni JF. Esophageal cancer among Black men in Washington DC. I. Alcohol, tobacco, and other risk factors. *JNCI* 1981; **67:** 777-83.
24. Day NE, Munoz N. Esophagus. In: Schottenfeld D, Fraumeni JF, eds. *Cancer Epidemiology and Prevention.* Philadelphia, PA: WB Saunders, 1982: 596-623.
25. Skinner DB, Walther BC, Riddell RH, Schmidt H, Iascone C, DeMeester TR. Barrett's esophagus: Comparison of benign and malignant cases. *Ann Surg* 1983; **198:** 554-65.
26. Gray JR, Coldman J, MacDonald WC. Cigarette and alcohol use in patients with adenocarcinoma of the gastric cardia or lower esophagus. *Cancer* 1992; **69:** 2227-31.
27. Nomura A, Grove JS, Stemmermann GN, Severson RK. A prospective study of stomach cancer and its relation to diet, cigarettes, and alcohol consumption. *Cancer Res* 1990; **50:** 627-31.
28. Saha SK. Smoking habits and carcinoma of the stomach: a case-control study. *Jpn J Cancer Res* 1991; **82:** 497-502.
29. Boeing H. Epidemiological research in stomach cancer: Progress over the last ten years. *J Cancer Res Clin Oncol* 1991; **117:** 133-43.
30. Hoshiyama Y, Sasaba T. A case-control study of stomach cancer and its relation to diet, cigarettes, and alcohol consumption in Saitama Prefecture, Japan. *Cancer Causes Control* 1992; **3:** 441-8.
31. Wynder El, Bross IJ. A study of etiological factors in cancers of the esophagus. *Cancer* 1961; **14:** 389-413.
32. Cook-Mozaffari PJ, Azordegan F, Day NE, *et al.* Oesophageal cancer studies in the Caspian littoral of Iran: results of a case-control study. *Br J Cancer* 1979; **39:** 293-309.
33. Hirayama T. An epidemiological study of cancer of the oesophagus in Japan, with special reference to the combined effect of selected environmental factors. In: *Monograph No. 1, Int. Seminar on Epidemiology of Oesophageal Cancer.* Bangalore, India, 4 November 1971: 45-60.
34. Graham S, Marshall J, Haughey B, *et al.* Nutritional epidemiology of cancer of the esophagus. *Am J Epidemiol* 1990; **131:** 454-67.
35. Tuyns AJ, Riboli E, Doornbos G, Pequignot G. Diet and esophageal cancer in Calvados (France). *Nutr Cancer* 1987; **9:** 81-92.
36. DeCarli A, Liati P, Negri E, Franceschi S, La Vecchia C. Vitamin A and other dietary factors in the etiology of esophageal cancer. *Nutr Cancer* 1987; **10:** 29-37.