

Gastroesophageal reflux disease, use of H₂ receptor antagonists, and risk of esophageal and gastric cancer

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Abstract

Objective: The incidence of esophageal adenocarcinoma has risen rapidly in the past two decades, for unknown reasons. The goal of this analysis was to determine whether gastroesophageal reflux disease (GERD) or the medications used to treat it are associated with an increased risk of esophageal or gastric cancer, using data from a large population-based case-control study.

Methods: Cases were aged 30–79 years, newly diagnosed with esophageal adenocarcinoma (n = 293), esophageal squamous cell carcinoma (n = 221), gastric cardia adenocarcinoma (n = 261), or non-cardia gastric adenocarcinoma (n = 368) in three areas with population-based tumor registries. Controls (n = 695) were chosen by random digit dialing and from Health Care Financing Administration rosters. Data were collected using an in-person structured interview.

Results: History of gastric ulcer was associated with an increased risk of non-cardia gastric adenocarcinoma (OR 2.1, 95% CI 1.4–3.2). Risk of esophageal adenocarcinoma increased with frequency of GERD symptoms; the odds ratio in those reporting daily symptoms was 5.5 (95% CI 3.2–9.3). Ever having used H₂ blockers was unassociated with esophageal adenocarcinoma risk (OR 0.9, 95% CI 0.5–1.5). The odds ratio was 1.3 (95% CI 0.6–2.8) in long-term (4 or more years) users, but increased to 2.1 (95% CI 0.8–5.6) when use in the 5 years prior to the interview was disregarded. Risk was also modestly increased among users of antacids. Neither GERD symptoms nor use of H₂ blockers or antacids was associated with risk of the other three tumor types.

Conclusions: Individuals with long-standing GERD are at increased risk of esophageal adenocarcinoma, whether or not the symptoms are treated with H₂ blockers or antacids.

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Introduction

The incidence of adenocarcinoma of the esophagus has risen more rapidly than that of any other tumor type during the past 20 years, for reasons that are unexplained [1]. Whereas in the 1970s adenocarcinoma represented only a small fraction of esophageal malignancies, it now represents over 50% of all esophageal tumors. Adenocarcinomas occurring in the gastric cardia and gastroesophageal junction have also increased in incidence, although not as dramatically as in the esophagus [1].

Given the rapid rate of change in the incidence rate of this disease, attention has focused on environmental exposures that may be responsible, and that have changed concomitantly over the past two decades [2–10]. Most esophageal adenocarcinomas arise in patients with a long history of gastroesophageal reflux disease (GERD) symptoms. It is reasonable to hypothesize that changes in the incidence of esophageal adenocarcinoma reflect changes in the prevalence of GERD, or changes in the use of medications to treat it.

The H₂ receptor antagonists cimetidine, ranitidine, famotidine, and nizatidine are frequently and effectively used to treat GERD symptoms. These medications became available in the US beginning in 1977. Duodenal and gastric ulcers were the primary indications for H₂ blocker use in the first years following their introduction. Increasingly thereafter, H₂ blockers were prescribed for other indications including GERD symptoms, non-ulcer dyspepsia, and other nonspecific gastrointestinal discomfort. The drugs have since become among the most widely prescribed medications in the US [11]. Since 1995, H₂ blockers have been available over the counter, and are widely advertised.

H₂ blockers suppress gastric acid secretion, rendering the gastric contents more alkaline. The increased gastric pH is accompanied by alterations in gut flora, and has engendered concern about possible carcinogenic effects in the stomach because of the resulting increased nitrosation of gastric contents [12]. Cimetidine is itself nitrosated in the stomach to form nitrosocimetidine, which chemically resembles the potent carcinogen N-nitroso-N-methylnitroguanidine (MNNG) [13], and as such has been the focus of particular attention. A number of studies have investigated whether the incidence of gastric cancer is increased among users of cimetidine and other H₂ blockers [14–20]. However, there has been little research on the possible effects of H₂ blockers on esophageal cancer risk. We undertook the present analysis to characterize the associations between GERD or its treatment and the risk of esophageal adenocarcinoma or other tumors of the esophagus or stomach.

Materials and methods

Detailed descriptions of the study methods have been published elsewhere [2]. Briefly, individuals diagnosed with any of four tumor types (esophageal adenocarcinoma, esophageal squamous cell carcinoma, gastric cardia adenocarcinoma, or non-cardia gastric adenocarcinoma) were recruited using rapid case identification mechanisms from three areas with population-based tumor registries: the state of Connecticut, a 15-county area of New Jersey, and a three-county area of western Washington. Patients were eligible for the study if they were between the ages of 30 and 79 years, and diagnosed from 1 February 1993 through 31 January 1995 for Connecticut, 1 April 1993 through 30 November 1994 for New Jersey, or 1 March 1993 through 28 February 1995 for Washington. All individuals diagnosed with adenocarcinoma of the esophagus or gastric cardia were eligible for the study; a sample of individuals with the other two tumor types was selected for eligibility by frequency matching to the expected distribution of the esophageal and gastric cardia adenocarcinoma cases on geographic area and 5-year age group in Connecticut, New Jersey, and Washington; on sex in New Jersey and Washington; and on race (white or other) in New Jersey. Study pathologists reviewed pathologic material on over 99% of cases to make final eligibility determinations. Controls were selected by random digit dialing (for controls ages 30–64 years) or through the rosters of the Health Care Financing Administration (for controls ages 65–79 years), and were similarly frequency matched to the esophageal and gastric cardia adenocarcinoma cases. Study procedures were approved by the Institutional Review Boards at the participating institutions, and each study subject provided signed informed consent.

We obtained interview data for 77.1% of eligible cases and 73.7% of eligible controls. Interviews were conducted with the closest next of kin (usually the spouse), rather than the study subject, for 31.1% of cases and 3.4% of controls. Cases and controls completed a structured in-person interview to collect information on medication use and other risk factors including demographic characteristics, smoking, alcohol consumption, medical history, and occupation. Respondents were asked about the frequency and duration of GERD symptoms including severe heartburn (defined as heartburn so painful that it awoke the subjects or prevented them from sleeping) or acid regurgitation (defined as a sour taste from contents of the stomach backing up into the mouth or throat). Prompted by show-cards that included both brand and generic names, subjects were asked whether they had used specific H₂

receptor antagonists at least once a week for 1 month or more. Subjects answering affirmatively to the initial question were asked which medication(s) they took, the age or year at which they started and stopped using the medication, the total duration of use, and how often the medication was taken during that time. Only exposures occurring before a specified reference date were included; that date was 1 year before interview for controls, and the earlier of 1 year before interview or the diagnosis date for cases. Exposed persons were classified as current users if they reported taking the medications at the reference date, and former users otherwise. Additional questions asked about the use of other prescription or over-the-counter medications for ulcers, heartburn, and a variety of other indications.

Because early symptoms of cancer might have led cases to seek out medical attention or to take the medications of interest in the analysis, we also evaluated exposure using lagged reference dates 2 and 5 years before the original reference date. In those analyses any exposure time accrued after the lagged reference date was excluded from the total duration of use.

Unconditional logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals comparing each of the four case groups to the controls. The analyses were adjusted for age, gender, study center, and cigarette smoking (five categories including never smokers and quartiles of pack-years). Analyses of medication use were also adjusted for body mass index (BMI) (quartiles), history of gastric or duodenal ulcer (ever vs. never), and GERD symptom frequency, categorized as never, once or twice per year, three to 12 times per year, 13–104 times per year, 105–364 times per year, or daily. In addition to those variables, analyses of esophageal squamous cell carcinoma were adjusted for alcohol consumption (none, ≤ 1 drink per day, > 1 but ≤ 2 drinks per day, > 2 but ≤ 6 drinks per day, or > 6 drinks per day), and analyses of esophageal adenocarcinoma were adjusted for history of hiatal hernia (ever vs. never).

Results

Demographic and other characteristics of the case and control groups have been described elsewhere [2, 5, 9, 21]. Among control subjects, 79.9% were male, compared to 83.6% of esophageal adenocarcinoma, 85.4% of gastric cardia adenocarcinoma, 79.6% of esophageal squamous cell carcinoma, and 69.0% of non-cardia gastric adenocarcinoma cases. Compared to controls, current smokers were more common in all four case groups, but particularly esophageal squamous cell

carcinoma. Cases of all four tumor types tended to have both lower income and lower education than controls [2].

Because of the nature of the exposures under investigation, we believed that proxy respondents would have limited recall of the index subject's exposure history. Analyses were conducted with and without the information provided by proxies. The observed pattern of results was similar across both analyses, but risk estimates obtained from analyses with proxies included were generally attenuated toward the null compared to estimates from analyses that excluded proxies. In the results presented here, we chose to omit subjects for whom only proxy information was available, to avoid the nondifferential misclassification introduced by incomplete knowledge on the part of surrogate respondents.

Risk of esophageal adenocarcinoma increased with increasing frequency of GERD symptoms; subjects reporting daily symptoms were at a 5.5-fold increased risk of the disease (95% CI 3.2–9.3) (Table 1). Increasing duration of GERD symptoms was also associated with esophageal adenocarcinoma risk, but with a less pronounced dose–response relationship than for increasing frequency of symptoms (Table 1). Risk of adenocarcinoma in the gastric cardia or elsewhere in the stomach was not increased among individuals with GERD. GERD symptoms were negatively associated with risk of esophageal squamous cell carcinoma, but there was no evidence of a dose–response relationship as the frequency or duration of symptoms increased.

Risk of non-cardia gastric adenocarcinoma was increased in individuals with a history of gastric ulcer (OR 2.1, 95% CI 1.4–3.2), but risk of the other tumor types was unaffected (Table 1). The increased risk of non-cardia gastric adenocarcinoma persisted when ulcers diagnosed within the 2 years or 5 years before reference date were excluded [ORs 2.0 (95% CI 1.3–3.1) and 1.7 (95% CI 1.1–2.7) respectively]. Duodenal ulcers were not significantly associated with any of the tumor types. Risk of esophageal adenocarcinoma, but not the other tumor types, was significantly increased among individuals reporting a history of hiatal hernia, as well as esophagitis or esophageal ulcers (Table 1).

The age, sex, and study center-adjusted OR for esophageal adenocarcinoma associated with ever use of an H₂ blocker was 1.6 (95% CI 1.2–2.0). After further adjustment for cigarette smoking, BMI, GERD symptom frequency, history of duodenal or gastric ulcers, and history of hiatal hernia, the OR for esophageal adenocarcinoma was 0.9 (95% CI 0.5–1.5) in individuals who reported ever using H₂ blockers before the reference date, compared to never users of the drugs. When

Table 1. Odds ratios (ORs) for history of selected gastrointestinal conditions and risk of esophageal and gastric cancer, by histologic type

	Controls			Esophageal adenocarcinoma			Gastric cardia adenocarcinoma			Esophageal squamous cell carcinoma			Non-cardia gastric adenocarcinoma		
	n	n	OR ^b	95% CI	n	OR ^b	95% CI	n	OR ^b	95% CI	n	OR ^b	95% CI		
<i>Frequency of GERD symptoms^a</i>															
Never	355	72	1.0	–	122	1.0	–	107	1.0	–	146	1.0	–		
1 or 2 times/year	84	8	0.5	(0.2–1.0)	5	0.2	(0.1–0.4)	7	0.3	(0.1–0.8)	11	0.3	(0.2–0.7)		
3–12 times/year	76	16	1.2	(0.6–2.2)	15	0.6	(0.3–1.1)	8	0.5	(0.2–1.4)	26	0.9	(0.6–1.6)		
13–104 times/year	78	35	2.0	(1.2–3.2)	18	0.6	(0.3–1.0)	14	0.5	(0.3–1.1)	28	0.8	(0.5–1.4)		
105–364 times/year	38	25	3.4	(1.9–6.1)	12	0.9	(0.5–1.9)	3	0.2	(0.1–0.9)	20	1.3	(0.7–2.3)		
365+ /year	40	42	5.5	(3.2–9.3)	20	1.2	(0.7–2.2)	5	0.5	(0.2–1.4)	23	1.4	(0.8–2.5)		
<i>Duration of GERD symptoms^a</i>															
Never	336	99	1.0	–	144	1.0	–	154	1.0	–	188	1.0	–		
≤ 10 years	186	81	1.6	(1.0–2.4)	59	0.5	(0.3–0.8)	32	0.5	(0.3–0.9)	99	1.0	(0.7–1.4)		
10.01–20 years	63	43	2.7	(1.6–4.5)	18	0.4	(0.2–0.8)	11	0.3	(0.1–0.7)	25	0.7	(0.4–1.2)		
20.01–30 years	36	21	2.3	(1.2–4.5)	17	0.9	(0.5–1.9)	7	1.2	(0.4–3.5)	16	1.0	(0.5–2.0)		
> 30 years	36	27	2.7	(1.4–5.0)	9	0.5	(0.2–1.2)	1	0.1	(0.0–0.6)	15	0.7	(0.4–1.5)		
<i>Hiatal hernia</i>															
No	569	120	1.0	–	166	1.0	–	128	1.0	–	226	1.0	–		
Yes	98	72	3.7	(2.5–5.5)	24	0.8	(0.5–1.4)	11	0.5	(0.2–0.9)	26	0.6	(0.3–0.9)		
<i>Esophagitis or esophageal ulcer</i>															
No	656	188	1.0	–	184	1.0	–	143	1.0	–	246	1.0	–		
Yes	15	10	2.6	(1.1–6.1)	8	1.9	(0.8–4.8)	1	0.3	(0.0–2.7)	8	1.4	(0.6–3.4)		
<i>Gastric ulcer</i>															
No	607	177	1.0	–	175	1.0	–	125	1.0	–	202	1.0	–		
Yes	62	19	0.9	(0.5–1.5)	17	0.8	(0.4–1.4)	16	0.9	(0.5–1.8)	48	2.1	(1.4–3.2)		
<i>Duodenal ulcer</i>															
No	626	176	1.0	–	182	1.0	–	136	1.0	–	221	1.0	–		
Yes	43	19	1.5	(0.8–2.7)	10	0.8	(0.4–1.6)	4	0.3	(0.1–1.2)	28	1.6	(0.9–2.6)		

^a Defined as severe heartburn or acid regurgitation.

^b All analyses are adjusted for center, sex, age, and cigarette smoking. Analyses of esophageal squamous cell carcinoma are adjusted for alcohol consumption in addition to the variables above. Proxy respondents are excluded from all analyses.

use within 2 or 5 years before the reference date was excluded, the respective OR were modestly and nonsignificantly elevated [OR 1.3 (95% CI 0.7–2.5), and OR 1.7 (95% CI 0.8–3.5)].

Duration of use of H₂ blockers was categorized as none, short-term (less than 4 years), or long-term (4 or more years). Odds ratios for esophageal adenocarcinoma were 0.7 and 1.3 in short- and long-term users, respectively (Table 2). The OR for long-term use increased to 1.9 (95% CI 0.8–4.4) and 2.1 (95% CI 0.8–5.6) with 2- and 5-year lag periods, respectively, but neither 95% confidence interval excluded 1.0 (Table 2).

Risk of esophageal adenocarcinoma associated with the use of cimetidine was similar to that for all H₂ blockers as a group. Excluding use within the 5 years before the reference date, OR were 1.2 (95% CI 0.4–3.1) for cimetidine use of less than 4 years duration and 2.3 (0.8–7.1) for use of 4 years or more.

Use of H₂ blockers was not associated with risk of gastric adenocarcinoma occurring either in the cardia or elsewhere in the stomach, regardless of lag periods (Table 2). Risk of esophageal squamous cell carcinoma was nonsignificantly lower among long-term users of H₂ blockers than among individuals who did not use the drugs, but this association was based upon only three exposed cases.

The association between use of H₂ blockers and risk of esophageal adenocarcinoma was not modified by age or by history of gastric or duodenal ulcer, but was limited to never and former cigarette smokers, rather than current smokers. Odds ratios for 4 or more years of use were 2.8 (95% CI 0.9–8.3) among never and former smokers, and 0.3 (95% CI 0.0–5.3) among current smokers (test for homogeneity $p = 0.06$). The excess risk associated with long durations of H₂ blocker use was also more pronounced among women [OR 8.6 (95% CI 0.8–94.1)] than among men [OR 1.5

Table 2. Odds ratios (OR) for use of H₂ blockers^a and risk of esophageal and gastric cancer, by histologic type

Duration of H ₂ blocker use	Controls n	Esophageal adenocarcinoma			Gastric cardia adenocarcinoma			Esophageal squamous cell carcinoma			Non-cardia gastric adenocarcinoma		
		n	OR ^b	95% CI	n	OR ^b	95% CI	n	OR ^b	95% CI	n	OR ^b	95% CI
<i>No lag</i>													
None	554	147	1.0	–	161	1.0	–	125	1.0	–	181	1.0	–
1–47 months	67	26	0.7	(0.4–1.3)	21	1.0	(0.6–1.9)	10	0.9	(0.4–2.3)	42	1.4	(0.9–2.4)
48+ months	33	21	1.3	(0.6–2.8)	6	0.7	(0.3–1.8)	3	0.2	(0.04–1.4)	17	0.8	(0.4–1.7)
<i>2-year lag</i>													
None	554	147	1.0	–	161	1.0	–	125	1.0	–	181	1.0	–
1–47 months	29	14	0.9	(0.4–2.1)	9	1.0	(0.4–2.4)	7	1.5	(0.5–5.0)	18	1.1	(0.6–2.3)
48+ months	24	19	1.9	(0.8–4.4)	5	1.0	(0.3–3.1)	1	0.2	(0.02–1.5)	14	1.0	(0.4–2.1)
<i>5-year lag</i>													
None	554	147	1.0	–	161	1.0	–	125	1.0	–	181	1.0	–
1–47 months	21	12	1.3	(0.5–3.4)	3	0.5	(0.1–1.8)	2	0.3	(0.1–2.0)	10	0.9	(0.4–2.1)
48+ months	18	14	2.1	(0.8–5.6)	5	1.6	(0.5–5.0)	1	0.4	(0.04–4.4)	10	0.9	(0.4–2.3)

^a Includes cimetidine, ranitidine, famotidine, and nizatidine.

^b All analyses are adjusted for age, center, sex, cigarette smoking, history of ulcers, body mass index, and GERD symptom frequency. In addition to those variables, analyses of esophageal adenocarcinoma are adjusted for history of hiatal hernia, and analyses of esophageal squamous cell carcinoma are adjusted for alcohol consumption. Proxy respondents are excluded from all analyses.

(95% CI 0.4–5.0)], although this difference could be due to chance (test for homogeneity $p = 0.39$). The pattern of results was similar, with somewhat higher risks for women and for never and former smokers, when the exposure was limited to cimetidine alone (data not shown).

To investigate the possibility that the underlying condition for which H₂ blockers were prescribed, rather than the drugs themselves, is responsible for the increased cancer risk, we conducted separate analyses in those individuals who reported frequent severe GERD (at least monthly) and in those with severe GERD infrequently (less than monthly) or never. The association between H₂ blocker use and esophageal adenocarcinoma risk was largely restricted to the group reporting severe GERD rarely or never, although the difference between the two groups was statistically nonsignificant (p for interaction = 0.33) (Table 3).

After adjustment for GERD symptom frequency and history of ulcers as well as cigarette smoking, age, sex, and study center, use of over-the-counter antacids was associated with an increased risk of esophageal and gastric cardia adenocarcinoma, but not other esophageal or gastric carcinoma (Table 4). These associations were not modified by age or cigarette smoking, but were somewhat more pronounced among women than among men (p value for interaction = 0.14). The OR for long-term use of over-the-counter antacids were 5.7 (95% CI 1.1–29.8) in women and 1.8 (1.0–3.2) in men.

Discussion

In this large population-based case-control study, both frequent GERD symptoms and a history of hiatal hernia were associated with increased risk of esophageal adenocarcinoma, but not of other cancers arising in the esophagus and stomach. Risk of non-cardia gastric adenocarcinoma was increased among subjects with a history of gastric ulcer. The latter OR remained elevated when we excluded ulcers diagnosed in the 2 or 5 years before the reference date, suggesting that the association cannot be attributed to detection bias arising from diagnostic procedures conducted among cases. After adjustment for GERD symptoms and other variables, risk of esophageal adenocarcinoma was moderately but largely nonsignificantly increased among long-term users of H₂ blockers and over-the-counter antacids.

The association between use of H₂ blockers and risk of esophageal adenocarcinoma in these data is unlikely to be an artifact of the treatment of early cancer symptoms. If such were the case, one would expect the association to be weaker when use in the 2 years prior to the reference date was excluded, and possibly weaker still after the exclusion of any use in the 5 years prior to the reference date. In our data the OR for long-term use increased as successively longer periods before diagnosis were excluded from the analysis. This trend is consistent with a true effect of use on disease risk, but it does not rule out the possibility that the indications for H₂ blocker use, rather than the drugs themselves, are responsible for the observed risk. Such an effect would

Table 3. Odds ratios (OR) for use of H₂ blockers^a and risk of esophageal adenocarcinoma, by history of GERD symptoms^b

Use of H ₂ blockers	Severe GERD less than monthly or never				Severe GERD at least monthly				
	Controls (n)	Cases (n)	OR ^c	95% CI	Use of H ₂ blockers	Controls (n)	Cases (n)	OR ^c	95% CI
None	443	74	1.0	–	None	111	73	1.0	–
1–47 months	8	2	3.1	(0.5–19.3)	1–47 months	13	10	0.9	(0.3–2.6)
48+ months	7	3	5.2	(0.9–30.6)	48+ months	11	11	1.3	(0.4–3.9)

p for interaction = 0.33

^a Any exposure occurring less than 5 years before reference date is excluded.

^b Defined as any history of heartburn so painful that it awoke the subject or prevented him/her from sleeping, or a sour taste from contents of the stomach backing up into the mouth or throat.

^c Adjusted for age, center, sex, cigarette smoking, history of ulcers, history of hiatal hernia, and BMI. Proxy respondents are excluded from all analyses.

Table 4. Odds ratios (OR) for use of over-the-counter antacids and risk of esophageal and gastric cancer, by histologic type

Duration of Over-the-counter antacid use	Controls n	Esophageal adenocarcinoma			Gastric cardia adenocarcinoma			Esophageal squamous cell carcinoma			Non-cardia gastric adenocarcinoma		
		n	OR ^a	95% CI	n	OR ^a	95% CI	n	OR ^a	95% CI	n	OR ^a	95% CI
<i>No lag</i>													
None	513	98	1.0	–	124	1.0	–	109	1.0	–	172	1.0	–
1–47 months	40	15	1.8	(0.9–3.6)	17	1.9	(0.9–3.7)	13	2.1	(0.9–5.0)	22	1.3	(0.7–2.4)
48+ months	115	79	1.9	(1.1–3.1)	49	1.8	(1.1–3.0)	15	0.9	(0.4–2.0)	50	0.9	(0.6–1.4)
<i>2-year lag</i>													
None	513	98	1.0	–	124	1.0	–	109	1.0	–	172	1.0	–
1–47 months	38	14	1.3	(0.6–2.8)	10	1.1	(0.5–2.5)	9	1.5	(0.6–4.1)	14	0.8	(0.4–1.6)
48+ months	102	72	1.9	(1.1–3.1)	47	2.0	(1.2–3.4)	13	0.8	(0.3–1.9)	45	0.9	(0.6–1.5)
<i>5-year lag</i>													
None	513	98	1.0	–	124	1.0	–	109	1.0	–	172	1.0	–
1–47 months	25	8	1.2	(0.5–3.1)	10	1.8	(0.8–4.4)	4	0.8	(0.2–3.0)	9	0.7	(0.3–1.7)
48+ months	91	69	2.1	(1.2–3.5)	43	1.9	(1.1–3.3)	13	0.9	(0.4–2.1)	42	0.9	(0.6–1.5)

^a All analyses are adjusted for age, center, sex, cigarette smoking, history of ulcers, BMI and GERD symptom frequency. In addition to those variables, analyses of esophageal adenocarcinoma are adjusted for history of hiatal hernia, and analyses of esophageal squamous cell carcinoma are adjusted for alcohol consumption. Proxy respondents are excluded from all analyses.

occur if confounding by GERD symptoms were incompletely controlled for in the analysis. We attempted to minimize this possibility by categorizing GERD frequency finely and using indicator terms in the logistic model for each level of symptom frequency. Even after such adjustment, however, there may be unmeasured case-control differences in the severity of GERD or other gastrointestinal symptoms that are reflected in cases' greater use of H₂ blockers, even if the drugs themselves do not contribute directly to cancer risk. Finally, the reporting of GERD symptoms by some study participants may have been affected by use of H₂ blockers, which ameliorate the symptoms of GERD. The association of H₂ blocker use and esophageal adenocarcinoma was most pronounced in individuals who did not report a history of frequent severe GERD,

but because of the strong association between GERD and esophageal adenocarcinoma risk, the number of such subjects was limited.

In these data, long-term use of over-the-counter antacids was associated with an increased risk of esophageal adenocarcinoma similar in magnitude to that observed for H₂ blockers. The occurrence of a similar effect across different drug types suggests that the indications for use of the drugs, rather than the drugs themselves, are responsible for the observed increased risks. Both H₂ blockers and over-the-counter antacids increase gastric pH, however, and the possibility of a true increased risk as a result of reduced gastric acidity cannot be ruled out.

Our findings with respect to reflux are consistent with those from a recent Swedish study, in which individuals

with GERD were at substantially increased risk of esophageal adenocarcinoma [4]. Unlike that study, however, we did not observe an association between GERD and risk of gastric cardia adenocarcinoma [4]. In a medical-records-based study, Chow *et al.* reported a two-fold increased risk of adenocarcinoma of the gastric cardia or esophagus in patients with GERD symptoms noted in the medical record, and some indication of a dose response with number of years since symptoms were first recorded in the chart [3].

Two previous studies have addressed the potential association between use of H₂ blockers and risk of esophageal malignancies [3, 18]. Chow *et al.* reported a four-fold increased risk of esophageal and gastric cardia adenocarcinoma in individuals who had filled four or more prescriptions for H₂ blockers (OR 4.0, 95% CI 1.3–12.4), but the risk was reduced to 1.5 (95% CI 0.4–5.4) after controlling for GERD symptoms, hiatal hernia, esophagitis, esophageal ulcer, or difficulty swallowing [3]. Concluding that this excess risk was probably attributable to residual confounding, the authors reported that “no excess risk was observed for users of the H₂ antagonists who did not have a gastroesophageal condition, regardless of the number of prescriptions. Among those who were affected, an excess risk was observed whether or not they used the drugs” [3]. In a British cohort of cimetidine users [18], the relative risk of esophageal tumors was elevated in the first year after initiation of H₂ blocker use and then declined to the same level as that in non-users, the same pattern observed for gastric cancer [14–18]. Relative risk was then significantly elevated again (RR = 3.7) in the seventh and eighth years after initiation of use [18]. No information was available in that study on duration of exposure or on important potential confounders, and the esophageal tumors included both squamous cell carcinoma and adenocarcinoma, suggesting that the estimate of effect may be conservative.

Our study was subject to some limitations, including our inability to obtain direct interview data from 31% of cases. Because of the nondifferential misclassification introduced by proxy respondents, we chose to include only information obtained from the subjects themselves. Nonetheless, the use of H₂ blockers, antacids, and other medications may have been reported somewhat differently by cancer patients than controls. The specificity of our findings, however, with positive associations for esophageal or cardia adenocarcinomas and not other cancers, argues against a major impact of differential recall. As described above, perhaps the major limitation was our inability to distinguish clearly the effects of H₂ blockers on cancer risk from the effects of the conditions for which they were prescribed. The risk of esophageal

adenocarcinoma associated with long-term use of H₂ blockers was attenuated after adjustment for GERD symptoms and history of hiatal hernia, but remained elevated. Regardless of the mechanism involved, our findings suggest that individuals with long-standing GERD are at an increased risk of esophageal adenocarcinoma, whether or not the symptoms are treated with H₂ blockers or over-the-counter medications. Patients with GERD are increasingly prescribed other medications such as proton-pump inhibitors, which may more effectively control the symptoms of reflux, if not the underlying pathophysiologic process. The effects of these new medications on subsequent cancer risk should be carefully monitored.

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