

The New England Journal of Medicine

© Copyright, 1999, by the Massachusetts Medical Society

VOLUME 340

MARCH 18, 1999

NUMBER 11



SYMPTOMATIC GASTROESOPHAGEAL REFLUX AS A RISK FACTOR FOR ESOPHAGEAL ADENOCARCINOMA

JESPER LAGERGREN, M.D., REINHOLD BERGSTRÖM, PH.D., ANDERS LINDGREN, M.D., PH.D.,
AND OLOF NYRÉN, M.D., PH.D.

ABSTRACT

Background The causes of adenocarcinomas of the esophagus and gastric cardia are poorly understood. We conducted an epidemiologic investigation of the possible association between gastroesophageal reflux and these tumors.

Methods We performed a nationwide, population-based, case-control study in Sweden. Case ascertainment was rapid, and all cases were classified uniformly. Information on the subjects' history of gastroesophageal reflux was collected in personal interviews. The odds ratios were calculated by logistic regression, with multivariate adjustment for potentially confounding variables.

Results Of the patients interviewed, the 189 with esophageal adenocarcinoma and the 262 with adenocarcinoma of the cardia constituted 85 percent of the 529 patients in Sweden who were eligible for the study during the period from 1995 through 1997. For comparison, we interviewed 820 control subjects from the general population and 167 patients with esophageal squamous-cell carcinoma. Among persons with recurrent symptoms of reflux, as compared with persons without such symptoms, the odds ratios were 7.7 (95 percent confidence interval, 5.3 to 11.4) for esophageal adenocarcinoma and 2.0 (95 percent confidence interval, 1.4 to 2.9) for adenocarcinoma of the cardia. The more frequent, more severe, and longer-lasting the symptoms of reflux, the greater the risk. Among persons with long-standing and severe symptoms of reflux, the odds ratios were 43.5 (95 percent confidence interval, 18.3 to 103.5) for esophageal adenocarcinoma and 4.4 (95 percent confidence interval, 1.7 to 11.0) for adenocarcinoma of the cardia. The risk of esophageal squamous-cell carcinoma was not associated with reflux (odds ratio, 1.1; 95 percent confidence interval, 0.7 to 1.9).

Conclusions There is a strong and probably causal relation between gastroesophageal reflux and esophageal adenocarcinoma. The relation between reflux and adenocarcinoma of the gastric cardia is relatively weak. (N Engl J Med 1999;340:825-31.)

©1999, Massachusetts Medical Society.

THE incidence of adenocarcinomas of the esophagus and gastric cardia has risen rapidly in the United States and western Europe, including Sweden, in recent decades.¹⁻⁴ The increase has been more pronounced for adenocarcinoma of the esophagus than for adenocarcinoma of the gastric cardia.¹⁻⁵ Only a few, moderately strong, risk factors have been identified, and the reasons for the rising incidence are unknown.⁶

There are reasons to suspect that gastroesophageal reflux plays an important part in the development of esophageal adenocarcinoma. Chronic reflux is the main cause of Barrett's esophagus,⁷ a columnar-cell metaplasia that replaces the native squamous-cell epithelium of the esophageal mucosa.⁸ The specialized epithelium of Barrett's esophagus has been linked to a substantially increased risk of esophageal adenocarcinoma.⁸ Recent studies have shown that adenocarcinoma of the gastric cardia may arise in a similar metaplasia adjacent to the squamocolumnar border.⁹

There is a paucity of epidemiologic data on the association between gastroesophageal reflux and the risk of adenocarcinoma of the esophagus or gastric cardia. A previous study based on the medical records of 196 patients with adenocarcinoma of the esophagus or cardia (mainly the latter) and 196 controls found an odds ratio of 2.1 (95 percent confidence interval, 1.2 to 3.6) for adenocarcinoma among patients whose records indicated that they had reflux disease.¹⁰ It is uncertain, however, how well medical records capture the occurrence of reflux.

We conducted a large-scale case-control study to identify risk factors for adenocarcinomas of the esoph-

From the Department of Medical Epidemiology, Karolinska Institute, Stockholm (J.L., R.B., O.N.); the Department of Surgery, Karolinska Institute and Danderyd Hospital, Stockholm (J.L.); the Department of Statistics, Uppsala University, Uppsala (R.B.); and the Department of Pathology, Falu Hospital, Falun (A.L.) — all in Sweden. Address reprint requests to Dr. Lagergren at the Department of Medical Epidemiology, Karolinska Institute, Box 281, S-171 77 Stockholm, Sweden, or at jesper.lagergren@mep.ki.se.

agus and gastric cardia. The aim of this investigation was to estimate the magnitude of the contribution of symptoms of reflux to the risk of these cancers.

METHODS

Study Design

The study encompassed the whole population of Sweden younger than 80 years, born in Sweden, and living there during the period from December 1, 1994, through December 31, 1997. All newly diagnosed cases of adenocarcinoma of the esophagus or gastric cardia and half the newly diagnosed cases of esophageal squamous-cell carcinoma (those in patients born on even-numbered days) were eligible. A comprehensive organization for the rapid ascertainment of cases, involving contact persons at all 195 departments of general surgery, thoracic surgery, otorhinolaryngology, oncology, and pathology in Sweden, as well as continuous collaboration with the six regional tumor registries, ensured that every potential case patient throughout the country was identified soon after diagnosis. The control subjects were selected randomly from among the persons matched for age (within 10 years) and sex in the entire Swedish population, through the use of the population register, which is computerized and is updated continuously. The numbers of controls selected in each stratum defined by sex and age group were adjusted to approximate the age and sex distribution among the patients with esophageal adenocarcinoma.

Classification of Cases

To reduce misclassification of the tumor site or histologic type, uniform routines for the documentation of the tumors were introduced at all participating sites. All patients were examined endoscopically. The distances between the gastroesophageal junction (defined as the point where the proximal longitudinal mucosal folds begin in the stomach) and the upper and lower borders of the tumor were measured. It was usually possible to pass the endoscope beyond obstructing tumors after dilatation, but in 22 patients in which this was impossible or the gastroesophageal junction could not be identified, the borders of the tumor were measured as distances to the incisor teeth, and endoscopy was supplemented with radiologic imaging. Serial biopsy specimens were obtained every 2 cm from the proximal stomach, the gastroesophageal junction, and the esophagus until normal squamous-cell epithelium was reached. Additional specimens were obtained proximal, distal, and lateral to the tumor. Surgeons and pathologists gave standardized, detailed descriptions of the location of the cancer in the 424 patients in whom resection was performed. Biopsy samples, surgical specimens, or both from 97 percent of the patients were reviewed by a single pathologist. Ambiguous cases were classified by a panel of investigators, who used all information available. For a case to be classified as a cancer of the gastric cardia, the tumor had to have its center within 2 cm proximal, or 3 cm distal, to the gastroesophageal junction. Barrett's esophagus was defined as columnar-cell metaplasia of the specialized type, with goblet cells and villiform surface configuration of the mucosa resembling the features of the intestines. Five patients with junctional or fundus metaplasia recorded more than 3 cm proximal to the gastroesophageal junction were also classified as having Barrett's esophagus. In seven patients in whom Barrett's esophagus was detected adjacent to an adenocarcinoma located in the gastric cardia, the tumors were classified as esophageal. Squamous-cell carcinomas were classified as esophageal even if the location was the gastric cardia.

Data on Symptoms of Reflux

All patients and controls underwent computer-aided personal interviews conducted by specially trained professional interviewers from Statistics Sweden (a government agency), mostly within a few weeks after diagnosis. We were unable to blind the interviewers to the case or control status of the subjects, but they were unaware

of the study hypotheses and were trained to treat the case patients and controls strictly the same. The total number of questions varied between 169 and 553, depending on the number of "question loops" entered (some questions could be skipped if a respondent answered "no" to an earlier question), and the average length of the interview was 80 minutes (range, 50 to 180). Questions were asked about recurrent heartburn and regurgitation, which are the cardinal symptoms of gastroesophageal reflux.¹¹ To avoid reverse causality — that is, to avoid collecting data on reflux caused by adenocarcinoma — we disregarded symptoms that had occurred less than five years before the interview. Information was collected about several potential confounding factors. In multivariate analyses, we adjusted for age (in five-year groups), sex, body-mass index (in quartiles), tobacco smoking (assessed as of two years before the interview and with the respondents classified as nonsmokers, former smokers, or current smokers), alcohol ingestion (total amount of all types of alcoholic beverages consumed, with the respondents categorized in four groups), socioeconomic status (reflected by the number of years of formal education, with the respondents categorized in three groups), dietary intake of fruit and vegetables (three groups), energy intake (estimated by the amounts of seven kinds of dishes eaten at each meal with the respondents categorized in three groups), whether the respondent worked in a stooped posture (hours per week, in three categories), physical activity at work (three categories), and extent of physical activities during leisure time (four categories).

Informed consent, both written and oral, was obtained from each subject before the interview, and the study was approved by all regional ethics committees in Sweden.

Statistical Analysis

Logistic regression was used in both univariate and multivariate modeling. Model parameters were estimated by the maximum-likelihood method.¹² From these estimates, odds ratios with 95 percent confidence intervals were computed. In multivariate modeling, adjustments were made for the 11 potential confounders. We also performed an analysis showing the association between gastroesophageal reflux and the risk of cancer after the successive inclusion of potentially confounding variables. Furthermore, we analyzed the relation between reflux and its potential predictors by means of logistic regression.

RESULTS

Altogether, 618 patients with cancer of the esophagus or gastric cardia and 820 control subjects were interviewed. The participation rates, characteristics of the respondents, and reasons for nonparticipation are shown in Table 1. The 451 cases of adenocarcinoma of the esophagus or gastric cardia together constituted 85 percent of all eligible cases of adenocarcinoma in Sweden during the study period. The participation rate among both controls and patients with esophageal squamous-cell carcinoma was 73 percent.

Esophageal Adenocarcinoma

The risk of esophageal adenocarcinoma was almost eight times as high among persons in whom heartburn, regurgitation, or both occurred at least once a week as among persons without these symptoms (Table 2). Symptoms of reflux at night were associated with a risk nearly 11 times as high. The estimates changed marginally as suspected confounders were added successively to the model (Table 3). The frequency of symptoms of reflux was strongly linked to the risk: the more frequent the symptoms, the higher

TABLE 1. CHARACTERISTICS OF THE SUBJECTS INTERVIEWED.*

SUBJECTS INTERVIEWED	PARTICIPANTS	MEDIAN AGE	MALE SEX	CURRENT OR FORMER SMOKING†	HIGH ALCOHOL CONSUMPTION‡	LOW EDUCATIONAL LEVEL§	REASON FOR NONPARTICIPATION	
							UNWILLINGNESS	PHYSICAL OR MENTAL IMPEDIMENTS OR EARLY DEATH
	no. enrolled/ no. eligible (%)	yr			number (percent)		no. (% of eligible subjects)	
Patients with cancer								
Esophageal adenocarcinoma	189/216 (88)	69	165 (87)	132 (70)	43 (23)	48 (25)	2 (1)	25 (12)
Adenocarcinoma of gastric cardia	262/313 (84)	66	223 (85)	219 (84)	76 (29)	43 (16)	10 (3)	41 (13)
Esophageal squamous-cell carcinoma	167/228 (73)	67	120 (72)	145 (87)	78 (47)	41 (25)	11 (5)	50 (22)
Control subjects	820/1128 (73)	68	679 (83)	495 (60)	178 (22)	182 (22)	210 (19)¶	70 (6)

*Because of rounding, percentages may not total 100.

†This category included smoking of cigarettes, cigars, and pipes and was assessed as of two years before the interview.

‡High alcohol consumption was defined as consumption of more than 70 g of alcohol per week.

§Low educational level was defined as less than seven years of formal education.

¶A further 28 control subjects (2 percent) could not be reached by mail or telephone.

TABLE 2. SYMPTOMS OF REFLUX FIVE YEARS OR MORE BEFORE THE INTERVIEW AND THE RISK OF ESOPHAGEAL ADENOCARCINOMA, ADENOCARCINOMA OF THE GASTRIC CARDIA, AND ESOPHAGEAL SQUAMOUS-CELL CARCINOMA.*

SYMPTOMS OF REFLUX	CONTROLS (N=820)	ESOPHAGEAL ADENOCARCINOMA		ADENOCARCINOMA OF GASTRIC CARDIA		ESOPHAGEAL SQUAMOUS-CELL CARCINOMA	
		PATIENTS (N=189)	ADJUSTED	PATIENTS (N=262)	ADJUSTED	PATIENTS (N=167)	ADJUSTED
			ODDS RATIO (95% CI)		ODDS RATIO (95% CI)		ODDS RATIO (95% CI)
	no. (%)			no. (%)		no. (%)	
Heartburn, regurgitation, or both at least once a week							
No	685 (84)	76 (40)	1.0	187 (71)	1.0	142 (85)	1.0
Yes	135 (16)	113 (60)	7.7 (5.3–11.4)	75 (29)	2.0 (1.4–2.9)	25 (15)	1.1 (0.7–1.9)
Heartburn, regurgitation, or both at night at least once a week							
No	754 (92)	88 (47)	1.0	217 (83)	1.0	157 (94)	1.0
Yes	66 (8)	101 (53)	10.8 (7.0–16.7)	45 (17)	2.4 (1.5–3.8)	10 (6)	0.9 (0.4–2.0)

*In the multivariate logistic-regression model, adjustments were made for age, sex, socioeconomic status, body-mass index, tobacco smoking, alcohol use, intake of fruit and vegetables, energy intake, work in a stooped posture, physical activity at work, and physical activity during leisure time. Subjects without symptoms served as the reference group. CI denotes confidence interval.

the risk (Table 4). To evaluate further the effect of the severity of the symptoms, the symptoms were graded with scores for heartburn only (1 point), regurgitation only (1), heartburn and regurgitation combined (1.5), nightly symptoms (yes=2 and no=0), and frequency of symptoms (once a week=0, 2 to 6 times a week=1, 7 to 15 times a week=2, and more than 15 times a week=3). Persons with a score of 4.5 or higher had a risk of esophageal adenocarcinoma 20 times as high as did those without symptoms of reflux (Table 4). The risk of esophageal adenocarcinoma also increased with an increasing duration of symptoms. Among persons with both long-standing

symptoms (duration, more than 20 years) and severe symptoms (reflux-symptom score, 4.5 or higher), the adjusted odds ratio for esophageal adenocarcinoma was 43.5 (95 percent confidence interval, 18.3 to 103.5), as compared with asymptomatic persons. Stratified analyses revealed no important variation in relative risk among age groups.

In 118 (62 percent) of the 189 patients with esophageal adenocarcinoma, Barrett's esophagus was detected. The strength of the association with symptoms of reflux was virtually identical for patients with esophageal adenocarcinomas who had Barrett's esophagus and those who did not (data not shown). We com-

TABLE 3. ASSOCIATION OF SYMPTOMS OF REFLUX WITH DISEASE AFTER THE SUCCESSIVE INCLUSION OF POTENTIAL CONFOUNDING VARIABLES IN THE MULTIVARIATE ANALYSIS.*

CONFOUNDING VARIABLE	ESOPHAGEAL ADENOCARCINOMA	GASTRIC CARDIA ADENOCARCINOMA	ESOPHAGEAL SQUAMOUS-CELL CARCINOMA
	odds ratio (95% confidence interval)		
Unadjusted	7.5 (5.4–10.6)	2.0 (1.5–2.8)	0.9 (0.6–1.4)
Age	7.6 (5.3–10.7)	2.0 (1.4–2.8)	0.9 (0.6–1.5)
Sex	7.5 (5.3–10.6)	2.0 (1.4–2.8)	1.0 (0.6–1.6)
Body-mass index	7.1 (4.9–10.2)	1.9 (1.4–2.7)	1.0 (0.6–1.6)
Tobacco smoking	7.1 (4.9–10.2)	2.0 (1.4–2.7)	1.1 (0.7–1.8)
Alcohol use	7.6 (5.2–11.0)	2.0 (1.4–2.8)	1.2 (0.7–2.1)
Educational level	7.6 (5.2–11.0)	2.0 (1.4–2.8)	1.2 (0.7–2.0)
Energy intake	7.6 (5.2–11.1)	2.0 (1.4–2.8)	1.2 (0.7–2.0)
Intake of fruit and vegetables	7.6 (5.2–11.1)	2.0 (1.4–2.8)	1.2 (0.7–2.0)
Work in a stooped posture	7.6 (5.2–11.1)	2.0 (1.4–2.8)	1.2 (0.7–2.0)
Physical activity at work	7.8 (5.3–11.4)	2.0 (1.4–2.9)	1.1 (0.7–1.9)
Physical activity during leisure time	7.7 (5.3–11.4)	2.0 (1.4–2.9)	1.2 (0.7–2.0)

*The odds ratios in each row have been adjusted for the variable noted in that row and all other variables listed above that row. Thus, the last row shows the odds ratios from the full multivariate model with 11 potential confounders included.

TABLE 4. FREQUENCY, SEVERITY, AND DURATION OF SYMPTOMS OF REFLUX FIVE YEARS OR MORE BEFORE THE INTERVIEW.*

VARIABLE	CONTROLS (N=820)	ESOPHAGEAL ADENOCARCINOMA		ADENOCARCINOMA OF GASTRIC CARDIA		ESOPHAGEAL SQUAMOUS- CELL CARCINOMA	
		PATIENTS (N=189)	ADJUSTED	PATIENTS (N=262)	ADJUSTED	PATIENTS (N=167)	ADJUSTED
			ODDS RATIO (95% CI)		ODDS RATIO (95% CI)		ODDS RATIO (95% CI)
no. (%)		no. (%)		no. (%)		no. (%)	
Frequency of reflux symptoms							
No symptoms	685 (84)	76 (40)	1.0	187 (71)	1.0	142 (85)	1.0
1 time per week	95 (12)	37 (20)	5.1 (2.8–9.4)	30 (11)	2.0 (1.1–3.6)	9 (5)	0.9 (0.4–2.4)
2 to 3 times per week	16 (2)	35 (19)	6.3 (3.8–10.3)	27 (10)	1.9 (1.2–3.1)	10 (6)	1.2 (0.6–2.5)
>3 times per week	24 (3)	41 (22)	16.7 (8.7–28.3)	18 (7)	2.3 (1.2–4.3)	6 (4)	1.4 (0.5–3.7)
Reflux-symptom score†							
No symptoms	685 (84)	76 (40)	1.0	187 (71)	1.0	142 (85)	1.0
1–2 points	58 (7)	10 (5)	1.4 (0.7–3.0)	27 (10)	1.7 (1.0–2.9)	14 (8)	1.7 (0.8–3.5)
2.5–4 points	43 (5)	39 (21)	8.1 (4.7–16.1)	21 (8)	1.8 (1.0–3.2)	5 (3)	0.6 (0.2–1.7)
4.5–6.5 points	34 (4)	64 (34)	20.0 (11.6–34.6)	27 (10)	2.8 (1.6–5.0)	6 (4)	1.1 (0.4–3.0)
Duration of reflux symptoms							
No symptoms	685 (84)	76 (40)	1.0	187 (71)	1.0	142 (85)	1.0
<12 yr	41 (5)	31 (16)	7.5 (4.2–13.5)	19 (7)	1.6 (0.9–2.9)	10 (6)	1.6 (0.7–3.7)
12–20 yr	67 (8)	42 (22)	5.2 (3.1–8.6)	34 (13)	1.8 (1.1–2.9)	10 (6)	0.9 (0.4–1.9)
>20 yr	27 (3)	40 (21)	16.4 (8.3–28.4)	22 (8)	3.3 (1.8–6.3)	5 (3)	1.2 (0.4–3.7)

*Because of rounding, percentages may not total 100. In the multivariate logistic-regression model, adjustments were made for age, sex, socioeconomic status, body-mass index, tobacco smoking, alcohol use, intake of fruit and vegetables, energy intake, work in a stooped posture, physical activity at work, and physical activity during leisure time. Subjects with no symptoms served as the reference group. CI denotes confidence interval.

†The index score included characteristics of symptoms (heartburn only=1 point, regurgitation only=1 point, heartburn and regurgitation combined=1.5 points), nightly symptoms (no=0 points, yes=2 points), and frequency of symptoms (once a week=0 points, 2–6 times a week=1 point, 7–15 times a week=2 points, >15 times a week=3 points).

pared the risk of esophageal adenocarcinoma among persons who used medication for symptoms of reflux at least five years before the interview with that among symptomatic persons who did not use such medication. The odds ratio was 3.0 (95 percent confidence interval, 2.0 to 4.6) without adjustment for the severity of symptoms and 2.9 (95 percent confidence interval, 1.9 to 4.6) with this adjustment. Among the 14 patients with esophageal adenocarcinoma and the 6 control subjects who had been surgically treated for reflux, the risk estimates were similar to those for the total group of patients with symptoms of reflux (data not shown).

Adenocarcinoma of the Gastric Cardia

Reflux symptoms were associated with the risk of adenocarcinoma of the gastric cardia, but not as strongly as with the risk of esophageal adenocarcinoma (Table 2). The risk among persons with symptoms of reflux was approximately two times as high as among those without such symptoms. We found no indication of confounding by the factors we evaluated (Table 3). The risk estimates increased with increases in the frequency of symptoms, the symptom score, and the duration of symptoms, but not as markedly as for esophageal adenocarcinoma. Only among persons with symptoms that were most severe or of the longest duration did the odds ratios approach 3 (Table 4). Persons who reported both long-standing and severe reflux symptoms had an adjusted odds ratio of 4.4 (95 percent confidence interval, 1.7 to 11.0). The relative risk was similar in all age groups.

Esophageal Squamous-Cell Carcinoma

Esophageal squamous-cell carcinoma was not associated with symptoms of reflux (Table 2), irrespective of the frequency, severity, or duration of the symptoms (Table 4). The odds ratio was 1.1 (95 percent confidence interval, 0.7 to 1.9) for persons with symptoms of reflux at least once a week, as compared with persons who had no such symptoms (Table 2).

Predictors of Gastroesophageal Reflux

The associations of age, sex, body-mass index, tobacco smoking, and alcohol use with symptoms of reflux are presented in Table 5. None of these factors were strongly associated with the presence of symptoms. We also analyzed the effects of the remaining suspected confounding factors but found no important associations with reflux (data not shown). The results were similar when we restricted the analysis to the control subjects (data not shown).

DISCUSSION

Our main finding is the strong association between symptoms of gastroesophageal reflux and the risk of esophageal adenocarcinoma, regardless of the pres-

TABLE 5. ASSOCIATION BETWEEN POTENTIAL PREDICTORS OF REFLUX AND THE OCCURRENCE OF SYMPTOMS.*

VARIABLE	ODDS RATIO (95% CI)
Age (yr)	
<55†	1.0
55–59	0.8 (0.5–1.4)
60–64	0.6 (0.4–1.0)
65–69	0.9 (0.5–1.4)
70–74	1.1 (0.7–1.7)
75–79	0.7 (0.4–1.2)
Sex	
Male†	1.0
Female	0.7 (0.5–1.1)
Body-mass index (quartile)‡	
First (<22.3)†	1.0
Second (22.3–23.9)	1.1 (0.7–1.7)
Third (24.0–25.5)	1.4 (1.0–2.2)
Fourth (>25.5)	1.3 (0.9–1.9)
Smoking status	
Nonsmoker†	1.0
Former smoker	1.0 (0.7–1.4)
Current smoker	0.8 (0.5–1.1)
Alcohol use (g of alcohol per week)	
0†	1.0
1–15	1.5 (0.9–2.3)
16–70	1.6 (1.0–2.5)
>70	1.4 (0.9–2.3)

*The results were obtained from a logistic-regression model in which the occurrence of reflux was the dependent variable and the covariates shown in Table 3 and dummy variables representing the case and control groups were the explanatory variables. Results for a selection of possible predictors of reflux are shown. CI denotes confidence interval.

†Subjects with this characteristic served as the reference group.

‡The body-mass index was defined as the weight in kilograms divided by the square of the height in meters.

ence of Barrett's esophagus. An association, although weaker, was also found for adenocarcinoma of the cardia, but not for esophageal squamous-cell carcinoma.

The strengths of the study include the population-based design, the uniform classification of tumors, and the complete and rapid case ascertainment, which enabled us to conduct personal interviews with all subjects. To avoid the problem of reverse causality, we restricted our analysis to symptoms that had begun at least five years before the interview. Patients with an esophageal tumor may be more inclined to remember previous esophageal symptoms (including reflux) than are other subjects. But because the patients were unaware of the histologic subtype of their tumors and of the possible differences in the pattern of risk among the subtypes, the effects of any recall bias should be similar for squamous-cell carcinoma and adenocarcinoma. For this reason, the totally negative finding with regard to squamous-cell carcinoma should allay concern about recall bias. Moreover, the clear dose-response relation points to a biologic effect rather than to bias.

We adjusted for tobacco smoking, body-mass index,¹³⁻¹⁵ and other possible confounders. None of them had a serious influence on the risk estimates. The effect of gastroesophageal reflux on the risk of esophageal adenocarcinoma thus appears to be independent of other variables. Moreover, associations of the magnitude found here are not plausibly explained by confounding. A nonparticipation rate of 27 percent among controls could have introduced bias. However, nonparticipation by patients and controls is unlikely to be linked to reflux.

Symptoms of reflux are considered to be fairly accurate, but not perfect, indicators of gastroesophageal reflux disease.^{11,16-19} The misclassification should be random, hence leading to underestimation rather than exaggeration of the association with the risk of cancer.²⁰

Some misclassification of tumors according to site was unavoidable in some cases as a result of anatomy that had become deranged by the tumor. To evaluate the contribution of misclassification to the moderate association we found between reflux and risk of adenocarcinoma of the gastric cardia, we reanalyzed our data after applying more conservative criteria for cancer near the gastroesophageal junction (69 tumors were located within 10 mm of the gastroesophageal junction in endoscopic, surgical, and histopathologic measures). The point estimates were unchanged, indicating the robustness of our findings. The differential association with the symptoms of reflux implies that adenocarcinomas of the esophagus and of the gastric cardia are different diseases, contrary to recent suggestions.¹⁵

Multiple comparisons involving three groups of patients and one control group inflated the risk of a type I error. However, the strength and consistency of the observed association and the clear dose dependency make an effect of chance unlikely.

As compared with the only previous epidemiologic study of gastroesophageal reflux and esophageal adenocarcinoma or adenocarcinoma of the gastric cardia,¹⁰ we found a considerably stronger association. Our more extensive data on symptoms of reflux and our ability to distinguish accurately between adenocarcinomas of the esophagus and those of the gastric cardia may explain the discrepancy.

Barrett's esophagus appears to be a common, but not necessary, step in the evolution of esophageal adenocarcinoma.²¹ Most such tumors arise in Barrett's metaplasia,²² a finding confirmed in our study. The risk of adenocarcinoma among patients with Barrett's esophagus has been estimated to be 30 to 60 times that in the general population.²³⁻²⁶ Because the risk among subjects in our study with the most severe and long-standing symptoms of reflux was of the same magnitude, and because the association was equally strong among patients with esophageal adenocarcinoma with Barrett's esophagus and those without it,

we hypothesize that gastroesophageal reflux, rather than Barrett's esophagus, may be the crucial factor. Admittedly, the prevalence of Barrett's esophagus may have been underestimated as a result of tumor overgrowth or sampling error. However, in view of our systematic efforts to identify this condition, it is remarkable that there was no important difference in the strength of the association between patients who had Barrett's esophagus and those who did not.

The mechanisms by which gastroesophageal reflux could cause cancer in the absence of Barrett's esophagus are unclear. The submucosal glands or ectopic gastric epithelium may constitute the starting point. Chronic irritation and inflammation are carcinogenic in several tissues,^{27,28} and animal studies have implicated reflux of bile as a key factor in esophageal carcinogenesis.^{29,30}

We found no indication that treatment of reflux reduced the risk of esophageal cancer. In fact, patients who received medical treatment had a higher risk than those who did not. Although we adjusted our data for the severity of symptoms, residual confounding by the severity of reflux may have affected our estimates. Moreover, the subjects in our survey had almost invariably received sporadic short-term courses of medical treatment. The effect of long-term treatment is unknown. It seems implausible that medical treatment itself increases the risk of esophageal cancer, but patients with symptoms of reflux were sometimes treated with anticholinergic drugs, which promote gastroesophageal reflux. The analysis of the risk of esophageal adenocarcinoma among surgically treated patients was hampered by small numbers, but no dramatic protective effect was found.

The possible clinical implications to be drawn from our data include the advisability of prophylactic treatment and endoscopic surveillance of patients with symptomatic reflux. Medical or surgical treatment does not seem to prevent cancer in patients with overt Barrett's esophagus, but therapy may be effective if administered before the development of irreversible precancerous changes. Our data do not, however, support this supposition. Furthermore, the advent of increasingly potent inhibitors of acid production in the past 20 years does not seem to have affected the rising incidence of esophageal adenocarcinoma. For this reason, pleas for more active treatment to prevent esophageal adenocarcinoma are based on speculation only.

The possible benefits of endoscopic surveillance should exceed the costs and inconvenience for patients and health care systems. In view of the relatively high number of esophageal adenocarcinomas detected early^{23-26,31-33} and the advantage in survival associated with an early diagnosis,³⁴ many clinicians consider endoscopic surveillance to be justified in patients with Barrett's esophagus.^{35,36} Reflux without Barrett's esophagus, however, is much more common. Symp-

toms severe enough to be associated with a risk of esophageal adenocarcinoma eight times as high as normal were reported by 9 percent of our control subjects. If endoscopic surveillance were restricted to men older than 40 who had symptoms of reflux that were so severe as to entail a risk 20 times as high as normal, a Swedish physician would need to follow more than 1400 such patients for one year to encounter a single case of esophageal adenocarcinoma; such a policy would surely overtax the available health care resources. Until the group at a sufficiently high risk to justify endoscopic surveillance is better delineated, it seems unwise to make dramatic changes in current practice.

There are no firm data to substantiate the idea that gastroesophageal reflux is becoming more common. Hence, the role of reflux as a cause of the rapid increase in the incidence of adenocarcinoma of the esophagus and cardia is uncertain.

In conclusion, our study identified symptomatic reflux as a strong risk factor for esophageal adenocarcinoma and a relatively weak risk factor for adenocarcinoma of the gastric cardia. The strength of the association, the dose dependency, and the biologic plausibility suggest causality. The proportion of cases of esophageal adenocarcinoma in the population that are attributable to reflux (the etiologic fraction³⁷) was estimated to be 53 percent in our study, and among the persons who had symptoms of reflux this proportion²⁰ was 87 percent. It is uncertain whether the risk can be reduced by medical or surgical means, and the need for endoscopic surveillance is debatable. Moreover, it may be necessary to reappraise the critical role of Barrett's esophagus in the carcinogenic pathway.

Funded by a grant (R01 CA57947-03) from the National Cancer Institute, by the Swedish Cancer Society, and by Dalarna Research Institute.

We are indebted to Leila Nyrén for invaluable coordination of the fieldwork, to Wolfgang Kraaz for expert guidance in pathology during the planning of the study and during the fieldwork, to Dr. Lars Backman and Dr. Lars Granström of the Department of Surgery at Danderyd Hospital, and to all 227 doctors who acted as contact persons at the participating departments or provided invaluable advice during the planning of this study.

REFERENCES

- Blot WJ, Devesa SS, Kneller RW, Fraumeni JF Jr. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA* 1991;265:1287-9.
- Powell J, McConkey CC. The rising trend in oesophageal adenocarcinoma and gastric cardia. *Eur J Cancer Prev* 1992;1:265-9.
- Hansson LE, Sparén P, Nyrén O. Increasing incidence of both major histological types of esophageal carcinomas among men in Sweden. *Int J Cancer* 1993;54:402-7.
- Pera M, Cameron AJ, Trastek VF, Carpenter HA, Zinsmeister AR. Increasing incidence of adenocarcinoma of the esophagus and esophagogastric junction. *Gastroenterology* 1993;104:510-3.
- Hansson LE, Sparén P, Nyrén O. Increasing incidence of carcinoma of the gastric cardia in Sweden from 1970 to 1985. *Br J Surg* 1993;80:374-7.
- Kim R, Weissfeld JL, Reynolds JC, Kuller LH. Etiology of Barrett's metaplasia and esophageal adenocarcinoma. *Cancer Epidemiol Biomarkers Prev* 1997;6:369-77.
- Winters C Jr, Spurling TJ, Chobanian SJ, et al. Barrett's esophagus: a prevalent, occult complication of gastroesophageal reflux disease. *Gastroenterology* 1987;92:118-24.
- Spechler SJ, Goyal RK. Barrett's esophagus. *N Engl J Med* 1986;315:362-71.
- Morales TG. Adenocarcinoma of the gastric cardia. *Dig Dis* 1997;15:346-56.
- Chow WH, Finkle WD, McLaughlin JK, Frankl H, Ziel HK, Fraumeni JF Jr. The relation of gastroesophageal reflux disease and its treatment to adenocarcinomas of the esophagus and gastric cardia. *JAMA* 1995;274:474-7.
- Ter RB, Castell DO. Gastroesophageal reflux disease in patients with columnar-lined esophagus. *Gastroenterol Clin North Am* 1997;26:549-63.
- Breslow NE, Day NE. Statistical methods in cancer research. Vol. 1. The analysis of case-control studies. Lyon, France: International Agency for Research on Cancer, 1980. (IARC scientific publications no. 32.)
- Gammon MD, Schoenberg JB, Ahsan H, et al. Tobacco, alcohol, and socioeconomic status and adenocarcinomas of the esophagus and gastric cardia. *J Natl Cancer Inst* 1997;89:1277-84.
- Chow WH, Blot WJ, Vaughan TL, et al. Body mass index and risk of adenocarcinoma of the esophagus and gastric cardia. *J Natl Cancer Inst* 1998;90:150-5.
- Zhang ZF, Kurtz RC, Sun M, et al. Adenocarcinomas of the esophagus and gastric cardia: medical conditions, tobacco, alcohol, and socioeconomic factors. *Cancer Epidemiol Biomarkers Prev* 1996;5:761-8.
- Klauser AG, Schindlbeck NE, Müller-Lissner SA. Symptoms in gastroesophageal reflux disease. *Lancet* 1990;335:205-8.
- Locke GR, Talley NJ, Weaver AJ, Zinsmeister AR. A new questionnaire for gastroesophageal reflux disease. *Mayo Clin Proc* 1994;69:539-47.
- Williford WO, Krol WF, Spechler SJ. Development for and results of the use of a gastroesophageal reflux disease activity index as an outcome variable in a clinical trial: VA Cooperative Study Group on Gastroesophageal Reflux Disease (GERD). *Control Clin Trials* 1994;16:335-48.
- Revicki DA, Wood M, Wiklund I, Crawley J. Reliability and validity of the Gastrointestinal Symptom Rating Scale in patients with gastroesophageal reflux disease. *Qual Life Res* 1998;7:75-83.
- Rothman KJ, Greenland S, eds. Modern epidemiology. 2nd ed. Philadelphia: Lippincott-Raven, 1998;53-6, 127-32.
- Cameron AJ. Epidemiology of columnar-lined esophagus and adenocarcinoma. *Gastroenterol Clin North Am* 1997;26:487-94.
- Clark GW, Smyrk TC, Burdiles P, et al. Is Barrett's metaplasia the source of adenocarcinomas of the cardia? *Arch Surg* 1994;129:609-14.
- Spechler SJ, Robbins AH, Rubins HB, et al. Adenocarcinoma and Barrett's esophagus: an overrated risk? *Gastroenterology* 1984;87:927-33.
- Cameron AJ, Ott BJ, Payne WS. The incidence of adenocarcinoma in columnar-lined (Barrett's) esophagus. *N Engl J Med* 1985;313:857-9.
- Van der Veen AH, Dees J, Blankensteijn JD, Van Blankenstein M. Adenocarcinoma in Barrett's oesophagus: an overrated risk. *Gut* 1989;30:14-8.
- Drewitz DJ, Sampliner RE, Garewal HS. The incidence of adenocarcinoma in Barrett's esophagus: a prospective study of 170 patients followed 4.8 years. *Am J Gastroenterol* 1997;92:212-5.
- Correa P, Miller MJ. Carcinogenesis, apoptosis and cell proliferation. *Br Med Bull* 1998;54:151-62.
- Wink DA, Vodovotz Y, Laval J, Laval F, Dewhirst MW, Mitchell JB. The multifaceted roles of nitric oxide in cancer. *Carcinogenesis* 1998;19:711-21.
- Miwa K, Segawa M, Takano Y, et al. Induction of oesophageal and forestomach carcinomas in rats by reflux of duodenal contents. *Br J Cancer* 1994;70:185-9.
- Marshall RE, Anggiansah A, Owen WJ. Bile in the oesophagus: clinical relevance and ambulatory detection. *Br J Surg* 1997;84:21-8.
- Hameeteman W, Tytgat GNJ, Houthoff HJ, van den Tweel JG. Barrett's esophagus: development of dysplasia and adenocarcinoma. *Gastroenterology* 1989;96:1249-56.
- Ovaska J, Miettinen M, Kivilaakso E. Adenocarcinoma arising in Barrett's esophagus. *Dig Dis Sci* 1989;34:1336-9.
- Robertson CS, Mayberry JF, Nicholson DA, James PD, Atkinson M. Value of endoscopic surveillance in the detection of neoplastic change in Barrett's oesophagus. *Br J Surg* 1988;75:760-3.
- Altorki NK, Skinner DB. Adenocarcinoma in Barrett's esophagus. *Semin Surg Oncol* 1990;6:274-8.
- Wright TA, Gray MR, Morris AI, et al. Cost effectiveness of detecting Barrett's cancer. *Gut* 1996;39:574-9.
- Streitz JM Jr, Ellis FH Jr, Tilden RL, Erickson RV. Endoscopic surveillance of Barrett's esophagus: a cost-effectiveness comparison with mammographic surveillance for breast cancer. *Am J Gastroenterol* 1998;93:911-5.
- Schlesselman JJ. Case-control studies: design, conduct, analysis. New York: Oxford University Press, 1982:43-5.