STOMACH

Gastric acid suppression and risk of oesophageal and gastric adenocarcinoma: a nested case control study in the UK

L A García Rodríguez, J Lagergren, M Lindblad

Gut 2006;55:1538–1544. doi: 10.1136/gut.2005.086579

See end of article for
authors' affiliations

Correspondence to:
Mr M Lindblad,
Department of Surgery,
P9: 03, Karolinska
University Hospital, SE-
171 76 Stockholm,
Sweden; mats.lindblad@
karolinska.se

Revised version received
12 April 2006
Accepted for publication
7 June 2006
Published online first
19 June 2006

Background: Gastric acid suppressing drugs (that is, histamine₂ receptor antagonists and proton pump inhibitors) could affect the risk of oesophageal or gastric adenocarcinoma but few studies are available. **Aims:** To study the association between long term treatment with acid suppressing drugs and the risk of oesophageal or gastric adenocarcinoma.

Patients: Persons registered in the general practitioners research database in the UK and aged 40–84 years during the period 1994–2001.

Methods: Population based nested case control study. Multivariable unconditional logistic regression was used to calculate odds ratios (ORs) with 95% confidence intervals (CI).

Results: In 4 340 207 person years of follow up, 287 patients with oesophageal adenocarcinoma, 195 with gastric cardia adenocarcinoma, and 327 with gastric non-cardia adenocarcinoma were identified, and 10 000 control persons were randomly sampled. "Oesophageal" indication for long term acid suppression (that is, reflux symptoms, oesophagitis, Barrett's oesophagus, or hiatal hernia) rendered a fivefold increased risk of oesophageal adenocarcinoma (odds ratio (OR) 5.42 (95% confidence interval (CI) 3.13–9.39)) while no association was observed among users with a group of other indications, including peptic ulcer and "gastroduodenal symptoms" (that is, gastritis, dyspepsia, indigestion, and epigastric pain) (OR 1.74 (95% CI 0.90–3.34)). "Peptic ulcer" indication (that is, gastric ulcer, duodenal ulcer, or unspecified peptic ulcer) was associated with a greater than fourfold increased risk of gastric non-cardia adenocarcinoma among long term users (OR 4.66 (95% CI 2.42–8.97)) but no such association was found in those treated for a group of other indications (that is, "oesophageal" or "gastroduodenal symptoms") (OR 1.18 (95% CI 0.60–2.32)).

Conclusions: Long term pharmacological gastric acid suppression is a marker of increased risk of oesophageal and gastric adenocarcinoma. However, these associations are most likely explained by the underlying treatment indication being a risk factor for the cancer rather than an independent harmful effect of these agents per se.

The role of long term use of acid suppressing drugs in the aetiology or prevention of adenocarcinoma of the oesophagus or stomach needs to be investigated. While the occurrence of adenocarcinoma of the oesophagus and gastric cardia are increasing rapidly in the USA,^{1 2} Australia,² and Western Europe,^{2 3} adenocarcinoma of the gastric non-cardia is becoming less common.⁴ The reasons for these striking trends are unclear.^{5 6} Gastro-oesophageal reflux disease (GORD) is, to date, the strongest independent known risk factor for adenocarcinoma of the oesophagus and gastric cardia.^{7–11} Gastric ulcer disease has been linked with an increased risk of non-cardia gastric adenocarcinoma in several publications,^{12 14–18} but not in all.¹³ A history of duodenal ulcer, on the other hand, has been associated in a few studies with a reduced risk of gastric cancer.^{14 15 17}

The introduction of the two histamine₂ receptor antagonists (H₂ blockers) ranitidine and cimetidine in the late 1970s, and the proton pump inhibitor (PPI) omeprazole in the late 1980s, revolutionised the therapeutic arsenal for GORD and peptic ulcer disease. These medications are increasingly widely used, both as short term pain relief and long term therapy for prevention of GORD and other upper gastrointestinal disorders. However, since their introduction there have been concerns regarding possible deleterious effects of longstanding acid suppression, particularly a potentially increased risk of gastric adenocarcinoma.^{19–24} On

the other hand, reduced acid exposure of the oesophagus mediated by acid suppressing drugs might reduce the development of oesophageal adenocarcinoma. A few studies have attempted to evaluate the association between long term use of acid suppressing therapy and risk of oesophageal or gastric adenocarcinoma, with no firm evidence.^{7–9 22 25–28} Most of these studies have been hampered by small sample sizes or retrospective exposure collection. Furthermore, this type of association could be explained by reversed causality or confounding by indication, biases that are common sources of error in pharmacoepidemiology.²⁹ To evaluate the nature of the association between chronic use of H₂ blockers and PPIs and the risk of oesophageal and gastric adenocarcinoma, we conducted a large study with prospective recording of exposure, including several potential confounding factors, and most important among these treatment indications.

METHODS

Design

The design of this case control study nested within the general practitioners research database (GPRD) has been

Abbreviations: BMI, body mass index; GORD, gastro-oesophageal reflux disease; GP, general practitioner; GPRD, general practitioners research database; H₂ blockers, histamine₂ receptor antagonists; OR, odds ratio; PPI, proton pump inhibitor

described in detail elsewhere.³⁰ The Scientific and Ethical Advisory Group of the GPRD in the UK approved the study protocol. In brief, a study cohort of all individuals registered in the GPRD, aged 40–84 years during the period 1 January 1994 to 31 December 2001, was identified. To be a member of the study cohort, the person had to be enrolled with a general practitioner (GP) for at least two years and had at least one year of prescription history recorded in the database. Persons with any cancer recorded in the GPRD before the start date were excluded. All persons in the cohort were considered at risk until one of the following events occurred, whichever came first: (1) detection of an oesophageal or gastric cancer, (2) detection of any other cancer (except skin cancer), (3) age 85 years, (4) death, or (5) end of study period (31 December 2001).

The general practitioners research database (GPRD)

The GPRD is a primary care automated database in the UK that was initiated in the late 1980s, and currently data have been collected on more than 3 million persons. It contains detailed information on patient demographics, diagnoses, and drug prescriptions, all prospectively recorded by the participating GPs during routine medical care. All prescriptions are automatically entered into the GPRD as they are directly generated from the GP's computer, thus ensuring an unselected and complete recording. Validation studies have shown that GPRD data are of high quality for research purposes.^{31–32}

Identification of case patients

Follow up of the study cohort detected 2128 patients with a new diagnosis code indicating an oesophageal or gastric cancer. To verify and further classify the tumours, information on site and histology as well as additional paper based information (for example, operation and pathology reports and letters from specialists) was requested from the GPs for a consecutive sample of 1280 patients. The reviewer of these records and additional information (ML) was blinded to the exposure data. Patients were excluded if: (1) the tumour was benign, (2) the origin of the cancer was unknown, (3) the tumour was a metastasis, (4) the patient had another concurrent cancer, (5) the cancer was first diagnosed before the start date, or (6) the histological type was not adenocarcinoma or squamous cell carcinoma. The effect of the review of the additional information provided by the GPs

was negligible with respect to the overall final case status compared with the information already present in the GPRD. Therefore, we did not request complementary information from the GPs for the remaining computer detected patients who were otherwise equally all reviewed individually by ML. The index date among the cases was set to be the date when the cancer was first recorded or when the manual review revealed an earlier date of clinical diagnosis.

Identification of control participants

Selection of control subjects followed a standard incidence density sampling technique.³³ Thus all members of the study cohort were assigned a random date within the study period. If the random date was within that individual's eligible person time, that person was marked as an eligible control subject and we used their random date as the index date. Thereafter we randomly frequency matched 10 000 controls on sex, age (within one year), and calendar year at index date.

Exposure data

We first classified drug exposure as never or ever recorded use of that drug. Ever use was further grouped into current or past use. Current use represented prescriptions for that drug issued within the year prior to the index date while past use represented whenever the most recent prescription for that drug was issued longer than one year before the index date. Among current users, duration of treatment was calculated adding the periods of "consecutive" prescriptions, defined as an interval of less than six months between two prescriptions of the same drug. Treatment duration was grouped into <1 year, 1–3 years, or >3 years. The latter duration category was defined as "long term use". To ascertain the indication for acid suppression, records of all long term users were reviewed by ML, who was kept blinded to the case or control status of the individual. Indications for treatment were grouped into "oesophageal" (reflux symptoms, oesophagitis, hiatal hernia, and Barrett's oesophagus), "peptic ulcer" (gastric ulcer, duodenal ulcer, and peptic ulcer unspecified), or "gastroduodenal symptom" (gastritis, dyspepsia, indigestion, and epigastric pain). A fourth group, "mixed", included unknown indication, prophylactic indication, or indication of mixed "oesophageal", "peptic ulcer", or "gastroduodenal symptom" type. To reduce the possibility that early symptoms of an as yet undetected cancer would affect any of the

Table 1 Selected characteristics among cases and controls

Exposure	Controls (n (%))	Oesophageal adenocarcinoma (n (%))	Gastric cardia adenocarcinoma (n (%))	Gastric non-cardia adenocarcinoma (n (%))
Total	10 000 (100)	287 (100)	195 (100)	327 (100)
Tobacco smoking status				
Non-smoker	5122 (51.2)	132 (46.0)	87 (44.6)	153 (46.8)
Ex-smoker	920 (9.2)	33 (11.5)	28 (14.4)	30 (9.2)
Current smoker	1668 (16.7)	66 (23.0)	34 (17.4)	80 (24.5)
Unknown	2290 (22.9)	56 (19.5)	46 (23.6)	64 (19.6)
Use of alcohol (units/day)				
0–2	3854 (38.5)	107 (37.3)	66 (33.8)	142 (43.4)
3–15	1873 (18.7)	64 (22.3)	39 (20.0)	65 (19.9)
16–34	621 (6.2)	17 (5.9)	18 (9.2)	18 (5.5)
>34	200 (2.0)	12 (4.2)	5 (2.6)	3 (0.9)
Unknown	3452 (34.5)	87 (30.3)	67 (34.4)	99 (30.3)
Body mass index (kg/m ²)				
<20	293 (2.9)	10 (3.5)	3 (1.5)	17 (5.2)
20–24	2429 (24.3)	51 (17.8)	42 (21.5)	80 (24.5)
25–29	2770 (27.7)	98 (34.1)	63 (32.3)	89 (27.2)
≥30	944 (9.4)	42 (14.6)	20 (10.3)	28 (8.6)
Unknown	3564 (35.6)	86 (30.0)	67 (34.4)	113 (34.6)

Table 2 Associations between upper gastrointestinal disorders and risk of adenocarcinoma of the oesophagus, gastric cardia, and gastric non-cardia, presented as odds ratios (OR) and 95% confidence intervals (95% CI)

Exposure	Controls (n (%))	Oesophageal adenocarcinoma		Gastric cardia adenocarcinoma		Gastric non-cardia adenocarcinoma	
		(n (%))	OR (95% CI)*	(n (%))	OR (95% CI)*	(n (%))	OR (95% CI)*
GOR symptoms							
Never	9105 (91.0)	244 (85.0)	1.00 (reference)	164 (84.1)	1.00 (reference)	292 (89.3)	1.00 (reference)
Ever	895 (9.0)	43 (15.0)	1.67 (1.16–2.40)	31 (15.9)	1.51 (0.99–2.30)	35 (10.7)	1.00 (0.69–1.46)
Hiatal hernia							
No	9490 (94.9)	256 (89.2)	1.00 (reference)	179 (91.8)	1.00 (reference)	309 (94.5)	1.00 (reference)
Yes	510 (5.1)	31 (10.8)	2.17 (1.44–3.27)	16 (8.2)	1.28 (0.75–2.22)	18 (5.5)	0.89 (0.54–1.47)
Peptic ulcer							
No	9373 (93.7)	258 (89.9)	1.00 (reference)	171 (87.7)	1.00 (reference)	280 (85.6)	1.00 (reference)
Gastric ulcer	157 (1.6)	7 (2.4)	1.65 (0.76–3.56)	7 (3.6)	2.47 (1.14–5.38)	16 (4.9)	3.32 (1.95–5.65)
Duodenal ulcer	385 (3.8)	18 (6.3)	1.53 (0.93–2.51)	13 (6.7)	1.72 (0.96–3.06)	24 (7.3)	2.07 (1.34–3.19)
Gastric + duodenal ulcer	9 (0.1)	0 (0.0)	NA	0 (0.0)	NA	5 (1.5)	15.16 (4.97–46.26)
Other peptic ulcer†	76 (0.8)	2 (0.7)	0.90 (0.22–3.72)	3 (1.5)	2.12 (0.66–6.80)	2 (0.6)	0.84 (0.20–3.45)
Dyspepsia							
Never	8193 (81.9)	229 (79.8)	1.00 (reference)	136 (69.7)	1.00 (reference)	241 (73.7)	1.00 (reference)
Ever	1807 (18.1)	58 (20.2)	0.90 (0.66–1.24)	59 (30.3)	1.70 (1.22–2.39)	86 (26.3)	1.44 (1.10–1.89)

*OR adjusted for age, sex, calendar year, smoking, alcohol consumption, body mass index, gastro-oesophageal reflux, hiatal hernia, peptic ulcer, and dyspepsia.

†Includes oesophageal ulcer and unspecified peptic ulcer.

GOR, gastro-oesophageal reflux; NA, Not applicable.

considered exposures (that is, protopathic bias) all analyses were performed with exposure and comorbidity history recorded one year or earlier before the index date (that is, one year lag time analysis).

Analysis

Unconditional logistic regression was used to compute odds ratios (ORs) with 95% confidence intervals (CIs). In multivariable analyses, all estimates of risk were adjusted for the following potential confounding factors: tobacco smoking (categorised into four groups, non-smoker, current smoker, ex-smoker, or unknown), alcohol consumption (categorised into five groups, 0–2, 3–15, 16–34, >34 units/day, or unknown, where one unit corresponded to 10 ml or 7.9 g of pure ethanol), body mass index (BMI) (categorised into five groups, <20, 20–24.9, 25–29.9, >30 kg/m², or

unknown), as well as the matching factors age, sex, and calendar year. In a second model, we further adjusted for the occurrence of upper gastrointestinal disorders, including gastro-oesophageal reflux symptoms (categorised as yes or no), hiatal hernia (categorised as yes or no), peptic ulcer (categorised as gastric ulcer, duodenal ulcer, both gastric and duodenal ulcer, other peptic ulcer, and no peptic ulcer), and dyspepsia (categorised as yes or no). All statistical analyses were performed using SAS 8.2, and the PROC GENMOD was used for logistic regression analyses.

RESULTS

Study participants

In 4 340 207 person years of follow up, we identified 2128 patients with a newly diagnosed oesophageal or gastric

Table 3 Associations between use of proton pump inhibitors (PPI) or histamine₂ receptor antagonists (H₂ blockers) and risk of adenocarcinoma of the oesophagus, gastric cardia, and gastric non-cardia, compared with non-users, presented as odds ratios (OR) and 95% confidence intervals (95% CI)

Exposure	Controls (n (%))	Oesophageal adenocarcinoma		Gastric cardia adenocarcinoma		Gastric non-cardia adenocarcinoma	
		(n (%))	OR (95% CI)	(n (%))	OR (95% CI)	(n (%))	OR (95% CI)
Use of PPI							
Never	9387 (93.9)	265 (92.3)	1.00 (reference)	173 (88.7)	1.00 (reference)	291 (89.0)	1.00 (reference)
Past	214 (2.1)	5 (1.7)	0.81 (0.33–1.99)*	8 (4.1)	1.96 (0.94–4.07)*	7 (2.1)	1.02 (0.48–2.20)*
Current (all durations)	399 (4.0)	17 (5.9)	1.51 (0.91–2.50)*	14 (7.2)	1.89 (1.08–3.32)*	29 (8.9)	2.31 (1.55–3.44)*
Current <1 year	246 (2.5)	7 (2.4)	0.84 (0.48–1.50)†		1.06 (0.57–2.00)†		1.75 (1.10–2.79)†
Current 1–3 years			1.05 (0.49–2.25)*	11 (5.6)	2.51 (1.34–4.71)*	17 (5.2)	2.17 (1.31–3.61)*
Current >3 years			0.64 (0.28–1.42)†		1.42 (0.72–2.81)†		1.67 (0.96–2.90)†
Current 1–3 years	117 (1.2)	8 (2.8)	2.34 (1.12–4.89)*	3 (1.5)	1.31 (0.41–4.21)*	8 (2.4)	2.15 (1.03–4.47)*
Current >3 years	36 (0.4)	2 (0.7)	1.22 (0.55–2.72)†		0.72 (0.22–2.42)†		1.61 (0.71–3.61)†
			1.78 (0.42–7.56)*	0 (0.0)	NA	4 (1.2)	3.89 (1.36–11.1)*
			0.87 (0.20–3.87)†				2.95 (0.97–8.97)†
Use of H ₂ blockers							
Never	8335 (83.4)	220 (76.7)	1.00 (reference)	147 (75.4)	1.00 (reference)	245 (74.9)	1.00 (reference)
Past	763 (7.6)	31 (10.8)	1.54 (1.04–2.26)*	19 (9.7)	1.39 (0.86–2.27)*	29 (8.9)	1.26 (0.85–1.87)*
Current (all durations)	902 (9.0)	36 (12.5)	1.55 (1.08–2.22)*	29 (14.9)	1.85 (1.23–2.79)*	53 (16.2)	1.96 (1.44–2.66)*
Current <1 year	413 (4.1)	10 (3.5)	1.20 (0.78–1.84)†		1.06 (0.65–1.72)†		1.41 (0.97–2.05)†
Current 1–3 years			0.92 (0.48–1.75)*	18 (9.2)	2.48 (1.50–4.10)*	31 (9.5)	2.47 (1.67–3.64)*
Current >3 years			0.75 (0.38–1.48)†		1.43 (0.81–2.52)†		1.91 (1.23–2.95)†
Current 1–3 years	221 (2.2)	8 (2.8)	1.42 (0.69–2.93)*	5 (2.6)	1.30 (0.52–3.20)*	10 (3.1)	1.53 (0.80–2.92)*
Current >3 years	268 (2.7)	18 (6.3)	1.03 (0.48–2.21)†		0.73 (0.28–1.88)†		1.06 (0.53–2.12)†
			2.68 (1.62–4.42)*	6 (3.1)	1.33 (0.58–3.03)*	12 (3.7)	1.50 (0.83–2.72)*
			2.10 (1.20–3.68)†		0.73 (0.30–1.76)†		0.93 (0.48–1.80)†

*OR adjusted for age, sex, calendar year, smoking, alcohol consumption, and body mass index.

†OR adjusted for age, sex, calendar year, smoking, alcohol consumption, body mass index, gastro-oesophageal reflux, hiatal hernia, peptic ulcer, and dyspepsia. NA, Not applicable.

Table 4 Associations between acid suppressing drugs (proton pump inhibitors (PPI) or histamine₂ receptor antagonists (H₂ blockers)) and risk of adenocarcinoma of the oesophagus, gastric cardia, and gastric non-cardia, compared with non-users, presented as odds ratios (OR) and 95% confidence intervals (95% CI)

Exposure	Controls (n (%))	Oesophageal adenocarcinoma		Gastric cardia adenocarcinoma		Gastric non-cardia adenocarcinoma	
		(n (%))	OR (95% CI)	(n (%))	OR (95% CI)	(n (%))	OR (95% CI)
Use of PPI or H ₂ blockers combined							
Never	8125 (81.2)	213 (74.2)	1.00 (reference)	140 (71.8)	1.00 (reference)	234 (71.6)	1.00 (reference)
Past	691 (6.9)	26 (9.1)	1.41 (0.93–2.15)*	16 (8.2)	1.32 (0.78–2.23)*	20 (6.1)	0.98 (0.61–1.56)*
Current (all durations)	1184 (11.8)	48 (16.7)	1.57 (1.14–2.17)*	39 (20.0)	1.93 (1.34–2.77)*	73 (22.3)	1.61 (1.12–2.30)*
			1.13 (0.75–1.72)†		1.09 (0.68–1.75)†		1.69 (1.19–2.41)†
Current <1 year	526 (5.3)	11 (3.8)	0.81 (0.44–1.50)*	24 (12.3)	2.69 (1.72–4.19)*	37 (11.3)	2.38 (1.61–3.33)*
			0.65 (0.34–1.26)†		1.54 (0.91–2.61)†		1.90 (1.26–2.88)†
Current 1–3 years	315 (3.2)	11 (3.8)	1.34 (0.72–2.49)*	9 (4.6)	1.63 (0.82–3.24)*	16 (4.9)	1.74 (1.03–2.93)*
			0.95 (0.47–1.85)†		0.88 (0.41–1.88)†		1.38 (0.77–2.47)†
Current >3 years	343 (3.4)	26 (9.1)	2.99 (1.95–4.59)*	6 (3.1)	1.03 (0.45–2.36)*	20 (6.1)	2.00 (1.24–3.20)*
			2.19 (1.30–3.70)†		0.53 (0.21–1.30)†		1.26 (0.71–2.23)†

*OR adjusted for age, sex, calendar year, smoking, alcohol consumption, and body mass index.

†OR adjusted for age, sex, calendar year, smoking, alcohol consumption, body mass index, gastro-oesophageal reflux, hiatal hernia, peptic ulcer, and dyspepsia.

cancer, and 10 000 control persons. The manual review rendered exclusion of 178 patients due to at least one of the reasons stated in the methods section. Of the remaining 1950 patients, 287 with oesophageal adenocarcinoma, 195 with gastric cardia adenocarcinoma, and 327 with gastric non-cardia adenocarcinoma constituted our case groups for final analysis. Among the remaining 1141 cases, 140 had squamous cell oesophageal carcinoma, 482 unspecified histological type of oesophageal cancer, 501 unspecified location of gastric cancer, and 18 adenocarcinoma of either oesophageal or gastric origin. An expected male predominance was found among cases of adenocarcinoma of the oesophagus (79%), gastric cardia (75%), and gastric non-cardia (64%). Also, age distribution was as expected (data not shown). Other characteristics of cases and controls are presented in table 1. A history of smoking was more common among each specific case group compared with controls, while no major differences in alcohol consumption were found between case groups and the control group. A high BMI was more frequent among cases of oesophageal

adenocarcinoma compared with controls and the other case groups (table 1).

Upper gastrointestinal disorders and risk of oesophageal and gastric adenocarcinoma

As presented in table 2, a history of gastro-oesophageal reflux and hiatal hernia were both associated with an approximate twofold increased risk of oesophageal adenocarcinoma. The corresponding increased risk estimates for gastric cardia adenocarcinoma were not statistically significant while no association was found between GORD and risk of gastric non-cardia adenocarcinoma (table 2). Gastric ulcer was associated with an increased risk of both gastric non-cardia (OR 3.32 (95% CI 1.95–5.65)) and gastric cardia adenocarcinoma (OR 2.47 (95% CI 1.14–5.38)), while no increased risk of oesophageal adenocarcinoma was observed (table 2). Patients with a history of duodenal ulcer were at a twofold increased risk of gastric non-cardia adenocarcinoma while dyspepsia was associated with both adenocarcinoma in the gastric cardia and the non-cardia (table 2).

Table 5 Distribution of indications for long term use of acid suppressing drugs (proton pump inhibitors or histamine₂ receptor antagonists) among cases and controls

Indication	Controls (n (%))	Oesophageal adenocarcinoma (n (%))	Gastric cardia adenocarcinoma (n (%))	Gastric non-cardia adenocarcinoma (n (%))
Total	343 (100)	26 (100)	6 (100)	20 (100)
GORD	57 (17)	1 (4)	2 (33)	3 (15)
Oesophagitis	37 (11)	4 (15)	0 (0)	0 (0)
Hiatal hernia	28 (8)	6 (23)	0 (0)	2 (10)
Barrett's	3 (1)	5 (19)	0 (0)	0 (0)
All "oesophageal" indications	125 (36)	16 (62)	2 (33)	5 (25)
Gastric ulcer	9 (3)	0 (0)	1 (17)	3 (15)
Duodenal ulcer	31 (9)	4 (15)	2 (33)	5 (25)
Peptic ulcer, unspecified	36 (10)	2 (8)	0 (0)	3 (15)
All "peptic ulcer" indications	76 (22)	6 (23)	3 (50)	11 (55)
Gastritis	20 (6)	0 (0)	0 (0)	1 (5)
Indigestion	9 (3)	0 (0)	0 (0)	0 (0)
Dyspepsia	63 (18)	0 (0)	1 (17)	2 (10)
Epigastric pain	22 (6)	2 (8)	0 (0)	1 (5)
All "gastroduodenal symptom" indications	114 (33)	2 (8)	1 (17)	4 (20)
Mixed*	28 (8)	2 (8)	0 (0)	0 (0)

*Including unknown indication, prophylactic indication, or indication of mixed "oesophageal", "peptic ulcer", or "gastroduodenal symptom" type.

GORD, gastro-oesophageal reflux disease.

Table 6 Associations between long term use of acid suppressing drugs and risk of adenocarcinoma of the oesophagus compared with non-users stratified by treatment indication, presented as odds ratios (OR) and 95% confidence intervals (95% CI)

Exposure	Controls (n (%))	Oesophageal adenocarcinoma	
		(n (%))	OR (95% CI) [¶]
Indication for long term use of PPI or H ₂ blockers*			
“Oesophageal”†	125 (1.2)	16 (5.6)	5.42 (3.13–9.39)
Other indications‡	218 (2.2)	10 (3.5)	1.74 (0.90–3.34)

*More than 3 years of current use of either proton pump inhibitors (PPI) or histamine₂ receptor antagonists (H₂ blockers).

†Including gastro-oesophageal reflux, oesophagitis, hiatal hernia, or Barrett's oesophagus.

‡Including gastric ulcer, duodenal ulcer and unspecified peptic ulcer, gastritis, dyspepsia, indigestion, epigastric pain, unknown indication, prophylactic indication, or indication of mixed type.

¶All ORs adjusted for age, sex, calendar year, smoking, alcohol consumption, and body mass index.

Acid suppressing drugs and risk of oesophageal and gastric adenocarcinoma

Overall use of H₂ blockers and PPIs was associated with increased risks of both oesophageal and gastric adenocarcinoma, as presented in table 3.

Adjusted analyses of long term users of acid suppressing drugs combined are presented in table 4.

Among patients with more than three years use of acid suppressing drug use there was a threefold increased risk of oesophageal adenocarcinoma (OR 2.99 (95% CI 1.95–4.59)) and a twofold increased risk of gastric non-cardia adenocarcinoma (OR 2.00 (95% CI 1.24–3.20)) compared with non-users. These risk estimates were attenuated in the model including adjustment for upper gastrointestinal disorders (OR 2.19 (95% CI 1.30–3.70) and OR 1.26 (95% CI 0.71–2.23), respectively). No association was found between long term use of acid suppressing drugs and risk of gastric cardia adenocarcinoma. We also analysed the risk of oesophageal cancer including oesophageal cancer cases with unspecified histology and of gastric cancer, adding those with an unspecified site. In the fully adjusted model, the OR of oesophageal cancer among long term users of acid suppressing drugs was 1.61 (95% CI 1.13–2.31) and 1.24 (95% CI 0.88–1.75) for gastric cancer compared with non-users. Treatment indications among users of long term gastric acid suppression are shown in table 5.

Indications categorised as “oesophageal” were more common among cases of oesophageal adenocarcinoma (62%) than among cases of gastric cardia (33%) and

non-cardia adenocarcinoma (25%), or controls (36%). As presented in table 6, long term use of acid suppressing drugs due to oesophageal indications carried a greater than fivefold increased risk of oesophageal adenocarcinoma (OR 5.42 (95% CI 3.13–9.39)) while no statistically significant increased risk was found in the group of long term users with other indications.

Among long term users of acid suppressing drugs, “peptic ulcer” indication was more commonly found among cases that subsequently developed gastric non-cardia (55%) and cardia adenocarcinoma (50%) than cases of oesophageal adenocarcinoma (23%) or controls (22%) (table 5). Long term acid suppressing drug users with a “peptic ulcer” indication presented an increased risk of gastric non-cardia adenocarcinoma (OR 4.66 (95% CI 2.42–8.97)) and a statistically non-significant risk of gastric cardia adenocarcinoma (OR 2.18 (95% CI 0.67–7.03)) compared with non-users (table 7). Long term users with other indications were not associated with gastric cardia or gastric non-cardia adenocarcinoma (table 7). When we used gastric and duodenal ulcer as separate indications, numbers were scarce, but the results were in the same direction as those observed for “peptic ulcer” (data not shown).

DISCUSSION

The results of this study indicate that use of H₂ blockers and PPIs are both markers of an increased risk of oesophageal and gastric adenocarcinoma. However, the increased risk of oesophageal adenocarcinoma and gastric non-cardia adenocarcinoma among persons on long term gastric acid suppressive drugs were highly driven by the indications of acid suppressing treatment. Thus the observed associations could be entirely due to the underlying indication being an independent risk factor of the specified cancer rather than to a harmful effect of the agents per se.

Some methodological considerations should be highlighted. Advantages of our design include the prospectively collected exposure and comorbidity data and the comparatively large sample size. Prospective recording ensures that the information is not affected by the occurrence of cancer. This provides exposure information free of recall bias among both cases and controls, a major concern in case control studies that are inherently dependent on retrospective exposure data collected by personal interviews or in patient administered questionnaires after the cancer diagnosis has been confirmed. The large sample size reduces chance errors and provides an opportunity to study subgroups of interest. Nevertheless, statistical power was limited in some of our subanalyses, in particular when examining associations with gastric cardia adenocarcinoma. The recordings in the database are based on the GPs' routine medical care with a

Table 7 Associations between long term use of acid suppressing drugs and risk of gastric adenocarcinoma compared with non-users stratified by treatment indication, presented as odds ratios (OR) and 95% confidence intervals (95% CI)

Exposure	Controls (n (%))	Gastric cardia adenocarcinoma		Gastric non-cardia	
		(n (%))	OR (95% CI) [¶]	(n (%))	OR (95% CI) [¶]
Indication for long term use of PPI or H ₂ blockers*					
“Peptic ulcer”†	76 (0.8)	3 (1.5)	2.18 (0.67–7.03)	11 (3.4)	4.66 (2.42–8.97)
Other indication‡	267 (2.7)	3 (1.5)	0.68 (0.21–2.14)	9 (2.8)	1.18 (0.60–2.32)

*More than 3 years of current use of either proton pump inhibitors (PPI) or histamine₂ receptor antagonists (H₂ blockers).

†Including gastric ulcer, duodenal ulcer, and unspecified peptic ulcer.

‡Including gastro-oesophageal reflux, oesophagitis, hiatal hernia, Barrett's oesophagus, gastritis, dyspepsia, indigestion, epigastric pain, unknown indication, prophylactic indication, or indication of mixed type.

¶All ORs adjusted for age, sex, calendar year, smoking, alcohol consumption, and body mass index.

certain amount of missing values and misclassification. Such missing data could be differential (that is, differ between cases and controls) regarding some potential confounders. However, we found that missing values were evenly distributed between cases and controls. Furthermore, missing values were included in the analyses as a separate category of each exposure variable, and this category was not associated with any extreme estimate of risk (data not shown). Any remaining exposure misclassification should be non-differential and could, at the most, slightly dilute the risk estimates.

Another potential source of error is case ascertainment and tumour classification. Validation studies of the GPRD have found that over 90% of all referrals are entered into the GP's computer with a diagnosis code that truly reflects the specialist's diagnosis.³¹ Furthermore, our manual review of all computer detected cases together with review of additional information provided by the GPs in a large sample of cases should have acted against major tumour misclassification. Notwithstanding, there remained a considerable number of missing histology classifications in oesophageal cancer and missing subsite classifications in gastric cancer. However, patients with unknown histology or unknown subsite were not found to be associated with any extreme relative risk estimates, indicating that they represent a proportional mix of the categorised oesophageal histology and gastric subsite, respectively.

Another source of error was that the GPRD does not contain adequate information regarding some potential risk factors, including dietary habits, socioeconomic factors, or heredity. However, it is unlikely that any of these factors could explain our results as they will most likely be equally distributed between users and non-users of acid suppressing drugs. If this is true, they would not act as confounding variables in our study. Also, no information on *Helicobacter pylori* status was available. On the other hand, we had access to data regarding several other and possibly more important variables, including clinical upper gastrointestinal disorders. Another limitation is that the computerised database started in the late 1980s and therefore lacks information before that period. The average treatment duration among users of three years and more was 1838 days (that is, slightly more than five years) and only two patients had a registered duration of 10 years or longer. Thus we did not have sufficient recorded information on the risk associated with very long durations (for example, greater than five years). Finally, we were unable to capture exposure to over the counter acid suppressing drugs but the impact of this possible error has been reported to be negligible, especially when the exposure of interest is long term use.³⁴

In line with most previous findings, our results confirm that gastro-oesophageal reflux symptoms, hiatal hernia, and oesophagitis increase the risk of adenocarcinoma of the oesophagus, and to a lesser degree of the gastric cardia.^{7-9 11 35} Hopes have been raised that reduction of gastric acid in the oesophagus, either by antireflux surgical procedure or pharmacological treatment, could reduce the risk of developing oesophageal adenocarcinoma. To date, no strong evidence of a protective effect of antireflux surgery¹⁰ or antireflux pharmacotherapy⁷⁻⁹ against oesophageal adenocarcinoma can be found however, and our study does not provide any evidence in favour of a protective effect. Our finding of increased risks of oesophageal adenocarcinoma among long term users of acid suppressing drugs is in agreement with the literature, although to our knowledge no previous prospective study has examined the association between use of PPIs and risk of oesophageal and gastric adenocarcinoma. The association was limited to current long term users, which should take care of protopathic bias (that

is, an as yet undiagnosed cancer prompting the need for acid suppression).

Three case control studies^{7 9 28} and one cohort study²² have shown that treatment with H₂ blockers is associated with an increased risk of oesophageal adenocarcinoma. However, after adjustment for GORD, no increased risk remained in the study by Chow and colleagues.⁷ A potential limitation of some of these studies was their inability to adjust for confounding by indication (that is, the inability to distinguish the effect of H₂ blockers on cancer risk from the effect of the conditions for which they were prescribed). The fact that gastro-oesophageal reflux is the strongest independent risk factor of oesophageal adenocarcinoma⁸ and at the same time one of the most common indications for long term acid suppression, could fully explain the reported associations. Indeed, we had access to valid prospectively recorded information on the indication for acid suppression, giving us the possibility of assessing separately different indications for long term use of H₂ blockers and PPIs. Our findings clearly indicated that the increased risk of oesophageal adenocarcinoma was much more dependent on the specific indication for acid suppressing treatment rather than on the treatment per se.

We found that a history of gastric ulcer was associated with an increased risk of gastric adenocarcinoma but not with adenocarcinoma of the oesophagus, results in line with previous findings.^{12 14-18} The relation found between duodenal ulcer and gastric adenocarcinoma is, however, in conflict with previous findings^{14 15 17}; this could be due to the limited number of cases or some misclassification of ulcer site. Peptic ulcer is also a common reason for using acid suppressive drugs. Concerns have been raised that reduction of gastric acidity could increase the risk of gastric cancer,^{21 23 24} possibly along the carcinogenic sequence suggested by Correa,³⁶ (that is, via inducing atrophic gastritis¹⁹ and intestinal metaplasia to dysplasia and carcinoma). Acid suppression has been shown to increase the rate of progression of *H. pylori* gastritis to multifocal atrophic gastritis,¹⁹ and to induce hypergastrinaemia, which has trophic effects on gastric mucosa.^{20 23 37} Clinical studies evaluating the effects of long term use of acid suppressive therapy have, however, reported lack of progressive changes (that is, dysplasia and neoplasia) in the gastric mucosal histology.^{38 39} Several observational studies have addressed the risk of gastric cancer among users of H₂ blockers^{22 25-27} and found a positive association which, however, was compelled within the first years of use, arguing against a causal association. We found that users of both H₂ blockers and PPIs were at an increased risk of gastric adenocarcinoma. When combining the use of either H₂ blockers or PPIs, the risk estimates of gastric cardia adenocarcinoma were mainly limited to short term users while the risk of gastric non-cardia adenocarcinoma remained elevated for long term users also, arguing against protopathic bias as an explanation for the latter relationship.

Our review revealed that the treatment indication of peptic ulcer disease was clearly associated with an increased risk of gastric non-cardia adenocarcinoma among long term users of acid suppressing drugs. Furthermore, peptic ulcer disease constituted 55% (11/20) of all long term indications for acid suppression among patients that subsequently developed gastric non-cardia adenocarcinoma, while the corresponding percentage was 22% (76/343) among controls. As shown in table 5, numbers were too small to validly report the association by ulcer site. Patients treated long term with acid suppressing drugs for other reasons (that is, gastro-oesophageal reflux or dyspeptic symptoms) were not associated with an increased risk of gastric non-cardia adenocarcinoma. There are, in theory, two different explanations for the relationship: (1) confounding by indication (that is, acid

suppressing drugs were prescribed mainly to treat risk factors for gastric non-cardia adenocarcinoma, for example, gastric ulcer), and (2) acid suppressing drugs are harmful and lead to an increased risk of gastric non-cardia adenocarcinoma, but mainly confined to patients treated for peptic ulcer disease. Our study could not prove which explanation was true even though confounding by indication seems the most plausible.

In conclusion, this large population based observational study revealed that long term use of gastric acid suppressing drugs is a marker of an increased risk of adenocarcinoma of the oesophagus, gastric cardia, and non-cardia. However, the association with these three types of upper gastrointestinal adenocarcinoma were strongly dependent on specific treatment indications that at the same time are known major risk factors for the respective adenocarcinoma. Even though we cannot with certainty exclude the possibility that very long treatment durations with these drugs could increase per se the risk of one of these adenocarcinomas, our results are most compatible with the hypothesis that confounding by indication is the "mechanism" responsible for the observed associations.

ACKNOWLEDGEMENTS

This study was financially supported by AstraZeneca R&D, Sweden, by the Swedish Cancer Society, and by the Swedish Research Council. AstraZeneca R&D, Swedish Cancer Society, and the Swedish Research Council did not have any influence on study design or conduct of the study, or collection, management, analysis, or interpretation of data, and did not participate in preparation, review, or approval of the manuscript or submission.

Authors' affiliations

L A García Rodríguez, Centro Español de Investigación Farmacoepidemiológica, Madrid, Spain

J Lagergren, M Lindblad, Unit of Oesophageal and Gastric Research, Department of Molecular Medicine and Surgery, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden

Conflict of interest: None declared.

REFERENCES

- Devesa SS, Blot WJ, Fraumeni JF Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer* 1998;**83**:2049-53.
- Bollschweiler E, Wolfgarten E, Gutschow C, et al. Demographic variations in the rising incidence of esophageal adenocarcinoma in white males. *Cancer* 2001;**92**:549-55.
- Hansson LE, Sjöström P, Nyrén O. Increasing incidence of both major histological types of esophageal carcinomas among men in Sweden. *Int J Cancer* 1993;**54**:402-7.
- Parkin DM. Global cancer statistics in the year 2000. *Lancet Oncol* 2001;**2**:533-43.
- Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med* 2003;**349**:2241-52.
- Kelley JR, Duggan JM. Gastric cancer epidemiology and risk factors. *J Clin Epidemiol* 2003;**56**:1-9.
- Chow WH, Finkle WD, McLaughlin JK, et al. The relation of gastroesophageal reflux disease and its treatment to adenocarcinomas of the esophagus and gastric cardia. *JAMA* 1995;**274**:474-7.
- Lagergren J, Bergström R, Lindgren A, et al. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 1999;**340**:825-31.
- Farrow DC, Vaughan TL, Sweeney C, et al. Gastroesophageal reflux disease, use of H2 receptor antagonists, and risk of esophageal and gastric cancer. *Cancer Causes Control* 2000;**11**:231-8.
- Ye W, Chow WH, Lagergren J, et al. Risk of adenocarcinomas of the esophagus and gastric cardia in patients with gastroesophageal reflux diseases and after antireflux surgery. *Gastroenterology* 2001;**121**:1286-93.
- Wu AH, Tseng CC, Bernstein L. Hiatal hernia, reflux symptoms, body size, and risk of esophageal and gastric adenocarcinoma. *Cancer* 2003;**98**:940-8.
- Lundegårdh G, Adami HO, Helmick C, et al. Stomach cancer after partial gastrectomy for benign ulcer disease. *N Engl J Med* 1988;**319**:195-200.
- Parsonnet J, Friedman GD, Vandersten DP, et al. Helicobacter pylori infection and the risk of gastric carcinoma. *N Engl J Med* 1991;**325**:1127-31.
- Hansson LE, Nyrén O, Hsing AW, et al. The risk of stomach cancer in patients with gastric or duodenal ulcer disease. *N Engl J Med* 1996;**335**:242-9.
- Mollay RM, Sonnenberg A. Relation between gastric cancer and previous peptic ulcer disease. *Gut* 1997;**40**:247-252.
- La Vecchia C, Braga C, Negri E, et al. Risk of stomach cancer in patients with gastric or duodenal ulcer. *Eur J Cancer Prev* 1997;**6**:20-3.
- Hansson LE. Risk of stomach cancer in patients with peptic ulcer disease. *World J Surg* 2000;**24**:315-20.
- Uemura N, Okamoto S, Yamamoto S, et al. Helicobacter pylori infection and the development of gastric cancer. *N Engl J Med* 2001;**345**:784-9.
- Kuipers EJ, Lundell L, Klinkenberg-Knol EC, et al. Atrophic gastritis and Helicobacter pylori infection in patients with reflux esophagitis treated with omeprazole or fundoplication. *N Engl J Med* 1996;**334**:1018-22.
- Havu N. Enterochromaffin-like cell carcinoids of gastric mucosa in rats after life-long inhibition of gastric secretion. *Digestion* 1986;**35**(suppl 1):P42-55.
- Elder JB, Ganguli PC, Gillespie IE. Cimetidine and gastric cancer. *Lancet* 1979;**1**:1005-6.
- Colin-Jones DG, Langman MJ, Lawson DH, et al. Post-cimetidine surveillance for up to ten years: incidence of carcinoma of the stomach and oesophagus. *Q J Med* 1991;**78**:13-19.
- Waldum HL, Brenna E, Sandvik AK. Long-term safety of proton pump inhibitors: risks of gastric neoplasia and infections. *Expert Opin Drug Saf* 2002;**1**:29-38.
- Gillen D, McColl KE. Problems associated with the clinical use of proton pump inhibitors. *Pharmacol Toxicol* 2001;**89**:281-6.
- La Vecchia C, Negri E, D'Avanzo B, et al. Histamine-2-receptor antagonists and gastric cancer risk. *Lancet* 1990;**336**:355-7.
- La Vecchia C, Negri E, Franceschi S, et al. Histamine-2-receptor antagonists and gastric cancer: update and note on latency and covariates. *Nutrition* 1992;**8**:177-81.
- Johnson AG, Jick SS, Perera DR, et al. Histamine-2 receptor antagonists and gastric cancer. *Epidemiology* 1996;**7**:434-6.
- Suleiman UL, Harrison M, Britton A, et al. H2-receptor antagonists may increase the risk of cardio-oesophageal adenocarcinoma: a case-control study. *Eur J Cancer Prev* 2000;**9**:185-91.
- Signorello LB, McLaughlin JK, Lipworth L, et al. Confounding by indication in epidemiologic studies of commonly used analgesics. *Am J Ther* 2002;**9**:199-205.
- Lindblad M, Lagergren J, García Rodríguez LA. Nonsteroidal anti-inflammatory drugs and risk of esophageal and gastric cancer. *Cancer Epidemiol Biomarkers Prev* 2005;**14**:444-50.
- Jick H, Jick SS, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. *BMJ* 1991;**302**:766-8.
- Jick SS, Kaye JA, Vasilakis-Scaramozza C, et al. Validity of the general practice research database. *Pharmacotherapy* 2003;**23**:686-9.
- Rothman KJ. *Epidemiology: an introduction*. New York: Oxford University Press Inc, 2002:76-86.
- Ulickas Yood M, Rothman KJ, Johnson CC, et al. Using prescription claims for drugs available over-the-counter (OTC). *Pharmacoepidemiol Drug Saf* 2000;**9**:S37.
- Avidan B, Sonnenberg A, Schnell TG, et al. Hiatal hernia size, Barrett's length, and severity of acid reflux are all risk factors for esophageal adenocarcinoma. *Am J Gastroenterol* 2002;**97**:1930-6.
- Correa P. Helicobacter pylori and gastric carcinogenesis. *Am J Surg Pathol* 1995;**19**(suppl 1):P37-43.
- Laine L, Ahnen D, McClain C, et al. Review article: potential gastrointestinal effects of long-term acid suppression with proton pump inhibitors. *Aliment Pharmacol Ther* 2000;**14**:651-68.
- Klinkenberg-Knol EC, Nelis F, Dent J, et al. Long-term omeprazole treatment in resistant gastroesophageal reflux disease: efficacy, safety, and influence on gastric mucosa. *Gastroenterology* 2000;**118**:661-9.
- Lamberts R, Brunner G, Solcia E. Effects of very long (up to 10 years) proton pump blockade on human gastric mucosa. *Digestion* 2001;**64**:205-13.