Obesity, Alcohol, and Tobacco as Risk Factors for Cancers of the Esophagus and Gastric Cardia: Adenocarcinoma *versus* Squamous Cell Carcinoma[1]

Thomas L. Vaughan,[2] Scott Davis, Alan Kristal, and David B. Thomas

Program in Epidemiology, Fred Hutchinson Cancer Research Center, Seattle, Washington 98104, and Department of Epidemiology, University of Washington, Seattle, Washington 98195

Abstract

Adenocarcinomas of the esophagus and gastric cardia were once rare. However, for unknown reasons, their incidence has been increasing rapidly over the past 15 years in the United States and parts of Western Europe. In contrast, the incidence of esophageal squamous cell carcinomas has remained relatively constant. To investigate possible reasons for these diverging incidence rates we analyzed data from two population-based case-control studies of cancers of the esophagus and gastric cardia that were conducted among male and female residents of western Washington between 1983 and 1990. Information on body mass index, cigarette use, alcohol intake, and other possible risk factors was collected via personal interviews with 404 cases or their next of kin (including 298 adenocarcinomas and 106 squamous cell carcinomas) and 724 controls identified by random digit dialing. Use of alcohol and cigarettes were significant risk factors for both histological types. The increase in risk for current smokers of 80 or more pack-years compared to nonsmokers was substantially higher for squamous cell cancer [odds ratio (OR) = 16.9; 95% confidence interval (CI) = 4.1–69.1] than for adenocarcinoma (OR = 3.4; 95% CI = 1.4–8.0), as was the increase for persons who typically drank 21 or more drinks/week compared to those who drank <7/week (OR = 9.5; 95% CI = 4.1–22.3 *versus* OR = 1.8; 95% CI = 1.1–3.1) For squamous cell carcinoma, body mass index was inversely associated with risk, whereas for adenocarcinoma, the highest risk was observed among persons who were in the highest decile of body mass index (OR = 1.9; 95% CI = 1.1–3.2). The risks associated with alcohol and tobacco use appeared to be similarly elevated for adenocarcinomas arising in the gastric cardia and esophagus; however, there was some evidence that obesity was more strongly associated with esophageal adenocarcinoma (OR = 2.5; 95% CI = 1.2–5.0 for persons in the highest decile). Together, obesity, cigarette smoking, and alcohol use accounted for approximately 50% of the adenocarcinoma cases diagnosed in the Seattle area over the period 1983–1990. In comparison, cigarette smoking and alcohol intake alone accounted for 87% of the squamous cell cases. Additional studies should focus on the role of obesity to determine whether adeno-carcinoma risk varies by the pattern of fat deposition and by patterns of weight over a lifetime. Intervention trials aimed at reducing weight among persons at high risk of esophageal adenocarcinoma, such as persons with Barrett's metaplasia, are also indicated to establish the causal role of obesity and to determine the usefulness of dietary intervention in reducing rates of neoplastic progression to cancer.

Introduction

Adenocarcinomas of the esophagus and gastric cardia were once rare, but during the past 15 years there has been a rapid increase in their incidence in the United States and western Europe (1–3). Recent data from nine population-based cancer registries in the United States indicate that the rate of esophageal adenocarcinomas among White males tripled between 1976 and 1990 and is now equal to the rate of squamous cell carcinomas (4). Although the incidence among Black males and among females of both racial groups is substantially lower than it is among White males, it now appears that rates in these groups are increasing just as rapidly (4). In contrast, the incidence of esophageal squamous cell carcinomas has remained relatively constant.

The reasons for this rise in incidence are unknown. It has been hypothesized that obesity may be an important factor behind the changing incidence (5). The physiological rationale is that increased abdominal girth promotes gastroesophageal reflux (6). Reflux, in turn, is a known risk factor for Barrett's metaplasia, a precursor lesion in the development of esophageal adenocarcinoma (7, 8). Two recent case-control studies examined body mass index as a risk factor for esophageal adenocarcinoma and found increased risk in the highest quartile (5, 9). These findings are particularly notable since there are also a number of studies suggesting that obesity is increasing in prevalence in the United States and other Western countries (10–15). In contrast, an inverse relationship between body mass index and risk of esophageal squamous cell carcinoma has been noted (9).

Other factors that also appear to play quite different roles in the etiology of the two histological types of esophageal cancer are tobacco products and alcoholic beverages.

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[2] To whom requests for reprints should be addressed, at Program in Epidemiology (MP474) Fred Hutchinson Cancer Research Center, 1124 Columbia Street, Seattle, Washington 98104.

While it is well known that the vast majority of squamous cell carcinomas of the esophagus are caused by these agents, there is evidence that they are less important in the development of esophageal adenocarcinomas (9, 16–19).

In this report we present combined results from two population-based case-control studies of cancer of the esophagus and gastric cardia that were conducted among residents of Western Washington between 1983 and 1990. The goal is to investigate the associations of body mass index, cigarette use, and alcohol intake with the two main histological types of cancer arising in these tissues. We also examined differences in risk factor profiles for adenocarcinomas arising in the gastric cardia *versus* the esophagus.

Materials and Methods

Subject Identification. Cases were identified by the Cancer Surveillance System of the Fred Hutchinson Cancer Research Center. This population-based registry is operated as part of the Surveillance, Epidemiology and End Results program of the National Cancer Institute. It attempts to identify all cancers occurring in 13 counties of Western Washington state, an area with a population of over 3 million.

Cases analyzed in this report were identified and interviewed as part of two studies that used identical data collection methods but different eligibility criteria. The first study included persons diagnosed between September 1983 and February 1987 with any histological type of esophageal ICD-O[3] site codes 150.0–150.9) or gastric cardia (ICD-O site code 151.0) cancer. The second study included persons diagnosed between March 1987 and November 1990 with adenocarcinoma (ICD-O histology codes 8140–8560) of the esophagus or gastric cardia. All cases were residents in one of the three largest urban counties around Seattle (King, Pierce, and Snohomish counties) and were between the ages of 20 and 74 years at the time of diagnosis.

For each study, a set of controls was identified by random digit dialing using a modification of the method of Waksberg (20). The first study also included other sites of the upper aerodigestive tract; one set of controls was shared by all of the case series. They were selected by frequency matching to the age (in 5-year intervals) and gender distribution of the largest case group, which was oral cavity cancer. Controls for the second study (which included only adenocarcinomas of the esophagus and gastric cardia) were also selected by frequency matching on age and gender.

The random digit dialing method is summarized as follows. From a list of all working exchanges (which is updated yearly using information provided from the local telephone companies) an exchange is randomly selected, and four random digits are appended, forming a telephone number. This number is then called up to nine times, at different times of the day and week, to determine whether the number is a residence. For numbers selected in this manner that identify a residence, the first five digits are used to generate additional phone numbers by appending two random digits. Secondary numbers generated in this way are then resolved one by one until two additional residences are reached.

For each residence identified, a household census was taken to determine whether an eligible subject resided there. In the rare event that multiple persons were eligible, one was selected randomly. Since controls were selected by random digit dialing, and therefore had a phone, only cases with telephones at the time of diagnosis were eligible.

Response Rates. Response rates are given in Table 1. Overall, 441 (82.9%) of 542 eligible cases were successfully interviewed. Exclusion of 37 cases after interview due to ineligible residence or histology other than squamous cell or adenocarcinoma yielded 404 cases for analysis. Of these, 106 cases were squamous cell cancers of the esophagus, 133 were adenocarcinomas of the esophagus, and 165 were adenocarcinomas of the gastric cardia (including gastroesophageal junction). In those instances where the case had died before an interview could be arranged, the closest next of kin was asked to participate in the study but not until at least 6 months had passed since the date of death. This occurred for 33% of the interviewed cases.

For controls, 5351 (95.4%) of 5608 residential phone numbers were successfully screened. This percentage does not include telephone numbers for which no answer was obtained after repeated attempts over several months (approximately 4% of phone numbers); studies indicate that few of these phone numbers are actually residences (21). We identified 908 eligible controls and successfully interviewed 729 (80.3%). Exclusion of five persons who were determined to be ineligible after the interview yielded 724 controls for analysis.

Table 1 Response rates for cases and controls

	Study #1	Study #2	Total
Cases			
Diagnosis dates	9/83–2/87	3/87–11/90	9/83–11/90
Total eligible	297	235	532
MD refusal	26	4	30
Non-interview	37	24	61
Completed interview	234	207	441
Overall response rate	78.8%	88.1%	82.9%
Exclusions	24	13	37
Cases to analyze	210	194	404
Controls			
Residential no.	4012	1596	5608
Refused screen	214	43	257
Completed screen	3798	1553	5351
Screening response rate	94.7%	97.3%	95.4%
Eligible	688	220	908
Non-interview	136	43	179
Completed interview	552	177	729
Interview response rate	80.2%	80.5%	80.3%
Overall response rate	76.0%	78.3%	76.6%
Exclusions	5	0	5
Controls to analyze	547	177	724

[3] The abbreviations used are: ICD-O, International Classification of Diseases for Oncology; OR, odds ratio; CI, confidence interval.

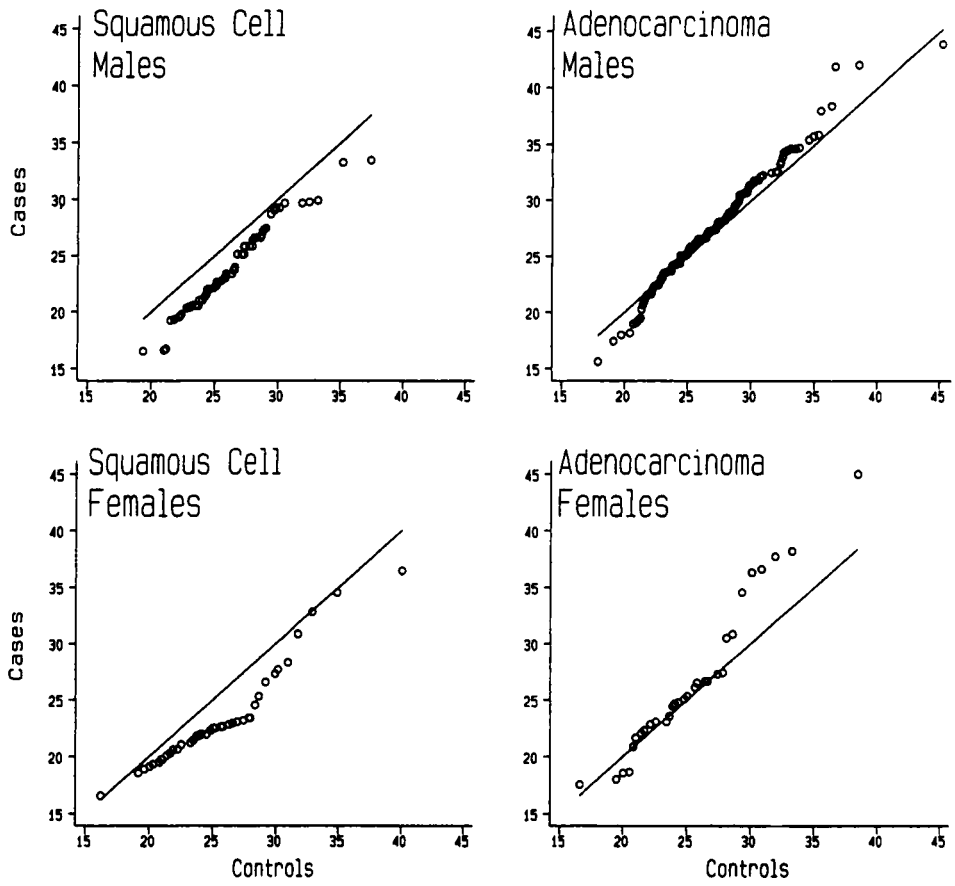

Fig. 1. Quantile-quantile plot of body mass index (kg/m^2) for cases and controls by gender and histological type.

Data Collection. Trained interviewers used a structured questionnaire to conduct personal interviews of approximately 1 h duration in the homes of the respondents. All questions referred to the period of time before the reference date, which was defined as 1 year before diagnosis for the cases and 1 year before ascertainment for the controls. We obtained information on demographics, height and weight at reference date, lifetime history of use of tobacco and alcohol products, past medical problems, occupational history, and diet. Information on age, gender, and race was abstracted from the medical records of the 91 eligible non-interviewed cases to enable us to compare their distributions to those of the 404 interviewed cases.

Statistical Analyses. The distribution of body mass index (in units of kg/m^2) for cases and controls is displayed using quantile-quantile plots (Fig. 1) (22). These are scatter plots of body mass index of each case *versus* each control after sorting the observations into ascending order of body mass index. The data point closest to the origin depicts the body mass of the thinnest control (abscissa) and the thinnest case (ordinate). Interpolated values for controls were used since there were more controls than cases of either histological type. The solid line represents the plot that would occur if cases and controls had an identical body mass distribution.

Logistic regression was used to calculate ORs and 95% CIs associated with body mass index, tobacco use, and alcohol consumption. The matching variables, age and gender, were taken into account in all analyses by using them to define matched sets for conditional analyses. Race and education were controlled in all analyses. Controls selected as part of the second study were excluded from analyses of squamous cell carcinomas; for analyses of adenocarcinomas, a dichotomous variable representing study period was entered into all models. Conditional logistic regression was also used to make direct comparisons between adenocarcinomas and squamous cell carcinomas and between adenocarcinomas of the gastric cardia and esophagus. Population attributable risks were calculated from the results of the logistic regression analyses as described by Bruzzi *et al.* (23).

Results

Demographics, Tobacco, and Alcohol. Compared to the interviewed cases, those that did not complete the interview were slightly older (mean age = 64.0 *versus* 61.7 years), more likely to be female (23.1 *versus* 18.1%), and more likely to be of Black, Asian, and other non-White races (11.0 *versus* 6.9%).

Table 2 shows selected demographic characteristics of the interviewed cases and controls. The adenocarcinoma cases were slightly younger than the squamous cell cases and much more likely to be male. Non-Whites were at a substantially higher risk of squamous cell carcinoma of the esophagus (OR = 4.6; 95% CI = 1.8–11.9) but at slightly lower risk of adenocarcinomas of the esophagus and gastric cardia (OR = 0.7; 95% CI = 0.3–1.9) when compared to Whites. Among the adenocarcinoma cases, 10 of the 12

Table 2 Selected demographic characteristics of cases and controls

	Controls		Squamous cell carcinoma		Adenocarcinoma	
	No. (n = 724)	%	No. (n = 106)	%	No. (n = 298)	%
Age						
Mean (± SD)	59.8 (10.1)		63.6 (7.5)		61.1 (9.3)	
20–39	36	5.0	0	0.0	8	2.7
40–49	72	9.9	6	5.7	31	10.4
50–59	183	25.3	19	17.9	64	21.5
60–69	315	43.5	54	50.9	141	47.3
70–74	118	16.3	27	25.5	54	18.1
Gender						
Male	506	69.9	64	60.4	267	89.6
Female	218	30.1	42	39.6	31	10.4
Race						
White	696	96.1	90	84.9	285	96.0
Black, other	28	3.9	16	15.1	12	4.0
Unknown	0		0		1	
Education						
Some college	382	52.8	25	24.5	127	43.5
No college	342	47.2	77	75.5	165	56.5
Unknown	0		4		6	

non-Whites (83%) had cancers arising in the gastric cardia compared to 54% of the Whites; however this could have occurred by chance (P = 0.07). Persons who had not attended college were at significantly higher risk for both squamous cell carcinomas (OR = 2.1; 95% CI = 1.1–4.0) and adenocarcinomas (OR = 1.6; 95% CI = 1.2–2.3). Direct Comparison of adenocarcinomas to squamous cell carcinomas revealed that the associations with race were significantly different (P < 0.001) for the two histological types, whereas the associations with education were consistent with a common OR (P = 0.46).

Information on the history of alcohol consumption and cigarette use is given in Table 3. Use of alcohol (as measured by usual number of drinks per week) and cigarettes (as measured by a composite variable including current smoking habits, usual number of cigarettes per day, and smoking duration) were significant risk factors for both histological types, although the increases in risk were substantially higher for squamous cell cancer. Direct comparison of the two histological types revealed that these differences in risk were significant for both alcohol consumption (P < 0.001) and cigarette use (P < 0.05). No association for either type of cancer was observed with frequency of use of pipes or cigars or inhalation practices (data not shown).

The associations with cigarettes and alcohol remained statistically significant and of similar magnitude when surrogate interviews were excluded from the analyses. The largest change was seen with the highest two levels of smoking for adenocarcinomas; the OR for current smokers of 80 or more pack-years decreased from 3.4 to 2.1, while the OR for current smokers of 40–79 pack-years increased from 2.4 to 2.6.

When the site of origin for the adenocarcinomas was considered, similar moderate associations were observed between cigarette and alcohol use and tumors arising in the esophagus and gastric cardia. The estimates for the highest level of cigarette use for esophagus and gastric cardia were OR = 3.0 (95% CI = 0.9–10.2) and OR = 4.0 (95% CI = 1.5–10.6), respectively. For the highest level of alcohol use, the estimates were OR = 1.7 (95% CI = 0.8–3.4) and OR = 1.6 (95% CI = 0.9–3.1), respectively.

Virtually all squamous cell cases (97.1%) had regularly consumed alcohol at one time, compared to 88.1% of adenocarcinoma cases and 87.9% of controls. However, among ever-drinkers a larger proportion of adenocarcinoma cases (22.4%) had quit drinking alcohol at the reference date than had squamous cell cases (18.0%) and controls (13.1%). In analyses where the reference group consisted of current alcohol consumers, the ORs for adenocarcinoma among those who had quit drinking within the last 15 years and 15 or more years before the reference date were 1.3 (95% CI = 0.7–2.3) and 1.9 (95% CI = 0.9–3.9), respectively. In contrast, there was little evidence of such a trend for squamous cell cancers; the ORs were 0.8 (95% CI = 0.3–2.0) and 1.0 (95% CI = 0.2–4.4), respectively.

When the type of alcoholic beverage was considered in analyses controlling for amount of alcohol consumption, an elevated risk for adenocarcinoma was observed among those who usually consumed straight liquor (Table 3). For squamous cell carcinomas the variations in risk could easily be attributed to chance. However, the proportion of subjects for whom the usual type of beverage was unknown was relatively high in both case groups.

There was little evidence of higher risk among exclusive nonfilter cigarette users when compared to exclusive filter cigarette users for either histological group (Table 3). However when compared to a reference group consisting of the exclusive filter users plus the much more numerous "mixed" users (those who began smoking nonfilter cigarettes but switched to filter cigarettes) the associations were strengthened. For adenocarcinomas and squamous cell carcinomas the ORs were 1.7 (95% CI = 1.1–2.7) and 1.6 (95% CI = 0.8–3.3), respectively.

Body Mass Index. Males and females with squamous cell carcinoma had consistently lower body mass indices at the reference date than controls (Fig. 1). The body mass index distribution of the adenocarcinoma cases was much broader, with overrepresentation at both ends of the range and a striking deviation among the heaviest females. Overall, 59.3% of the adenocarcinoma cases had a body mass index over the median value of the controls (26.2 kg/m^2 for males and 25.4 kg/m^2 for females), with 17.3% over the value defining the highest decile of the controls.

After adjustment for alcohol consumption, cigarette use, and demographic factors, there was a strong and monotonic decrease in risk of squamous cell carcinoma associated with increasing body mass index (Table 4). The pattern of risk did not vary by site of origin in the esophagus; that is, persons with squamous cell tumors diagnosed in the lower third of the esophagus (where the vast majority of esophageal adenocarcinomas arise) also tended to have lower body mass indices. When cases with distant or unknown stage of disease at diagnosis were excluded from analyses, the point estimates were closer to the null value [OR = 2.2 (95% CI = 0.8–5.9) for those in the lowest decile and OR = 0.3 (95% CI = 0.1–1.7) for those in the highest decile]. When persons who typically drank 14 or more drinks/week were excluded from analyses, the associations with body mass index changed very little.

Table 3 Odds ratios associated with alcohol intake and cigarette use by histology

	Controls	Squamous cell carcinoma			Adenocarcinoma		
	No. (n = 724)	No. (n = 106)	Odds ratio	(95% CI)	No. (n = 298)	Odds ratio	(95% CI)
Alcohol intake (drinks per week)[a]							
0–6	533	27	1.0		147	1.0	
7–13	92	20	6.0	(2.7–13.5)	39	1.1	(0.7–1.8)
14–20	34	11	6.3	(2.2–17.9)	18	1.2	(0.6–2.3)
21+	54	30	9.5	(4.0–22.3)	44	1.8	(1.1–3.1)
Unknown	11	18			50		
Cigarette use (pack-years)[b]							
Never	240	10	1.0		56	1.0	
Former	308	20	1.9	(0.7–5.3)	123	1.5	(1.0–2.3)
Current: 1–39	69	14	5.2	(1.7–16.2)	21	1.4	(0.7–2.7)
Current: 40–79	83	36	7.9	(2.8–22.1)	54	2.4	(1.4–4.1)
Current: 80+	17	16	16.9	(4.1–69.1)	21	3.4	(1.4–8.0)
Unknown	7	10			23		
Usual type of alcohol[c]							
Beer	257	27	1.0		82	1.0	
Wine	84	8	1.9	(0.6–5.8)	14	1.0	(0.5–2.0)
Mixed liquor	222	27	0.7	(0.3–1.6)	64	1.2	(0.8–1.8)
Straight liquor	46	13	1.7	(0.6–4.7)	32	2.6	(1.4–4.6)
Unknown	28	28			71		
Type of cigarette[d]							
Filter	61	11	1.0		23	1.0	
Mixed	297	47	0.6	(0.2–1.9)	115	0.8	(0.4–1.6)
Nonfilter	112	28			78		
Vs. filter only			1.1	(0.3–3.5)		1.4	(0.7–3.0)
Vs. filter and mixed			1.6	(0.8–3.3)		1.7	(1.1–2.7)
Unknown	14	10			26		

[a] Odds ratios adjusted for cigarette use, body mass index, age, gender, race, and education. Trend test for both histological types, $P < 0.001$.
[b] Odds ratios adjusted for alcohol intake, body mass index, age, gender, race, and education. Trend test for squamous cell carcinoma, $P < 0.001$; for adenocarcinoma, $P = 0.03$.
[c] Among ever drinkers, odds ratios adjusted for cigarette use, alcohol intake, body mass index, age, gender, race, and education.
[d] Among ever-smokers, odds ratios adjusted for cigarette use, alcohol intake, body mass index, age, gender, race, and education.

Table 4 Odds ratios associated with body mass index by histology and site

	Squamous cell			Adenocarcinoma								
	Esophagus			All			Esophagus			Gastric cardia		
	No. (n = 106)	Odds ratio[a]	(95% CI)	No. (n = 298)	Odds ratio[a]	(95% CI)	No. (n = 133)	Odds ratio[a]	(95% CI)	No. (n = 165)	Odds ratio[a]	(95% CI)
Body mass index[b]												
1–10%	34	3.2	(1.4–7.1)	25	1.2	(0.6–2.1)	12	1.6	(0.7–3.6)	13	0.8	(0.4–1.8)
10–49%	41	1.0		95	1.0		43	1.0		52	1.0	
50–89%	24	0.7	(0.3–1.4)	124	1.3	(0.9–1.9)	50	1.2	(0.7–2.1)	74	1.3	(0.8–2.1)
90–100%	6	0.2	(0.1–1.0)	51	1.9	(1.1–3.2)	26	2.5	(1.2–5.0)	25	1.6	(0.8–3.0)
Unknown	1			3			2			1		

[a] Odds ratios adjusted for age, gender, education, race, cigarette use, and alcohol consumption.
[b] Calculated as kg/m^2. Percentiles are based on distribution of controls for each gender (separately).

In contrast, the opposite association was observed for adenocarcinomas; persons in the 90th percentile and above had a significant 90% increase in risk compared to those in the 10th–49th percentile. Direct comparison of the two histological types of cancer revealed the differences in risk associated with body mass index to be statistically significant ($P < 0.001$). There was some evidence that obesity was a stronger risk factor for adenocarcinomas arising in the esophagus (OR = 2.5) than the gastric cardia (OR = 1.6), although this could be attributed to chance ($P = 0.24$). When adenocarcinoma cases with a distant or unknown stage of disease at diagnosis were excluded, the OR for those in the lowest decile was reduced to 0.7 (95% CI = 0.3–1.6), whereas the OR for those in the highest decile remained unchanged (OR = 1.9; 95% CI = 1.1–3.5).

Population-attributable Risk. Population-attributable risk estimates were calculated using the adjusted odds ratios from Tables 3 and 4. For adenocarcinomas the separate estimates were 34% for cigarette smoking, 10% for alcohol consumption of 7 or more drinks/week, and 18% for body

mass index above the 50th percentile. All three factors together accounted for 50% of the adenocarcinoma cases observed in the population under study. For squamous cell carcinomas the population attributable risk estimates for cigarettes and alcohol were 73 and 62%, respectively; together they accounted for 87% of the cases.

Discussion

The incidence of adenocarcinoma of the esophagus and gastric cardia has been rising steadily since the mid-1970s for reasons that are not yet clear. The present study suggests that cigarette smoking is one important risk factor for the disease. The dose-response relationship with amount and duration of smoking, and the slight reduction in risk associated with smoking cessation provide good evidence for a causal relationship.

The estimate of the relative risk associated with current cigarette smoking from this study is in close agreement with others that have focused on esophageal adenocarcinomas (9, 17). The results of the present study and those of Kabat *et al.* (9), but not of Brown *et al.* (17), indicate a slight reduction in risk with cigarette cessation. We found some evidence for increased risk of adenocarcinoma among lifetime nonfilter cigarette users. These results are consistent with, but weaker than the 2-fold increase in adenocarcinoma risk for exclusive nonfilter cigarette users compared to exclusive filter cigarette users reported by Brown *et al.* (17). The moderate increase in risk associated with cigarette smoking that we found for cancers of the gastric cardia is consistent with most (17, 24–26), but not all (16, 27), studies of this subsite. After controlling for cigarette use, we found little evidence that cigar or pipe smoking was related to risk of either histological type of cancer, although the statistical power to detect such associations was low.

Given the recent downward trend in prevalence of cigarette smoking among males in the United States, and the leveling off or reduction in incidence that has been observed for cancers that are more strongly associated with smoking (*e.g.*, lung and larynx), it appears that cigarette smoking can not account for the recent rise in incidence adenocarcinomas of the esophagus and gastric cardia (28, 29).

We also found that alcohol intake was significantly associated with increased risk of adenocarcinoma. As with cigarette smoking, the association with adenocarcinoma was much weaker than for squamous cell cancer.

The association between adenocarcinoma risk and alcohol consumption in this study was intermediate in strength between reports by Brown *et al.* (17) and Kabat *et al.* (9). Regarding type of alcoholic beverage, we found a significant association between usual intake of undiluted hard liquor and adenocarcinoma and a weaker (and not significant) association with squamous cell carcinoma. Similar results regarding hard liquor consumption have been reported by several others (9, 17, 25, 30). Our findings relating alcohol intake to increased risk of adenocarcinomas arising in the gastric cardia or gastroesophageal junction are also consistent with most studies that have focused on these sites (9, 25–27).

As with cigarette smoking, the moderate association with alcohol and the recent leveling off or decrease in incidence of cancers more strongly related to alcohol consumption (*e.g.*, oral cavity and pharynx) indicate that alcohol consumption cannot explain the recent rise in esophageal and gastric cardia adenocarcinoma incidence (29).

Persons who consume a high number of drinks per day (including alcoholics) are also more likely to abstain from alcohol use for some periods in their lives. This may explain the higher proportion of squamous cell cases relative to controls who had quit drinking at the reference date (18 *versus* 13%). An unexpected finding among the adenocarcinoma cases, given the only modest association with alcohol intake, was that 22% had ceased drinking alcohol. After controlling for the number of drinks typically consumed, the ORs for adenocarcinoma increased with the number of years since cessation. A possible explanation is that alcohol may increase adenocarcinoma risk by promoting gastroesophageal reflux, and that persons prone to reflux may reduce or eliminate alcohol intake in order to relive symptoms (31). Unfortunately no information was available on the history of reflux symptoms, hiatal hernia, or other related conditions that would enable us to evaluate this possibility.

We found strikingly different distributions of body mass among the three groups of subjects. The risk of adenocarcinoma of the esophagus or gastric cardia was significantly increased among those above the 50th percentile in body mass index (based on the control distribution). If this is a causal relationship, we estimate the obesity alone may account for 18% of the cases observed in the Seattle area over the study period.

A number of considerations support a causal role for obesity: (*a*) a sound biological rationale exists. Obesity is known to cause or exacerbate gastroesophageal reflux, which is a known risk factor for esophageal adenocarcinoma (6–8). This may be especially so among those with abdominal patterns of fat deposition, which is more commonly seen among men (6). However, we found similar associations for men and women. This study did not collect data on body fat distribution; (*b*) there was a trend of increasing risk with increasing level of obesity, whereas there was little variation in risk among those below the 50th percentile; (*c*) the association was stronger for adenocarcinoma of the esophagus than of the gastric cardia, where reflux would appear to be less of an issue; and (*d*) positive associations with obesity have been noted by others. A similar, although weaker, pattern of risk was reported by Kabat *et al.* (9) for a combined group of esophageal and gastric cardia cancers, and a 3-fold increase in risk for esophageal adenocarcinoma among persons with body mass index in the highest quartile was observed by Brown *et al.* (5).

Given the above findings, it is worrisome that the prevalence of obesity appears to be rising rapidly in the United States and several countries in Europe (10–15). For example, Shah *et al.* (10) report annual increases in body mass index of 0.6% for men and 1.0% for women in the upper Midwestern part of the United States between 1980 and 1987. Analysis of the United States National Health and Nutrition Examination surveys also revealed dramatic increases in the prevalence of obesity among men, women, Whites, and Blacks over a 17-year period (11). In the National Health and Nutrition Examination Survey the overall age-adjusted prevalence increased from 25.0% in the 1971–1974 survey I to 33.3% in the 1988–1991 survey III. Similarly, using data from Swedish studies in 1980 and 1988, Kuskowskawolk (12) and Bergstrom (13) calculated annual increases in body mass index of 2.2% for men and

1.4% for women. Thus if obesity is causally related to these cancers, it appears that at least some of the recent rise in adenocarcinoma incidence may be attributable to its increasing prevalence. The similar increases in obesity observed among men and women and among Whites and Blacks is consistent with the increases in incidence of adenocarcinomas which have been noted in all of these groups. However, the overall pattern of obesity in the population, with the highest prevalence among Black women (49.2%), and similar prevalence among White females (33.5%), White males (32.0%), and Black males (31.8%), clearly does not explain the large differences in absolute incidence in these groups (4, 11).

In contrast, for squamous cell carcinoma there was a strong inverse relationship between body mass index and risk of disease after controlling for alcohol and smoking intake. This pattern was also evident among squamous cell cases arising in the lower third of the esophagus, although the number of cases was small. This would suggest that obesity-associated reflux is not a risk factor for squamous cell carcinoma. The reasons for this inverse association with body mass index are unclear, although it has been reported previously (9). The strength of the relationship was somewhat weakened when those with the most advanced disease at diagnosis were excluded, suggesting that effects of the disease may account for a part of the association. Dietary deficiencies associated with alcoholism may also explain this pattern of risk. Evidence against this hypothesis, however, is the finding of quite similar point estimates of relative risk for body mass index when analysis was limited to those who were light or moderate drinkers.

We also found increased risk of both histological types of cancer among persons who had not attended college, even after adjustment for gender, race, alcohol use, cigarette use, and body mass index. This may indicate the existence of additional unknown environmental factors that are correlated with education or socioeconomic status, or the presence of residual confounding by alcohol and tobacco. Somewhat conflicting results were observed by Brown *et al.* (17), where increased adenocarcinoma risk was found among persons with low income and persons with jobs classified as low socioeconomic status, and paradoxically among persons with higher education (17). Kabat *et al.* (9) also reported a higher proportion of adenocarcinoma cases among those with higher education.

Several potential limitations of this study should be noted. In particular, the short survival times among persons diagnosed with esophageal or stomach cancer necessitated interviewing proxy respondents for approximately one-third of the interviewed cases. However, with the exception of a reduction in the odds ratios for the highest smoking category, the risk estimates changed little when proxy interviews were excluded from analyses, indicating that this was not an important limitation. Also, information on weight was limited in nature, referring only to the reference year (1 year before diagnosis for cases and 1 year before interview for controls). A lifetime weight history, together with anthropometric measurements, would yield a more complete picture of the associations with different obesity patterns and the ages when obesity is most strongly associated with cancer risk. It also would be important to take into account typical amounts of fat intake, a known reflux promoter for which data was unavailable in the present study, in assessing the potential role of obesity in the development of adenocarcinoma.

In summary, we found large differences between squamous cell carcinoma of the esophagus and adenocarcinoma of the esophagus and gastric cardia with regard to the strength of their associations with body mass index, cigarette smoking, and alcohol use. Cigarette smoking and alcohol consumption were quite strong risk factors for squamous cell cancers; together they accounted for 87% of the incident cases in the Seattle metropolitan area. In contrast, adenocarcinomas were only weakly associated with these factors. Thus, there is no reason to believe that use of cigarettes or alcohol is playing a role in the recent rise in adenocarcinoma incidence. On the other hand, there is mounting evidence that high body mass index is associated with increased adenocarcinoma risk, particularly of the esophagus. The growing prevalence of obesity that has been documented in a number of Westernized countries suggests that obesity and/or associated dietary patterns may account for part of the rising incidence of this disease. Nevertheless, the fact that 50% of the incident adenocarcinoma cases during the study period were not attributable to obesity, cigarettes, or alcohol suggests that other risk factors may also be important. Additional studies should focus on the role of obesity to determine whether adenocarcinoma risk varies by the pattern of fat deposition and by patterns of weight over a lifetime. Intervention trials aimed at reducing weight among persons at high risk of esophageal adenocarcinoma, such as persons with Barrett's metaplasia, are also indicated to establish its causal role and determine the usefulness of dietary intervention in reducing rates of neoplastic progression to cancer.

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