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Association between use of antacid medications (proton pump inhibitors and histamine-2 receptor antagonists) and the incidence of lung cancer

A population-based cohort analysis

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Abstract

This study investigated the association between antacid administration and lung cancer incidence in a real-world setting.

This was a nationwide, retrospective cohort study. The cohort comprised random samples (n = 1,031,392) from the entire South Korean population in 2002. The duration of antacid administration between January 2006 and December 2010 was recorded for each participant. Newly developed lung cancers were counted during the 5-year observation period (January 1, 2006 to December 31, 2010). A total of 437,370 participants aged ≥ 40 years were included, of whom 301,201 (68.9%) had antacid exposure before the diagnosis of lung cancer. A total of 1230 (0.28%) antacid-exposed patients developed lung cancer. Among patients with no antacid exposure or underexposure (n = 136,171), 597 (0.44%) developed lung cancer. In the multivariable analysis, antacid exposure before the diagnosis of lung cancer was independently associated with a reduced incidence of lung cancer (hazard ratio: 0.64; 95% confidence interval: 0.55–0.74; $P < .001$). Antacid use might be independently associated with a decreased risk of lung cancer development in this cohort study.

Abbreviations: GERD, gastroesophageal reflux disease, H-2, histamine H_2 receptor-2, ICD-10, International Classification of Diseases, 10th revision, KNHIS, Korean National Health Insurance Service, PPI, proton pump inhibitor, V-ATPase, vacuolar H+-ATPase.

Keywords: antacid, incidence, lung cancer

1. Introduction

Proton pump inhibitors (PPIs) and histamine H_2 receptor-2 (H-2) antagonists are widely used to treat acid-peptic diseases, including duodenal and gastric ulcers, gastroesophageal reflux disease (GERD), and common heartburn.[1,2] Reflux of gastric acid may cause not only symptoms but also molecular injuries. If gastric acid reaches the airway, it may induce cellular damage to the epithelial lining.[3] Acid aspiration may promote cytosolic phospholipase A2 (cPLA2) activation.[4] The activation of cPLA2 in the tumor microenvironment leads to increased vasculature, enhanced tumourigenesis, and cancer progression.[5–9] Therefore, it may be necessary to investigate these molecular effects on the development of lung cancer in the clinical setting.

However, these drugs may also be effective antitumour therapies. In tumor cells, increased glucose metabolism results in the production of H^+ ions.[10] This cytoplasmic acidification is harmful to cells. To address this, vacuolar H+-ATPase (V-ATPase) is overexpressed to maintain the cytoplasmic pH inside the tumor cells, which causes extracellular acidification.[11] Acidification of tumor cells may enhance proliferation, tumourigenesis, drug resistance, metastasis, and tumor progression.[12] PPI can inhibit V-ATPase activity and augment cell death in colon adenocarcinoma cell lines.[13] Histamine may induce the proliferation of nonsmall cell lung cancer cells.[14] H-2 antagonists inhibit angiogenesis and tumor growth in an in vivo model of colon cancer[15,16] Additionally, H-2 is involved in mitogen-activated protein kinase pathway activation, which is important for tumor growth.[17] Moreover, the H-2 antagonist cimetidine

SG and DYL contributed equally to this study

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The authors have no conflicts of interest to disclose.

The data that support the findings of this study are available from the Korean National Health Insurance Service, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Korean National Health Insurance Service.

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reduces tumor volume by restoring the expression of cytokines such as lymphotoxin-β, tumor necrosis factor-α, interferon-γ, interleukin-10, and interleukin-15.[18] Furthermore, PPIs and H-2 antagonists may improve the survival of patients with various cancers, including lung cancer.[19–24]

Taken together, these results suggest that antacid medications (PPIs and H-2 antagonists) may have chemopreventive potential against lung cancer. It is important to determine the chemopreventive potential of antacid medications to better inform decisions regarding the appropriate medication. Therefore, we conducted a population-based study to investigate the association between antacid medication use and the incidence of lung cancer.

2. Methods

2.1. Study population and setting

This observational, population-based, longitudinal cohort study used data from the Korean National Health Insurance Database. There is only one health insurance system in South Korea, and each citizen has a unique resident registration number, thereby avoiding duplication of subjects. The Korean National Health Insurance Service (KNHIS) covers more than 97% of all South Korean residents and includes all health claims such as diagnostic codes, procedures, prescribed drugs, patient personal information, and hospital information. This study used data from the National Health Insurance Service–National Sample Cohort released by the KNHIS in 2015. The data included all medical claims filed from January 2002 to December 2015 for 1,031,392 nationally representative randomly selected subjects, accounting for ≈2.2% of the entire population in the KNHIS in 2002. The data were produced by the KNHIS using a systematic sampling method to generate a representative sample of all 46,605,433 South Korean residents in 2002.[25] The KNHIS data were linked to Statistics Korea (National Statistical Office) data, resulting in the accurate identification of deaths via the death certificate record. The current study (2020-02-004) was approved by the institutional review board (IRB) of Myongji Hospital. The IRB waived the requirement for informed consent.

2.2. Study design

Data were collected from 1 January 2002 to 31 December 2010. Data were reviewed for 4 years (January 2002 to December 2005) to identify information on smoking history and body mass index from health examinations, which were conducted every 2 years in South Korea. Patients with lung cancer between 2002 and 2005 were excluded. We defined exposure to antacids as a documented prescription. Data on cumulative antacid prescriptions and lung cancer diagnoses from January 2006 to December 2010 were extracted. The duration of antacid administration was calculated for patients newly diagnosed with lung cancer during the follow-up period (from January 2006 until lung cancer diagnosis). For patients without lung cancer, the antacid prescription period was calculated for the 5-year follow-up period.

2.3. Study population

Patients diagnosed with lung cancer between January 2006 and December 2010 were enrolled in this study (Fig. 1). This

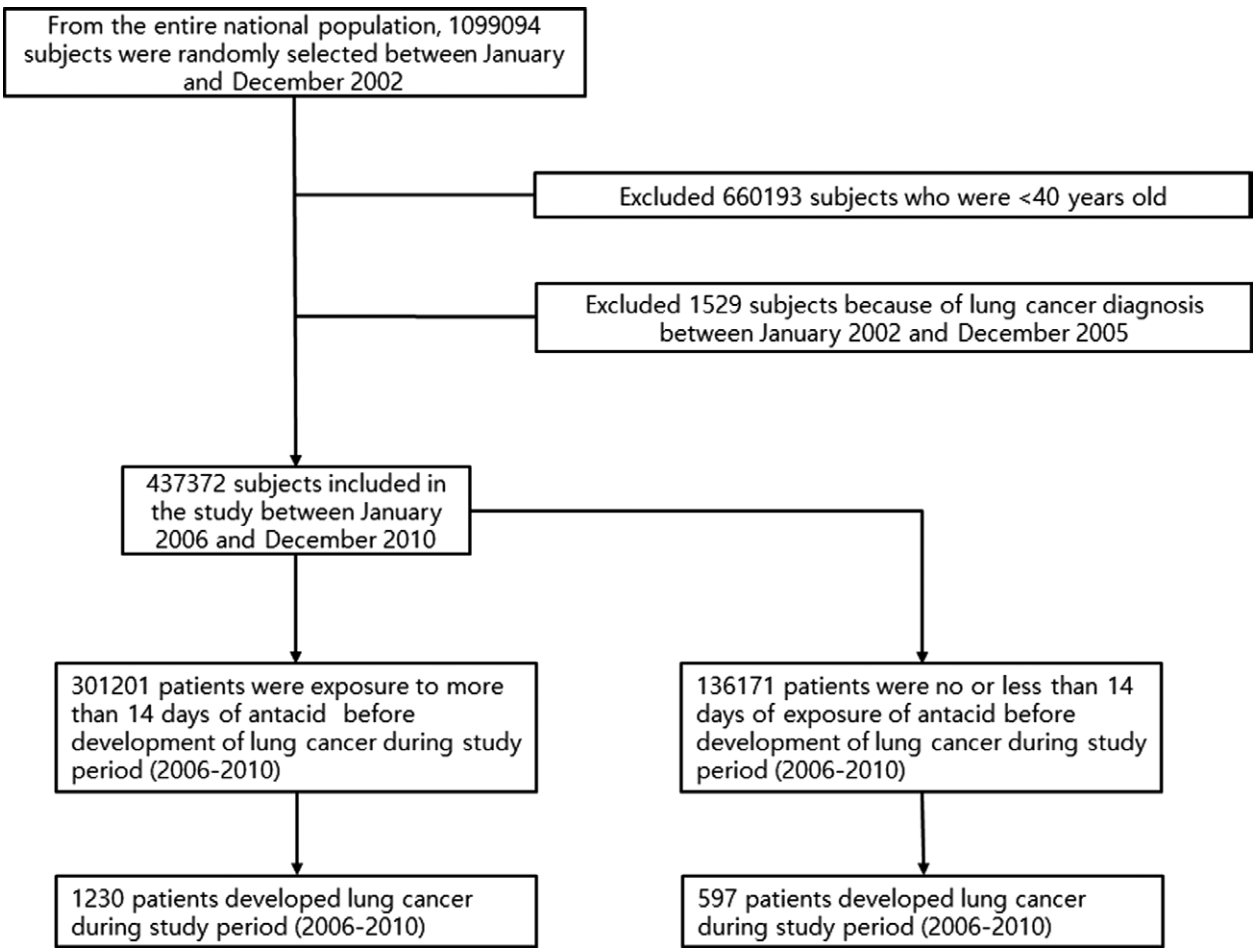

Figure 1. Flow chart of patient selection.

study enrolled only those patients aged ≥ 40 years. Subjects were excluded if lung cancer was diagnosed between January 2002 and December 2005. The International Classification of Diseases, 10th revision (ICD-10) codes were used as a key reference for diagnosing diseases and for identifying data within the National Health Insurance (NHI) database. Patient comorbidities, which were diagnosed and identified using ICD-10 codes from 2002 until the index date, included diabetes (E11.x), chronic kidney disease (N18.x), hypertension (I10.x), myocardial infarction (I21.x, I25.x), chronic obstructive pulmonary disease (J44.x), GERD (K21.x), and peptic ulcer (K27.x). In health examination, a questionnaire related to cigarette smoking (number of cigarettes per day, cigarette smoking period, and nonsmoking period) is being conducted every 2 years. By collecting these data, cigarette smoking history was evaluated in individual patients from 2006 to 2010.

2.4. Definition of lung cancer

The diagnostic codes for lung cancer cases diagnosed before 2006 were maintained in the NHI database based on ICD-10. New lung cancer cases were identified and counted by including new cases registered during the calendar year, after excluding preexisting lung cancer cases. Patients with lung cancer (C34) were included only if they were identified with the codes V193 or V194, which were installed by the NHI to reduce patient payment.

2.5. Assessment of antacid use

Antacids were defined as either H-2 antagonists or PPIs. The cumulative duration of antacid use between January 2006 and December 2010 was calculated for each participant until the diagnosis of lung cancer or the end of the follow-up. If the duration of antacid administration was < 14 days, the patients were placed in the underexposure group.[26] If the duration was ≥ 14 days, the patients were placed into the exposure group. As biological potency and half-life are variable for each drug, we could not take such characteristics into account. We considered only the duration of antacid treatment in this study. There were not enough patients treated with PPIs alone to assess the incidence of lung cancer based on the antacid type. The antacid drug codes that were counted are listed in Supplemental Table 1, http://links.lww.com/MD/H266.

Although we could not find the exact indication for antacids in each patient, we did consider common antacid indications, such as GERD and peptic ulcer diseases, in the statistical analysis.

2.6. Statistical analysis

Baseline characteristics at the initiation date (age, sex, residential area, household income, smoking status, body mass index, and comorbidities) for cases and controls were summarized using descriptive statistics, such as proportions. The chi-square test was used to compare the frequencies of risk factors between the exposed and underexposed groups. Cox proportional hazards models were used to evaluate risk factors for lung cancer development. Multivariate Cox regression models were constructed using patient age groups (40–49, 50–59, 60–69, 70–79, and ≥ 80 years), sex, household income (high, middle, low, very low, and Medicaid), geographic location (capital, large cities, and others), smoking status (current/ex-smoker, and never smoker), comorbidities, body mass index, and antacid exposure. The Kaplan–Meier method was used to calculate the 5-year risk of lung cancer development between the exposed and underexposed groups. Considering the rapid incidence of lung cancer in people aged 60 years or older,[27] sensitivity analyses of lung cancer risk stratified by age 40 to 59 and ≥ 60 years and smoking history. We performed additional analyses to assess the association between the incidence of lung cancer and H-2 alone and H-2 and proton pump inhibitor groups, as well as the presence or absence of GERD and the duration of use of an antacid, which was defined as the sum of prescription days (categorized by interquartile rage as none and < 14 days, 14–34 days, 35–77 days, 78–207 days, and ≥ 208 days). Statistical significance was set at $P < .05$. All statistical analyses were performed using the SAS ver. 9.2 (SAS Institute, Cary, NC), and SPSS ver. 21 (IBM Corp., Armonk, NY).

3. Results

3.1. Patient characteristics

A total of 437,372 participants aged > 40 years were included, of whom 301,201 (68.9%) had > 14 days of antacid exposure (exposed group). A total of 1230 (0.28%) patients in the exposed group were diagnosed with lung cancer (Fig. 1). The median duration of antacid treatment in the exposed group was 78 (interquartile range: 35–208) days (Table 1). There were 136,171 patients who had < 14 days of antacid exposure (underexposed group), of whom 597 (0.44%) were diagnosed with lung cancer. The median follow-up time was 49.5 months. Patients in the exposed group were older than those in the underexposed group. More than half of the patients in the exposed group were women (n = 170,154, 56.5%), whereas less than half of the patients in the no or underexposed group were women (n = 56,603, 41.6%). Patients in the exposed group were 4 and 5 times more likely to have experienced peptic ulcer and GERD, respectively, than those in the underexposed group. Among the H-2 blocker and PPI groups in the exposed group, PPI prescription duration was approximately 30%.

3.2. Association between antacid use and incidence of lung cancer

In the multivariable analysis, antacid exposure before the diagnosis of lung cancer was independently associated with a reduced incidence of lung cancer (hazard ratio [HR]: 0.64; 95% confidence interval [CI]: 0.55–0.74; $P < .001$) (Table 2) (Fig. 2).

3.3. Sensitivity analysis

The risk associated with lung cancer was analyzed in the H-2 alone, H-2, and proton pump inhibitor groups, and the risk of lung cancer according to the presence or absence of GERD was also analyzed (Fig. 3). Next, we compared the risk of lung cancer development based on the duration of antacid exposure. Compared to an antacid duration of < 14 days, the HRs for lung cancer development were 0.80 (95% CI: 0.67–0.96; $P = .01$) for an antacid duration of 14 to 34 days, 0.58 (95% CI: 0.48–0.70; $P < .001$) for an antacid duration of 35 to 77 days, 0.61 (95% CI: 0.50–0.74; $P < .001$) for an antacid duration of 78 to 207 days, and 0.49 (95% CI: 0.40–0.61; $P < .001$) for an antacid duration of ≥ 208 days (Fig. 3). The effect of antacid treatment was similar in ever smokers (adjusted HR: 0.62; 95% CI: 0.51–0.75; $P < .001$) and never smokers (adjusted HR: 0.65; 95% CI: 0.53–0.80; $P < .001$).

4. Discussion

Our longitudinal population-based study showed that antacid use might be independently associated with a decreased risk of lung cancer development. Exposure to antacids (PPIs and/or H-2 antagonists) in individuals reduced the incidence of lung cancer by 6 patients per 1000 patients over 5 years, which is a 36% reduction in lung cancer risk compared to the no or underexposure group.

Table 1

Baseline characteristics of participants.

Characteristic	Exposure to antacid (n = 301,201)	No or underexposure to antacid (n = 136,171)	*P* value
Sex			<.001
Male	131,047 (43.5)	79,568 (58.4)	
Age (yr)			<.001
40–49	103,483 (34.4)	72,592 (53.3)	
50–59	85,739 (28.5)	35,832 (26.3)	
60–69	64,255 (21.3)	16,571 (12.2)	
70–79	38,796 (12.9)	8452 (6.2)	
≥80	8928 (3.0)	2724 (2.0)	
Baseline comorbidity			
Hypertension	138,358 (45.9)	36,530 (26.8)	<.001
Diabetes	83,247 (41.6)	19,999 (14.7)	<.001
GERD	142,342 (47.3)	12,947 (9.5)	<.001
Peptic ulcer	134,232 (44.6)	15,570 (11.4)	<.001
Chronic kidney disease	3687 (1.2)	739 (0.5)	<.001
History of myocardial infarction	6591 (12.6)	1399 (1.0)	<.001
Chronic obstructive pulmonary disease	28,134 (9.3)	3911 (2.9)	<.001
Cerebrovascular diseases	46,486 (15.4)	8028 (5.9)	<.001
Risk factors			
BMI ≥ 25	94,368 (36.1)	35,556 (34.3)	<.001
Smoking status (missing n = 85,160)			<.001
Current	48,299 (16.0)	28,445 (20.9)	
Ex-smoker	23,318 (7.7)	11,530 (8.5)	
Never smoker	180,271 (59.8)	60,347 (44.3)	
Place of residence			<.001
Seoul, capital city	58,055 (19.3)	31,035 (22.8)	
Large cities	76,744 (25.5)	35,790 (26.3)	
Small cities and rural area	166,402 (55.2)	69,346 (50.9)	
Household income relative to the median (%)			<.001
90–100	86,851 (28.8)	38,576 (28.3)	
60–89	86,609 (28.8)	40,314 (29.6)	
30–59	64,712 (21.5)	32,183 (23.6)	
10–29	44,368 (14.7)	20,327 (14.9)	
0–9	18,861 (6.2)	4771 (3.5)	
Year of enrollment			<.001
2006	197,444 (65.6)	77,478 (56.9)	
2007	57,726 (19.2)	19,061 (14.0)	
2008	26,259 (8.7)	15,215 (11.2)	
2009	13,290 (4.4)	13,113 (9.6)	
2010	6482 (2.2)	11,304 (8.3)	
Antacid treatment duration (d)			<.001
<14	0 (0)	136,171 (100)	
14–34	73,565 (24.4)	0 (0)	
35–77	76,163 (25.3)	0 (0)	
78–207	75,963 (25.2)	0 (0)	
≥208	75,510 (25.1)	0 (0)	
Antacid medication			
H-2 alone	170,249 (56.5)		
H-2 and proton pump inhibitor	127,519 (42.3)		
Proton pump inhibitor alone	3433 (1.2)		
Pneumonia, hospitalized	8613 (2.8)	1475 (1.0)	<.001
Lung cancer development	1230 (0.28)	597 (0.43)	.15

Values are presented as number (%).

BMI = body mass index, GERD = gastroesophageal reflux disease, H-2 = histamine H_2 receptor.

As the mutation burden increases with age,[28,29] it is likely that cancer can develop even with a small trigger in the elderly. However, the ability of H-2 antagonists and PPIs to reduce the incidence of lung cancer in the elderly (≥60 years) and younger than 60 years were similar. The incidence of lung cancer is dependent on the duration of antacid exposure. The HR for lung cancer development was the lowest among patients who had antacid exposure ≥ 208 days over 5 years (average, 42 days a year). Based on these results, active prescription of antacids should be considered for patients aged ≥40 years. Active prescriptions may be especially valuable, as many patients have only minimal respiratory symptoms or chest discomfort, and some patients have no complaints, also known as silent aspiration.[30–32]

It has been reported that PPI acts as a chemosensitizer for the treatment of osteosarcoma, and it is reported that it has an anticancer effect in breast cancer and gastrointestinal cancer.[33] In animals with refractory cancer, the effect of reversing chemoresistance was also observed when high-dose PPIs were used.[34] Since PPI use is associated with a reduction in the incidence of breast cancer,[35,36] it has been suggested that PPIs may also have a preventive effect on cancer. There is an excellent review on the repurposing of PPIs for anticancer treatment.[37] In this study, there were few patients in the PPI-only group, so we could not analyze only the PPI group, but in the H-2 and proton pump inhibitor groups, 72% of the drugs consisted of PPI, so the effect of PPI is likely to be greater than that of H-2. From this point of view, it was estimated that PPIs would be effective in preventing lung cancer in this study. Further analysis showed that H-2 alone, H-2, and proton pump inhibitors were effective, suggesting that the development of lung cancer is also likely related to acid aspiration.

A disadvantage of this cohort study was that the latency period of antacids in cancer development was not considered. Therefore, when interpreting the association between antacid use and lung cancer in this study, cancer prevention does not seem to mean cancer prevention alone. These results may be due to the effects of antacids in all processes, such as initiation, promotion, progression, invasion, and metastasis of lung cancer.

The relationship between antacid administration and the incidence of lung cancer was similar in ever smokers and never smokers (adjusted HRs 0.65 and 0.62, respectively). Therefore, the effect of antacids on lung cancer development may be independent of cigarette smoking-related carcinogenesis.

This study had some limitations. First, among the 301,201 patients in the exposed group, approximately 3400 were administered PPIs alone. Therefore, the relationship between the administration of PPIs alone and the incidence of lung cancer could not be analyzed. Second, our data source did not provide information on lung cancer staging or histology; therefore, we could not assess these variables. Third, comorbidities were defined based on ICD codes, which should have been validated using patient records. However, this database consists of random samples of national insurance claims data, without identification numbers. Therefore, it was not possible to validate the data of the individual cases through a chart review.

5. Conclusion

In this population-based observational study, patients exposed to antacid medications (PPIs and/or H-2 antagonists) had a lower incidence of lung cancer than those with no exposure or underexposure. This finding may have implications for the chemoprevention of lung cancer.

Table 2

Univariate and multivariate Cox regression analyses for factors associated with the development of lung cancer.

	Cases, n		Univariate		Multivariate	
Variables	**Lung cancer**	**No lung cancer**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Men (reference: women)	1289	209,328	2.59 (2.35–2.87)	<.001	2.16 (1.85–2.51)	<.001
Age group (yr)						
40–49 (reference)	117	175,958				
50–59	329	121,242	4.09 (3.31–5.05)	<.001	4.08 (3.16–5.26)	<.001
60–69	628	80,198	11.90 (9.77–14.50)	<.001	12.38 (9.69–15.81)	<.001
70–79	625	46,623	21.00 (17.23–25.58)	<.001	21.56 (16.70–27.83)	<.001
≥80	128	11,524	18.87 (14.69–24.25)	<.001	20.69 (14.59–29.35)	<.001
Hypertension	962	173,926	1.69 (1.54–1.85)	<.001	0.89 (0.79–1.02)	.09
Diabetes	568	102,678	1.47 (1.34–1.63)	<.001	1.00 (0.87–1.13)	.99
GERD	545	154,744	0.76 (0.69–0.84)	<.001	0.83 (0.72–0.95)	.007
Peptic ulcer	601	149,201	0.93 (0.85–1.03)	.19	0.90 (0.79–1.02)	.11
Chronic kidney disease	24	4402	1.41 (0.94–2.11)	.09	0.72 (0.39–1.30)	.28
History of myocardial infarction	53	7937	1.68 (1.28–2.22)	<.001	1.01 (0.72–1.42)	.92
Chronic obstructive pulmonary disease	568	31,477	5.89 (5.33–6.51)	<.001	3.11 (2.72–3.55)	<.001
Cerebrovascular diseases	330	54,184	1.60 (1.41–1.80)	<.001	0.91 (0.77–1.06)	.24
BMI ≥ 25 (reference: BMI < 25)	322	129,602	0.65 (0.57–0.74)	<.001	0.75 (0.65–0.85)	<.001
Current or ex-smoker (reference: never smoker)	589	111,003	2.19 (1.95–2.45)	<.001	1.67 (1.46–1.91)	<.001
Residential area						
Seoul, Capital city (reference)	331	88,759				
Large cities	423	112,111	1.01 (0.87–1.17)	.85	1.03 (0.85–1.24)	.71
Small cities and rural area	1073	234,675	1.23 (1.08–1.39)	.001	1.16 (0.98–1.36)	.07
Household income relative to the median (%)						
90–100 (reference)	520	124,907				
60–89	492	126,431	0.93 (0.82–1.05)	.28	0.95 (0.82–1.11)	.57
30–59	398	96,497	0.99 (0.87–1.12)	.89	1.05 (0.89–1.23)	.53
10–29	268	64,427	1.00 (0.86–1.16)	.98	0.95 (0.79–1.14)	.60
0–9	149	23,283	1.58 (1.32–1.90)	<.001	0.74 (0.51–1.07)	.11
Antacid exposure (reference: no or underexposure)	1230	299,971	0.61 (0.54–0.68)	<.001	0.64 (0.55–0.74)	<.001

BMI = body mass index, CI = confidence interval, GERD = gastroesophageal reflux disease, HR = hazard ratio.

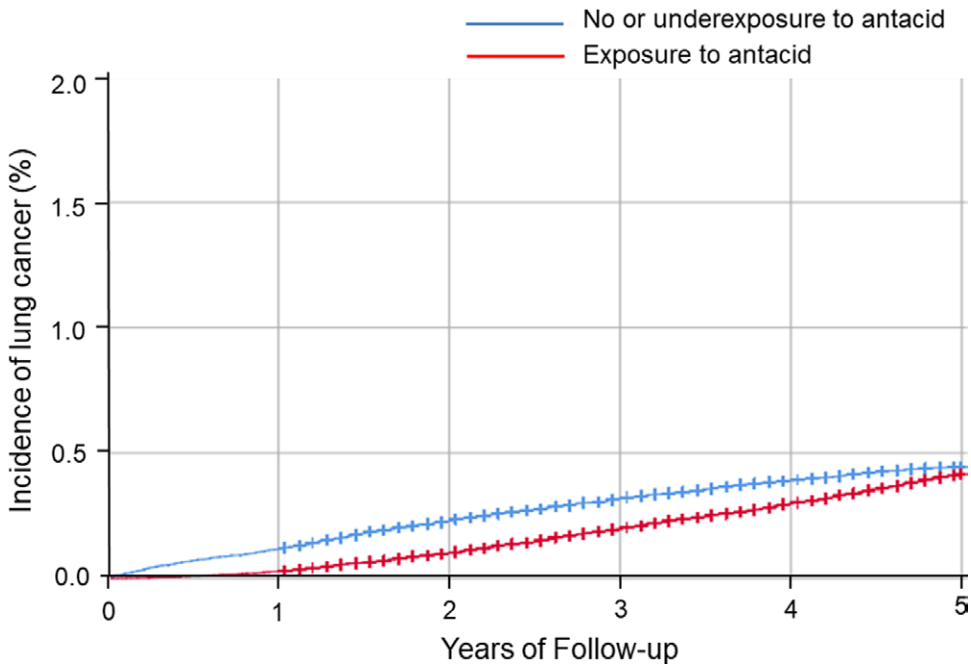

Figure 2. Kaplan–Meier analyses for the development of lung cancer based on antacid medications (proton pump inhibitors and/or histamine-2 receptor antagonists).

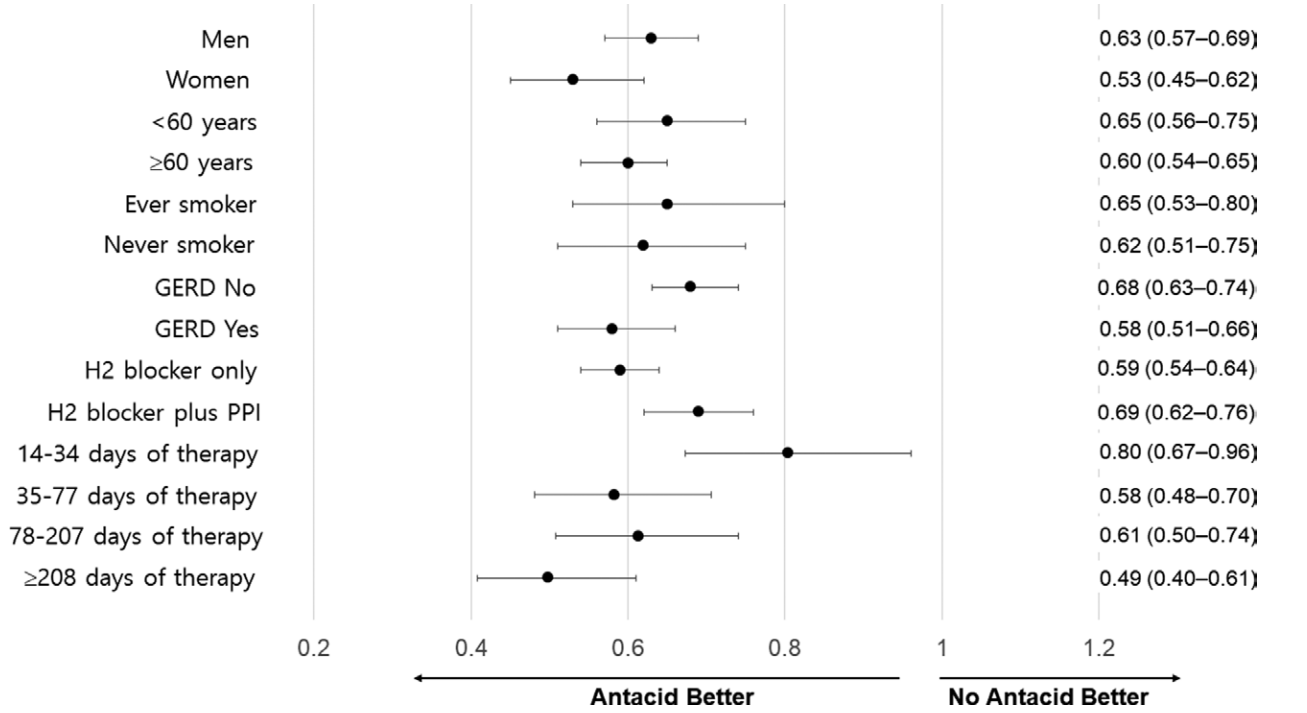

Figure 3. Adjusted hazard ratios (confidence interval) for the development of lung cancer according to sex, age, history of cigarette smoking, presence or absence of GERD, type of antacid medications (histamine-2 receptor antagonists alone, or proton pump inhibitors and histamine-2 receptor antagonists), and duration of antacid medication (interquartile range). All analyses have been adjusted for the age at baseline, sex, smoking history, presence of obesity, comorbidities, place of residence, and household income. GERD = gastroesophageal reflux disorder, H-2 = histamine H_2 receptor-2, PPI = proton pump inhibitor.

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References

[1] Wolfe MM, Sachs G. Acid suppression: optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. Gastroenterology. 2000;118:S9–31.
[2] Sontag SJ. The medical management of reflux esophagitis. Role of antacids and acid inhibition. Gastroenterol Clin North Am. 1990;19:683–712.
[3] Kennedy TP, Johnson KJ, Kunkel RG, et al. Acute acid aspiration lung injury in the rat: biphasic pathogenesis. Anesth Analg. 1989;69:87–92.
[4] Nagase T, Uozumi N, Ishii S, et al. Acute lung injury by sepsis and acid aspiration: a key role for cytosolic phospholipase A2. Nat Immunol. 2000;1:42–6.
[5] Linkous AG, Yazlovitskaya EM, Hallahan DE. Cytosolic phospholipase A2 and lysophospholipids in tumor angiogenesis. J Natl Cancer Inst. 2010;102:1398–412.
[6] Park JB, Lee CS, Jang JH, et al. Phospholipase signalling networks in cancer. Nat Rev Cancer. 2012;12:782–92.
[7] Weiser-Evans MC, Wang XQ, Amin J, et al. Depletion of cytosolic phospholipase A2 in bone marrow-derived macrophages protects against lung cancer progression and metastasis. Cancer Res. 2009;69:1733–8.
[8] Xin C, Chu L, Zhang L, et al. Expression of Cytosolic Phospholipase A2 (cPLA2)-Arachidonic Acid (AA)-Cyclooxygenase-2 (COX-2) Pathway Factors in Lung Cancer Patients and Its Implication in Lung Cancer Early Detection and Prognosis. Med Sci Monit. 2019;25:5543–51.
[9] Avis IM, Jett M, Boyle T, et al. Growth control of lung cancer by interruption of 5-lipoxygenase-mediated growth factor signaling. J Clin Invest. 1996;97:806–13.
[10] Warburg O. On the origin of cancer cells. Science. 1956;123:309–14.
[11] Nelson N, Harvey WR. Vacuolar and plasma membrane proton-adenosinetriphosphatases. Physiol Rev. 1999;79:361–85.
[12] Fais S. Evidence-based support for the use of proton pump inhibitors in cancer therapy. J Transl Med. 2015;13:368.
[13] Luciani F, Spada M, De Milito A, et al. Effect of proton pump inhibitor pretreatment on resistance of solid tumors to cytotoxic drugs. J Natl Cancer Inst. 2004;96:1702–13.
[14] Stoyanov E, Uddin M, Mankuta D, et al. Mast cells and histamine enhance the proliferation of non-small cell lung cancer cells. Lung Cancer. 2012;75:38–44.
[15] Natori T, Sata M, Nagai R, et al. Cimetidine inhibits angiogenesis and suppresses tumor growth. Biomed Pharmacother. 2005;59:56–60.
[16] Tomita K, Izumi K, Okabe S. Roxatidine- and cimetidine-induced angiogenesis inhibition suppresses growth of colon cancer implants in syngeneic mice. J Pharmacol Sci. 2003;93:321–30.
[17] Cricco G, Martin G, Medina V, et al. Histamine regulates the MAPK pathway via the H(2) receptor in PANC-1 human cells. Inflamm Res. 2004;53(Suppl 1):S65–6.
[18] Takahashi K, Tanaka S, Ichikawa A. Effect of cimetidine on intratumoral cytokine expression in an experimental tumor. Biochem Biophys Res Commun. 2001;281:1113–9.

[19] Papagerakis S, Bellile E, Peterson LA, et al. Proton pump inhibitors and histamine 2 blockers are associated with improved overall survival in patients with head and neck squamous carcinoma. Cancer Prev Res (Phila). 2014;7:1258–69.
[20] Kapoor S, Pal S, Sahni P, et al. Effect of pre-operative short course famotidine on tumor infiltrating lymphocytes in colorectal cancer: a double blind, placebo controlled, prospective randomized study. J Surg Res. 2005;129:172–5.
[21] Nielsen HJ, Christensen IJ, Moesgaard F, et al. Ranitidine as adjuvant treatment in colorectal cancer. Br J Surg. 2002;89:1416–22.
[22] Deva S, Jameson M. Histamine type 2 receptor antagonists as adjuvant treatment for resected colorectal cancer. Cochrane Database Syst Rev. 2012;15:CD007814.
[23] Sardesai S, Thomas A, Gallagher C, et al. Abstract OT1-03-01: Inhibiting fatty acid synthase to improve efficacy of neoadjuvant chemotherapy. Cancer Research 2020;80:OT1-03-01.
[24] Hsu CL, Chang CH, Lin JW, et al. Histamine-2 receptor antagonists and risk of lung cancer in diabetic patients - an exploratory analysis. Pharmacoepidemiol Drug Saf. 2013;22:632–40.
[25] Lee J, Lee JS, Park SH, et al. Cohort Profile: The National Health Insurance Service-National Sample Cohort (NHIS-NSC), South Korea. Int J Epidemiol. 2017;46:e15.
[26] Sinnott SJ, Polinski JM, Byrne S, et al. Measuring drug exposure: concordance between defined daily dose and days' supply depended on drug class. J Clin Epidemiol. 2016;69:107–13.
[27] Park JY, Jang SH. Epidemiology of lung cancer in korea: recent trends. Tuberc Respir Dis (Seoul). 2016;79:58–69.
[28] Blokzijl F, de Ligt J, Jager M, et al. Tissue-specific mutation accumulation in human adult stem cells during life. Nature. 2016;538:260–4.
[29] Yokoyama A, Kakiuchi N, Yoshizato T, et al. Age-related remodelling of oesophageal epithelia by mutated cancer drivers. Nature. 2019;565:312–7.
[30] Exarhos ND, Logan WD Jr, Abbott OA, et al. The importance of Ph and volume in tracheobronchial aspiration. Dis Chest. 1965;47:167–9.
[31] James CF, Modell JH, Gibbs CP, et al. Pulmonary aspiration--effects of volume and pH in the rat. Anesth Analg. 1984;63:665–8.
[32] Marik PE. Aspiration pneumonitis and aspiration pneumonia. N Engl J Med. 2001;344:665–71.
[33] Wang BY, Zhang J, Wang JL, et al. Intermittent high dose proton pump inhibitor enhances the antitumor effects of chemotherapy in metastatic breast cancer. J Exp Clin Cancer Res. 2015;34:85.
[34] Spugnini EP, Baldi A, Buglioni S, et al. Lansoprazole as a rescue agent in chemoresistant tumors: a phase I/II study in companion animals with spontaneously occurring tumors. J Transl Med. 2011;9:221.
[35] Chen CH, Lee CZ, Lin YC, et al. Negative association of proton pump inhibitors with subsequent development of breast cancer: a Nationwide Population-Based Study. J Clin Pharmacol. 2019;59:350–5.
[36] Ding DC, Sung FC, Chen W, et al. Proton pump inhibitors reduce breast cancer risk in gastric ulcer patients: A population-based cohort study. Breast J. 2020;26:474–8.
[37] Spugnini EP, Fais S. Drug repurposing for anticancer therapies. a lesson from proton pump inhibitors. Expert Opin Ther Pat. 2020;30:15–25.