European Journal of Clinical Pharmacology (2020) 76:1437–1456
https://doi.org/10.1007/s00228-020-02927-8

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

The association between acid-suppressive agent use and the risk of cancer: a systematic review and meta-analysis

Hyun Jin Song[1,2] · Nakyung Jeon[3] · Patrick Squires[2]

Received: 22 February 2020 / Accepted: 1 June 2020 / Published online: 16 June 2020

Abstract

Background Acid-suppressive agents (ASAs) may be associated with cancer; previous studies reported that the risk of cancer with acid suppressants has differed depending on the site of cancer. Here, we conducted a systematic review and meta-analysis of the association between ASA use and the type of cancer risk.

Methods MEDLINE, EMBASE, and Cochrane library databases were searched for publications up to the end of September 2019 for MeSH terms and text words related to cancer and ASAs. Studies on the association between ASAs and cancer risk, which included a control group and reported the relative risk of cancer, were included. The inverse-variance random effect model was used to estimate the pooled relative risk (RR) and 95% confidence interval (CI), and subgroup analysis for type of acid suppressants, drug uptake duration, and cumulative doses was performed. Heterogeneity was assessed using the I^2 test and Q statistic.

Results Thirty-nine cohort and case–control studies were included. ASA use was found to be significantly associated with a 46% higher risk of gastric cancer (RR, 1.46; 95% CI, 1.18–1.80) and a 53% higher risk of liver cancer (RR, 1.53; 95% CI, 1.31–1.78) compared with nonuse; however, there was no significant association for esophageal, colorectal, pancreatic, lung, breast, prostate, and kidney cancer; melanoma; and lymphoma.

Conclusions ASAs were significantly associated with an increased risk of gastric and liver cancer; therefore, special attention of ASA use considering the potential risk of gastric and liver cancer is needed.

Keywords Acid-suppressive agent · Cancer · Proton pump inhibitor · Histamine 2-receptor antagonist · Systematic review · Meta-analysis

Introduction

Histamine 2-receptor antagonists (H_2RAs) and proton pump inhibitors (PPIs), common acid-suppressive agents (ASAs), are the mainstay treatments for gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD). Both classes of drugs can effectively alleviate patient symptoms and decrease the frequency and duration of gastroesophageal reflux, although through different mechanisms of action [1].

During acid-suppressive therapy, hypergastrinemia, defined as an excessive gastrin level (> 100–150 pg/mL), has been implicated as a potential factor in the pathogenesis of carcinoid, which can subsequently spread to different organs. According to a large population-based study analyzing Surveillance, Epidemiology, and End Results (SEER) data, the most frequent sites for carcinoids were the colon (35.9%); small intestine (32.9%); respiratory system, including the larynx, trachea, bronchi, and lung (25.1%); and

Hyun Jin Song and Nakyung Jeon contributed equally to this work as first authors.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00228-020-02927-8) contains supplementary material, which is available to authorized users.

✉ Hyun Jin Song
hyunjin.song@cop.ufl.edu

[1] Department of Pharmaceutical Policy and Outcomes Research, School of Pharmacy, Sungkyunkwan University, Suwon, South Korea

[2] Department of Pharmaceutical Outcomes and Policy, College of Pharmacy, University of Florida, HPNP Building Room 2320, 1225 Center Drive, Gainesville, FL 32610, USA

[3] College of Pharmacy, Chonnam National University, Gwangju, South Korea

stomach (3.2%) for more than 8000 patients with carcinoid tumors [2]. Rare carcinoids were also found in the esophagus (0.04%), liver (0.2%), gallbladder (0.2%), pancreas (0.6%), and female reproductive organs (0.6%). H_2RAs and PPIs, which inhibit gastrin secretion by decreasing gastric acidity, may cause hypergastrinemia. The association between hypergastrinemia and cancer is well documented in the literature [3–5].

Decreased gastric acidity during acid-suppressive therapy may result in bacterial overgrowth in the gut. Studies have postulated that gastric bacterial overgrowth is predictive of several nongastrointestinal clinical outcomes, including lung and liver disease, and even cancer [6, 7]. For example, small intestinal bacterial overgrowth, defined as bacterial culture of $> 10^5$ CFU/mL in the upper jejunal aspirate, is known to be directly related to the severity of liver disease [8]. Another recent study found that the alteration of gut microbiome occurred at a higher rate in patients with lung cancer compared with that in cancer-free individuals [9].

Considering these mechanisms, ASAs may be associated with cancers, and the results of previous studies regarding this association have differed by the site of cancer [10]. A meta-analysis showed an increased risk of gastric cancer in patients using PPI or H_2RA, whereas it showed a lack of association between colorectal and pancreatic cancers and long-term PPIs. However, a definitive conclusion could not be made because of the limited studies included [10–12]. In addition, the correlation between PPI use and chronic kidney disease and liver dysfunction has been investigated [10, 13–15]. Thus, pooled estimates combining hazard ratios from each study according to different types of cancer and the use of PPI/H_2RA are needed. We performed a systematic review and meta-analysis of the association between ASA use and the risk of various types of cancer.

Methods

Literature search

The MEDLINE, EMBASE, and the Cochrane library core databases were searched for articles published up until the end of September 2019. We used MeSH terms and text words related to cancer ("neoplasm," "tumor," and "adenoma") and ASAs ("proton pump inhibitor" and "histamine H2 antagonist"). The drug name, brand name, and chemical name of all acid-suppressive agents, including PPIs (omeprazole, esomeprazole, pantoprazole, rabeprazole, lansoprazole, dexlansoprazole, tenatoprazole, and benatoprazole) and H_2RAs (azacitidine, cimetidine, famotidine, lafutidine, nizatidine, ranitidine, and roxatidine), were used in the search. The details of the search strategy are noted in Supplement Table 1.

Study selection

Only studies that met the following criteria were included: (1) the study reported the association between ASAs and the risk of cancer; (2) the study compared at least two independent groups (i.e., ASA receiving group and a nonuse group); (3) the study quantified and reported the relative risk of cancer between groups by calculating parameters, such as the risk ratio (RR), hazard ratio (HR), or odds ratio (OR); (4) the studies were randomized controlled trials, nonrandomized controlled studies, and observational studies; (5) peer-reviewed original studies; and (6) English-language studies. Two reviewers independently conducted the study selection, quality assessment, and data extraction (HJS, NJ). Disagreement between the two reviewers was resolved by consensus with the third reviewer (PS). We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [16], and the study protocol was registered to PROSPERO (CRD42019131274) prior to conducting the study.

Quality assessment

The quality assessment tool used was the Risk of Bias Assessment for Non-randomized Studies (ROBANS) since we could only include observational studies. ROBANS is a domain-based evaluation tool and is developed using 39 nonrandomized studies in 2013; it shows moderate reliability and validity [17]. It is composed of five items (selection of participants, confounding variables, measurement of intervention, blinding for outcome assessment, and incomplete outcome data) and was assessed at three levels (high, unclear, or low) for each study. We added the item of recall bias as another risk of bias since some of the included studies investigated the use of ASAs using patient-reported survey.

Data extraction

We extracted the baseline characteristics, exposures, and outcomes of included studies using the prespecified protocol. The study design, country, study period, number of participants (control/case), mean age, and percentage of male participants were collected. Interventions (PPI/H_2RA) and outcomes, including relative risk and 95% confidence interval (CI), exposure/follow-up period, and covariates in regression analysis or matching, were also extracted.

Data analysis

The primary outcome was the adjusted estimates of the risk of cancer associated with ASAs. We used the best-adjusted relative risks with a 95% CI after controlling the confounding

variables from each included study for the meta-analysis. In the base-case analysis, we prioritized data from groups with any use of ASAs ever, PPI use, prescription drug, long-term follow-up, and the highest cumulative defined cumulative daily drug dose (cDDD), in this order. If the study only reported the relative risk of cancer by subdivision, we used the result of the most common cancer type. For example, the studies of gastric cancer reported the results of both gastric cardia and noncardia adenocarcinoma. We used the gastric cardia adenocarcinoma data in the base-case analysis and performed a subgroup analysis for each type of gastric cancer.

The inverse-variance random effect model was used to estimate the pooled data. Each study reported a different type of relative risk, such as HR, RR, or OR. In the meta-analysis, HRs were considered as RRs [18, 19], and ORs were converted to RRs using the method described by Zhang and Yu [20]. In addition, we performed subgroup analysis according to PPI/H_2RA use, types of cancer (if possible), drug uptake duration, cDDD, specific subgroup patients (e.g., different types of cancers, patients with *Helicobacter pylori*, patients with hepatitis B or C virus), and studies of low risk of bias of measurement of intervention (i.e., ASAs taken by both prescription and over-the-counter [OTC]). Heterogeneity was assessed using the I^2 test and Q statistic, with significance of the Q-statistic test being considered at $P < 0.05$. Heterogeneity was considered for I^2 values of more than 50% [21]. The funnel plot was used to estimate possible publication bias owing to the tendency to publish studies with positive results. We used Review Manager 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

Literature search

Our literature search identified 49,694 articles (Fig. 1). After removal of duplicate articles, title or abstract screening was conducted for 43,585 articles. In the title/abstract review, 39,864 articles were removed and 3682 articles were excluded from the full-text review owing to one of the following reasons: no patients with cancer, no acid-suppressant therapy, ineligible study design, no comparator group available, no outcomes of interest reported, and nonoriginal studies. Finally, 39 studies were included in the systematic review and meta-analysis [22–60].

General characteristics of the included studies

The 39 studies investigated esophageal cancer ($n = 6$), gastric cancer ($n = 10$), colorectal cancer ($n = 7$), liver cancer ($n = 5$), pancreatic cancer ($n = 7$), lung cancer ($n = 2$), breast cancer ($n = 6$), prostate cancer ($n = 3$), kidney cancer ($n = 1$), melanoma ($n = 2$), non-Hodgkin lymphoma ($n = 1$), and other cancers ($n = 2$). Some studies have included the results of association with more than one cancer; thus, each outcome for different types of cancer, respectively, was analyzed in the meta-analysis of each cancer. There were 30 case–control studies and 11 cohort studies in total, including two cohort studies in the study by Kao et al. and a case–control and a cohort study by Tran et al. (Table 1). The studies were from several countries: the USA, Canada, the UK, Italy, Denmark, Netherlands, Iceland, Taiwan, Hong Kong, and South Korea.

Quality assessment

The items estimating a low risk of bias with more than 75% were selection of participants, blinding for outcome assessment, incomplete outcome data, and other risk of bias (recall bias) (Fig. 2). The confounding variables and measurement of intervention were assessed as more than 50% of unclear or high risk of bias, because there were studies that only reported crude estimates, and the suitable confounding covariates for the adjusted estimates were not included. ASAs can also be bought as OTC drugs in many countries; thus, we evaluated an unclear risk of bias for the measurement of intervention if the included studies indicated the possibility that the patients assessed were taking OTCs.

Acid-suppressive agents and esophageal cancer

Five studies with 15,161 individuals reported that ASAs and the risk of esophageal cancer were not significantly associated (RR, 1.00; 95% CI, 0.77–1.29), with no significant heterogeneity ($I^2 = 13\%$, $P = 0.33$) (Fig. 3a). We did not include the study by Habel et al. in the meta-analysis as they reported the combined relative risk of esophageal and stomach cancer. In the subgroup analysis, both PPI use and H_2RA use did not show a significant association with esophageal cancer (RR, 0.75; 95% CI, 0.55–1.03 in PPI users and RR, 0.98; 95% CI, 0.72–1.32 in H_2RA users) (Table 2). The association according to the treatment duration or type of esophageal cancer (adenocarcinoma and squamous cell carcinoma) was also insignificant.

Acid-suppressive agents and gastric cancer

Nine studies including 130,074 individuals estimated that ASA users showed a 46% higher risk of gastric cancer compared with that of nonusers (RR, 1.46; 95% CI, 1.18–1.80), with slight significant heterogeneity ($I^2 = 51\%$, $P = 0.04$) (Fig. 3b). There was no evidence of publication bias based on the funnel plot (Fig. 4b). Both PPI use and H_2RA use were associated with an increased risk of gastric cancer (RR, 1.53; 95% CI, 1.13–2.07 in PPI users and RR, 1.32; 95% CI, 1.08–1.60 in H_2RA users) (Table 2). The significant association was also

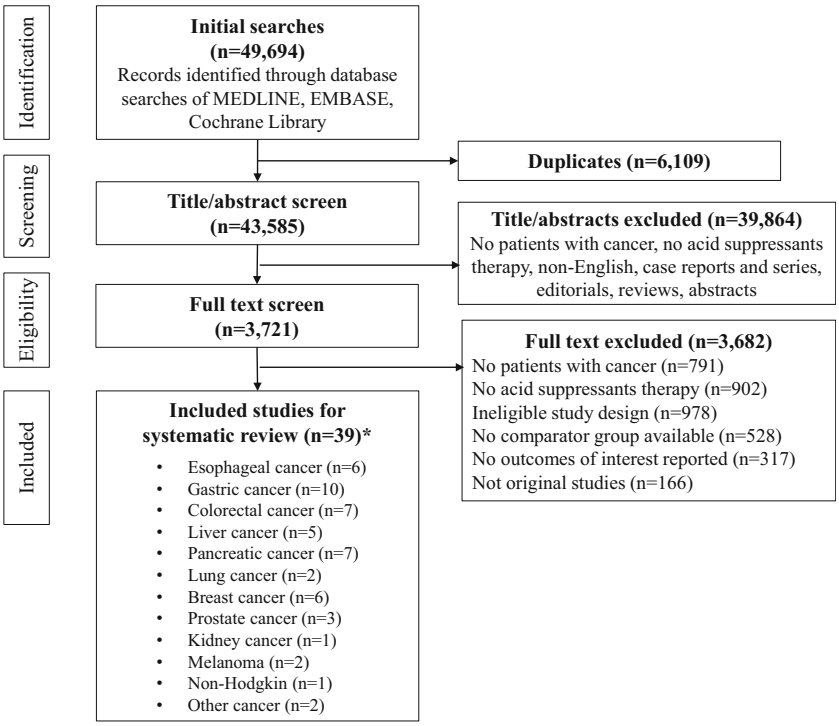

Fig. 1 PRISMA flow diagram of the study selection. * Some studies have included the results of associations with several different types of cancer

shown in patients with *Helicobacter pylori*. For the group consisting of individuals who used ASAs for 1 year or more/less than 1 year, the subgroup of cardia or noncardia cancer, a significant association with gastric cancer was not shown.

Acid-suppressive agents and colorectal cancer

In total, 605,043 individuals in seven studies showed no significant association between ASAs and colorectal cancer (RR, 1.02; 95% CI, 0.91–1.14) (Fig. 3c). We could not detect any evidence for heterogeneity (I^2 = 0%, P = 0.74) or publication bias (Fig. 4c). In the subgroup analysis, the results were consistent with those of the base-case analysis: PPI/H_2RA, drug intake duration of less than 1 year/1 year or more, and fewer than 60 cDDDs/60 cDDDs or more (Table 2).

Acid-suppressive agents and liver cancer

Seven cohorts from five studies of the association between ASAs and liver cancer included 809,465 individuals. ASA use was significantly associated with a 53% increased risk of liver cancer compared with nonuse (RR, 1.53; 95% CI, 1.31–1.78) (Fig. 3d). Significant heterogeneity was detected (I^2 = 84%, P < 0.001) and there was no evidence of publication bias based on the funnel plot (Fig. 4d). In the subgroup analysis by type of ASAs, there was no significant association between H_2RA users and the risk of liver cancer, whereas PPIs were significantly associated with liver cancer (Table 2). According to the cDDD, ASA users with 365 DDDs or more and those with less than 365 DDDs did not show a significant association with the risk of liver cancer. With regard to the type of liver cancer, ASA use associated with an increased risk of hepatocellular carcinoma (RR, 1.40; 95% CI, 1.17–1.68), but not of intrahepatic bile duct carcinoma. PPI use was also associated with the increasing risk of hepatocellular carcinoma in patients with hepatitis B or C virus (RR, 1.45; 95% CI, 1.03–2.03).

Acid-suppressive agents and pancreatic cancer

Seven studies including 554,115 individuals demonstrated that the use of ASAs was not significantly related with the risk of pancreatic cancer compared with nonuse (RR, 1.50; 95% CI, 0.92–2.45) (Fig. 3e). Significant heterogeneity was shown (I^2 = 84%, P < 0.001), and there was no evidence of publication bias (Fig. 4e). The subgroup analyses of PPI or H_2RA, drug intake duration, and cDDDs between ASA use and the risk of pancreatic cancer did not show a significant association (Table 2).

Acid-suppressive agents and breast cancer

In total, 209,329 individuals were included in six studies to estimate the association between ASAs and breast cancer. ASA use was not significantly associated with the risk of breast cancer (RR, 0.90; 95% CI, 0.80–1.01) with significant heterogeneity (I^2 = 86%, P < 0.001) (Fig. 5a). The results of subgroup analyses were consistent with those of the base-case analysis (Table 2).

Table 1 Characteristics of included studies

Author, year	Country	Study design	Study period	Number of participants (control/case)	Drugs	Mean age (SD)/male	Exposure/follow-up	Adjustments (matching variables in case–control studies)	Results (95% confidence interval)
Digestive system									
Esophageal cancer									
Suleiman et al., 2000	UK	Case–control	1990–1992	56/56	H_2RA	NA 70%	2 years	Social class	Esophageal adenocarcinoma: aRR, 2.56 (0.17–38.09)
Tan et al., 2018	USA	Case–control	2004–2011	798/300	PPI H_2RA	64.8 (9.2) 100%	1 year to 3 months	Barrett's diagnosis, smoking, BMI, number of EGDs after Barrett's diagnosis, statin, aspirin, NSAID, H_2RA/PPI	Esophageal adenocarcinoma • PPI: aOR, 0.59 (0.35–0.99) • H_2RA: aOR, 0.70 (0.50–0.99)
Esophageal/gastric cancer									
Duan et al., 2009	USA	Case–control	1992–1997	1356/938 (220, 277, 441)	PPI H_2RA	58.7 (11.5) to 60.0 (9.4) 73.5%	3 years	Age, gender, race, BMI, smoke, history of upper gastrointestinal disorders	Esophageal adenocarcinoma: aOR, 1.27 (0.65–2.51) Gastric cardia adenocarcinoma: aOR, 1.29 (0.70–2.36) Distal stomach adenocarcinoma: aOR, 1.15 (0.58–2.29)
Farrow et al., 2000	USA	Case–control	1993–1995	654/760 (194, 188, 138, 240)	H_2RA	NA 79.2%	1 year	Age, center, sex, cigarette smoking, history of ulcers, BMI, GERD symptom frequency, history of hiatal hernia (esophageal adenocarcinoma), alcohol consumption (esophageal squamous cell carcinoma)	Esophageal adenocarcinoma: aOR, 1.3 (0.6–2.8) Esophageal squamous cell carcinoma: aOR, 0.2 (0.04–1.4) Gastric cardia adenocarcinoma: aOR, 0.7 (0.3–1.8) Gastric noncardia adenocarcinoma: aOR, 0.8 (0.4–1.7)
Habel et al., 2000	USA	Cohort	1982–1985	29,229/4125	Cimetidine	NA	More than 10 years	Age, gender, pharmacy data source	Esophagus/stomach: aRR, 1.98 (1.27–3.07)
García Rodríguez et al., 2006	UK	Case–control	1994–2001	10,000/809 (287, 195, 327)	PPI H_2RA	NA 72.0% (case group)	More than 3 years	Age, sex, year, smoking, alcohol consumption, BMI, GERD, hiatal hernia, peptic ulcer, dyspepsia	Esophageal adenocarcinoma: aOR, 1.13 (0.75–1.72) Gastric cardia adenocarcinoma: aOR, 1.09 (0.68–1.75) Gastric noncardia adenocarcinoma: aOR, 1.69 (1.19–2.41)
Gastric cancer									
Cheung et al., 2018	Hong Kong	Cohort	2003–2012	56,918/139	PPI	Median, 54.7 (range 46.0–65.4) 46.5%	More than 3 years	Age, sex, smoking, alcohol, gastric ulcer, duodenal ulcer, diabetes mellitus, hypertension, dyslipidemia, obesity, ischemic heart disease, atrial fibrillation, congestive heart failure, stroke,	Gastric cancer: aHR, 2.44 (1.42–4.20) • Cardia gastric cancer: aHR, 1.97 (0.57–6.82) • Noncardia gastric cancer: aHR, 2.59 (1.42–4.72)

Table 1 (continued)

Author, year	Country	Study design	Study period	Number of participants (control/case)	Drugs	Mean age (SD)/male	Exposure/follow-up	Adjustments (matching variables in case–control studies)	Results (95% confidence interval)
								chronic renal failure, cirrhosis, statin, metformin, aspirin, NSAIDs, COX-2 inhibitors, clopidogrel, H_2RA	
Johnson et al., 1996	USA	Case–control	1988–1992	452/113	Cimetidine, ranitidine	NA Case 68%	10 years	–	RR, 2.0 (1.0–3.9)
La Vecchia et al., 1990	Italy	Case–control	NA	1501/563	H_2RA	Control median 58 (23–74), case median 60 (27–74) 59.7%	More than 10 years	Age, sex, area of residence, education, smoking	aRR, 1.8 (1.2–2.8)
Niikura et al., 2018	Japan	Cohort	1998–2017	415/156	PPI H_2RA	NA 56%	Median follow-up: PPI 1.3 years, H_2RA 2.3 years	Age, sex, PPI/H_2RA, intestinal metaplasia	PPI: aHR, 3.61 (1.49–8.77) H_2RA: aHR, 2.65 (0.69–10.2)
Poulsen et al., 2009	Denmark	Cohort	1990–2003	PPI 18,790 H_2RA 17,478	PPI H_2RA	PPI 62 H_2RA 61 46.2%	More than 5 years	Age, gender, calendar period, gastroscopy, NSAIDs, *H. pylori* eradication	PPI: aIRR, 1.2 (0.8–2.0) H_2RA: aIRR, 1.2 (0.8–1.8)
Tamim et al., 2008	Canada	Case–control	1995–2003	12,991/1598	PPI H_2RA	Control 75.9 (8.8), case 75.7 (9.3) 59.8%	5 years to 5 months	Number of prescriptions to any drug, total length of hospitalization, number of visits to GPs, specialists, and emergency rooms	PPI and/or H_2RA: aOR, 1.37 (1.22–1.53) • PPI: aOR, 1.46 (1.22–1.74) • H_2RA: aOR, 1.28 (1.08–1.51)
Colorectal cancer									
Chubak et al., 2009	USA	Case–control	2000–2003	641/641	PPI H_2RA	70 48.4%	NA	Race, smoking, NSAID, aspirin, PUD, *H. pylori* infection, diabetes (age, gender, length of enrollment)	PPI: aOR, 1.7 (0.8–4.0) H_2RA: aOR, 0.8 (0.6–1.1) PPI and H_2RA: aOR, 0.9 (0.5, 1.4)
Habel et al., 2000	USA	Cohort	1982–1985	49,229/4125	Cimetidine	NA	More than 10 years	Age, sex, pharmacy data source	aRR, 1.12 (0.82–1.52)
Hwang et al., 2017	South Korea	Cohort	2002–2006	451,284	PPI	NA 53.5%	5 years	Age, BMI, socioeconomic status, smoking, alcohol consumption, physical activity, type 2 diabetes, CCI score, aspirin, metformin, statin	aOR, 0.98 (0.78–1.24)
Robertson et al., 2007	Denmark	Case–control	1989–2005	55,890/5589	PPI	71.0 50.2%	More than 7 years	H_2RA, aspirin, NSAIDs, statin, antidiabetic medication, history of cholecystectomy, alcoholism (birth year, sex, place of residence)	aOR, 1.14 (0.98–1.34)
Siersema et al., 2006	USA	Case–control	1998–2002	268/268	PPI	Control 64 (12), case 66 (11)	NA	Barrett's esophagus, age, BMI, other malignancies, aspirin, NSAIDs, alcohol, smoking	aOR, 0.99 (0.66–1.48)

Table 1 (continued)

Author, year	Country	Study design	Study period	Number of participants (control/case)	Drugs	Mean age (SD)/male	Exposure/follow-up	Adjustments (matching variables in case–control studies)	Results (95% confidence interval)
						97.8%			
Yang et al., 2007	UK	Case–control	1987–2002	44,292/4432	PPI	Control 63.6 (9.1), case 67.5 (8.9) 45.1%	More than 5 years	Age, sex, alcohol, smoking, BMI, H_2RA, hormone replacement therapy, NSAIDs, aspirin, colonoscopy or flexible signoidoscopy	aOR, 1.1 (0.7–1.9)
Van Soest et al., 2008	Netherlands	Case–control	1996–2005	7790/594	PPI	Control 69.3 (11.9), case 69.5 (11.9) 51.7%	5 years	Chronic disease score: obesity or BMI, smoking, alcohol abuse, diabetes mellitus, inflammatory bowel disease, and other comorbidities (age, sex, calendar time, duration of follow-up)	aOR, 0.85 (0.63–1.16)
Liver/bile duct cancer									
Kao et al., 2019	Taiwan	Cohort	2003–2013	HBV cohort—5577/5577 HCV cohort—1915/1915	PPI	HBV cohort PPI 48.9 (12.8), control 48.9 (13.9) HCV cohort PPI 59.0 (13.7), control PPI 58.9 (14.4) HBV cohort 61.7%, HCV cohort 47.7%	1 year	• Age, sex, year of cohort entry • Comorbidities: cirrhosis, nonalcoholic liver disease, alcoholic liver disease, hypertension, chronic kidney disease, hyperlipidemia, diabetes • Concomitant medication: interferon/nucleotides, non-aspirin NSAIDs, histamine 2 receptor antagonist, aspirin, statin, fibrate, insulins, metformin	HBV cohort: aHR, 1.25 (0.80–1.73) HCV cohort: aHR, 1.19 (0.88–1.61)
Li et al., 2017	US	Cohort	2001–2015	5774/5752	PPI	Median 53 (IQR 49–57) 96.1%	Median follow-up—93.4 months (IQR 62.8–125.9) among PPI users and 89.5 months (IQR 62.8–125.9) for controls	• Age, sex, race • Diabetes, obesity, alcohol abuse history, smoking history, statin use • HCV genotype, HCV RNA, baseline ALT, AST, platelet count, FIB-4 score, attainment of SVR	aHR, 2.01 (1.5–2.7)
Peng et al., 2018	Taiwan	Case–control	2006–2011	2293/2293	PPI H_2RA	Control 68.3 (13.8), case 67.3 (10.9) 50.1%	5 years	Age, biliary tract disease, COPD (sex, age, year of diagnosis CCA, medications [H_2RA (H2-receptor antagonist), aspirin, metformin] and comorbidities [gastric polyp, gastritis, cirrhosis, diabetes, chronic pancreatitis, hepatitis B	PPI: aOR, 2.57 (2.24–2.94) H_2RA: OR, 0.94 (0.79, 1.12)

Table 1 (continued)

Author, year	Country	Study design	Study period	Number of participants (control/case)	Drugs	Mean age (SD)/male	Exposure/follow-up	Adjustments (matching variables in case–control studies)	Results (95% confidence interval)
								infection, hepatitis C infection, inflammatory bowel disease, biliary tract disease, stroke, coronary arterial disease (CAD), chronic obstructive pulmonary disease (COPD), alcohol-related illness, *Clonorchis* and *Opisthorchis*, *Helicobacter pylori*], oral steroid)	
Shao et al., 2018.	Taiwan	Case–control	2000–2013	274,508/29,473	PPI	N/A 68%	Mean follow-up duration—60 months (SD 48)	• Hypertension, diabetes, COPD, acute coronary syndrome, cerebrovascular accident, peptic ulcer disease, gastroesophageal disease, cirrhosis, hyperlipidemia	aOR, 2.86 (2.69–3.04)
Tran et al., 2018	UK	(i) PCCIU: case–-control (ii) UK Biobank: cohort	(i) 1999–2-011 (ii) 2006–1-010	2103/434 471,669/182	PPI H_2RA	N/A (i) 67.2% (ii) 46.1%	(i) Median exposure 5.5 years (ii) Median follow-up 5.6 years	(i) • Obesity, alcohol, smoking • Comorbidities: diabetes, CHD, MI, HF, peripheral vascular disease, cerebrovascular disease, cerebrovascular accident, COPD, mental illness, liver disease, PUD (ii) • Age, sex, deprivation, BMI, alcohol, smoking • Comorbidities: GERD, PUD, cirrhosis, hepatitis, diabetes	(i) PCCIU PPI: aOR, 1.80 (1.34–2.41) H_2RA: aOR, 1.21 (0.84–1.76) (ii) UK Biobank PPI: aHR, 1.99 (1.34–2.94) H_2RA: aHR, 1.70 (0.82–3.53)
Pancreatic cancer									
Bradley et al., 2012	UK	Case–control	1995–2006	7954/1141	PPI H_2RA	57.3 (9.8)/53.7-%	2 years	Smoking, BMI, alcohol, history of chronic pancreatitis, NSAIDs, steroids, HRT, diabetes, prior cancer (year of birth, sex, general practice site)	PPI: aOR, 0.93 (0.65–1.32) H_2RA: aOR, 0.95 (0.71–1.29)
Habel et al., 2000	USA	Cohort	1982–1985	29,229/4125	Cimetidine	NA	More than 10 years	Age, sex, pharmacy data source	aRR, 1.10 (0.57–2.10)
Hicks et al., 2018	Denmark	Case–control	2000–2015	25,809/4998	PPI	NA/56.7%	2 years	Age, sex, education, calendar time, diabetes, alcohol-related disease, COPD, chronic pancreatitis, gallstones, peptic ulcer, *H. pylori* infection, HBV, HCV, low-dose aspirin, NSAIDs, statin, HRT, CCI (age, sex, calendar time)	aOR, 1.04 (0.97–1.11)
	South Korea	Cohort	2002–2013	403,826/49,789	PPI	NA/53.5%	More than 1 year	Age, sex, socioeconomic status, BMI, smoking, alcohol consumption,	aHR, 1.32 (1.03–1.70)

Table 1 (continued)

Author, year	Country	Study design	Study period	Number of participants (control/case)	Drugs	Mean age (SD)/male	Exposure/follow-up	Adjustments (matching variables in case–control studies)	Results (95% confidence interval)
Hwang et al., 2018								physical activity, type 2 diabetes, chronic pancreatitis, CCI	
Kearns et al., 2017	UK	Case–control	1995–2013	16,072/4113	PPI	Control 71.1 (11.4), case 70.9 (11.5)/51.-5%	Control 6.36 years (4.10), case 6.33 years (4.09)	Diabetes, smoking, alcohol use, obesity (age, sex, practice site, calendar time, follow-up)	aOR, 1.85 (1.67–2.06)
Lai et al., 2014	Taiwan	Case–control	2000–2010	3908/977	PPI H_2RA	Control 68.1 (11.2), case 68.4 (11.2)/60.-1%	Control 9.5 months, case 4.5 months	Acute/chronic pancreatitis, diabetes, obesity, H_2RA (PPI), statin, nonstatin lipid-lowering drugs, aspirin, COX-2 inhibitors (age, sex, year of pancreatic cancer diagnosis)	PPI: aOR, 9.28 (7.77–11.08) H_2RA: aOR, 1.90 (1.53–2.35)
Peng et al., 2018	Taiwan	Case–control	2006–2011	1087/1087	PPI H_2RA	Control 68.3 (60.9), case 67.4 (11.5)/60.-3%	2 years	Age, chronic pancreatitis (propensity score: sex, age, year of pancreatic cancer diagnosis, H_2RA, aspirin, metformin, gastric polyp, gastritis, cirrhosis, diabetes, chronic pancreatitis, HBV, HCV, IBD, biliary tract disease, stroke, coronary arterial disease, COPD, alcohol-related illness)	PPI: aOR, 1.69 (1.42, 2.03) H_2RA: OR, 1.20 (0.95, 1.52)
Respiratory system									
Lung cancer									
Habel et al., 2000	USA	Cohort	1982–1985	29,229/4125	Cimetidine	NA	More than 10 years	Age, sex, pharmacy data source	Lung/bronchus: aRR, 1.24 (0.94–1.62)
Hsu et al., 2013	Taiwan	Case–control	2000–2007	14,108/3527	H_2RA	70.9 (9.1)/61.2-%	Median 7.4 years	Short-acting human insulin, insulin glargine, metformin, glinides, NSAIDs, chronic lung disease, calcium channel blockers, retinopathy, angiotensin receptor blockers, PPIs, cerebrovascular disease, aspirin	aOR, 1.02 (0.93–1.11)
Breast cancer									
Chen et al., 2019	Taiwan	Case–control	2004–2013	64,234/64,234	PPI	Control 53.2 (11.9), case 53.1 (11.8)/0%	5 years	Age, income, location, hypertension, hyperlipidemia, diabetes, obesity, year	aOR, 0.75 (0.72–0.78)
Coogan et al., 2005	USA	Case–control	1977–2002	8482/6994	H_2RA	NA/0%	More than 1 year	(Age, center, year)	Cimetidine: OR, 0.9 (0.6–1.2) Other H_2RA: OR, 0.9 (0.6–1.3)
	Taiwan	Case–control	2000–2013	4838/4838	PPI	44 years/0%		Age, pregnancy, *Helicobacter pylori* infection, GERD, Crohn's disease,	aHR, 0.32 (0.20–0.49)

Table 1 (continued)

Author, year	Country	Study design	Study period	Number of participants (control/case)	Drugs	Mean age (SD)/male	Exposure/follow-up	Adjustments (matching variables in case–control studies)	Results (95% confidence interval)
Ding et al., 2019								obesity, endometriosis, polycystic ovarian syndrome, alcohol-related disease, estradiol, premarin, NSAIDs	
Habel et al., 2000	USA	Cohort	1982–1985	29,229/4125	Cimetidine	NA	More than 10 years	Age, sex, pharmacy data source	aRR, 1.09 (0.83–1.43)
Hálfdánarson et al., 2018	Iceland	Case–control	2005–2014	17,390/1739	PPI	Median 62 years (IQR 52–72)/0-%	More than 5 years	NSAIDs (birth year, sex, calendar time)	aOR, 1.03 (0.92–1.16)
Mathes et al., 2008	USA	Case–control	2000–2004	1390/1836 (1148, 688)	H_2RA	Range 55–79/0%	More than 2 years	Age, year, hormone therapy, study center (race, income, marital status, education, age at menarche, parity, age at first birth, type of menopause, age at menopause, duration of contraceptive use, family history of breast cancer, BMI, smoking, alcohol intake	Ductal carcinoma: aOR, 0.9 (0.8–1.2) Lobular carcinoma: aOR, 0.9 (0.7–1.2)
Prostate cancer									
Habel et al., 2000	USA	Cohort	1982–1985	29,229/4125	Cimetidine	NA	More than 10 years	Age, sex, pharmacy data source	aRR, 1.01 (0.77–1.32)
Hálfdánarson et al., 2018	Iceland	Case–control	2005–2014	18,968/1897	PPI	Median 70 years (IQR 63–77)/1-00%	More than 5 years	NSAIDs (birth year, sex, calendar time)	aOR, 1.12 (1.00–1.25)
Velicer et al., 2006	USA	Cohort	2000–2003	29,220/1083	H_2RA	Control 61.6 (7.3), cimetidine 62.9 (7.4)/100-%	1–3 years	Age, prostate-specific antigen testing	Cimetidine: aRR, 0.97 (0.61–1.53) Other H_2RA: aRR, 0.86 (0.64–1.14)
Urinary system									
Kidney cancer									
Nayan et al., 2017	Canada	Case–control	1997–2014	35,939/10,377	PPI	Range ≥ 65 years/57.3%	36–42 months	(Age, sex, comorbidity score, area, history of hypertension)	OR, 0.99 (0.88–0.91)
Skin									
Melanoma									
Habel et al., 2000	USA	Cohort	1982–1985	29,229/4125	Cimetidine	NA	More than 10 years	Age, sex, pharmacy data source	aRR, 0.94 (0.55–1.63)
	Iceland	Case–control	2005–2014	3850/385	PPI		More than 5 years		aOR, 0.84 (0.69–1.12)

Table 1 (continued)

Author, year	Country	Study design	Study period	Number of participants (control/case)	Drugs	Mean age (SD)/male	Exposure/follow-up	Adjustments (matching variables in case–control studies)	Results (95% confidence interval)
Hálfdánarson et al., 2018						Median 55 years (IQR 42–68)/0-%		NSAIDs (birth year, sex, calendar time)	
Lymphoma									
Non-Hodgkin									
Beiderbeck et al., 2003	Netherlands	Case–control	1991–1998	800/211	H_2RA	59.7 (16.4)/53.-2%	5 years	Comorbidity indicator, follow-up time (sex, year of birth, community pharmacy, calendar period, duration of follow-up)	aOR, 0.68 (0.41–1.41)
Other cancer									
Chien et al., 2016	Taiwan	Case–control	2000–2010	76,762/7681	PPI	69.5 (11.6)/58.-1%	NA	Choledochal cysts, cholangitis, cholelithiasis, cirrhosis, alcoholic liver disease, NAFLD, HBV, HCV, diabetes, chronic pancreatitis, IBD, PUD, GERD, cardiovascular disease, H_2RA, aspirin, NSAIDs, statins, metformin, insulins, other antidiabetic drugs, *H. pylori* eradication therapy (age, sex, follow-up period of PPI exposure)	Periampullary cancer: aOR, 1.35 (1.16–1.57)
Habel et al., 2000	USA	Cohort	1982–1985	29,229/4125	Cimetidine	NA	More than 10 years	Age, sex, pharmacy data source	Uterine: aRR, 0.73 (0.34–1.56) Ovarian: aRR, 0.64 (0.23–1.75) Kidney/bladder: aRR, 1.32 (0.90–1.96) Lymphoma/myeloma/leukemia: aRR, 1.09 (0.74–1.61)

PPI proton pump inhibitor, *H_2RA* histamine 2-receptor antagonist, *BMI* body mass index, *EGD* esophagogastroduodenoscopies, *GERD* gastroesophageal reflux disease, *PUD* peptic ulcer disease, *IRR* incidence rate ratio, *OR* odds ratio, *HR* hazard ratio, *COX-2* cyclooxygenase-2, *NSAID* nonsteroidal anti-inflammatory drug, *CCI* Charlson comorbidity index, *COPD* chronic obstructive pulmonary disease, *HRT* hormone replacement therapy, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *IBD* inflammatory bowel disease, *NAFLD* nonalcoholic fatty liver disease

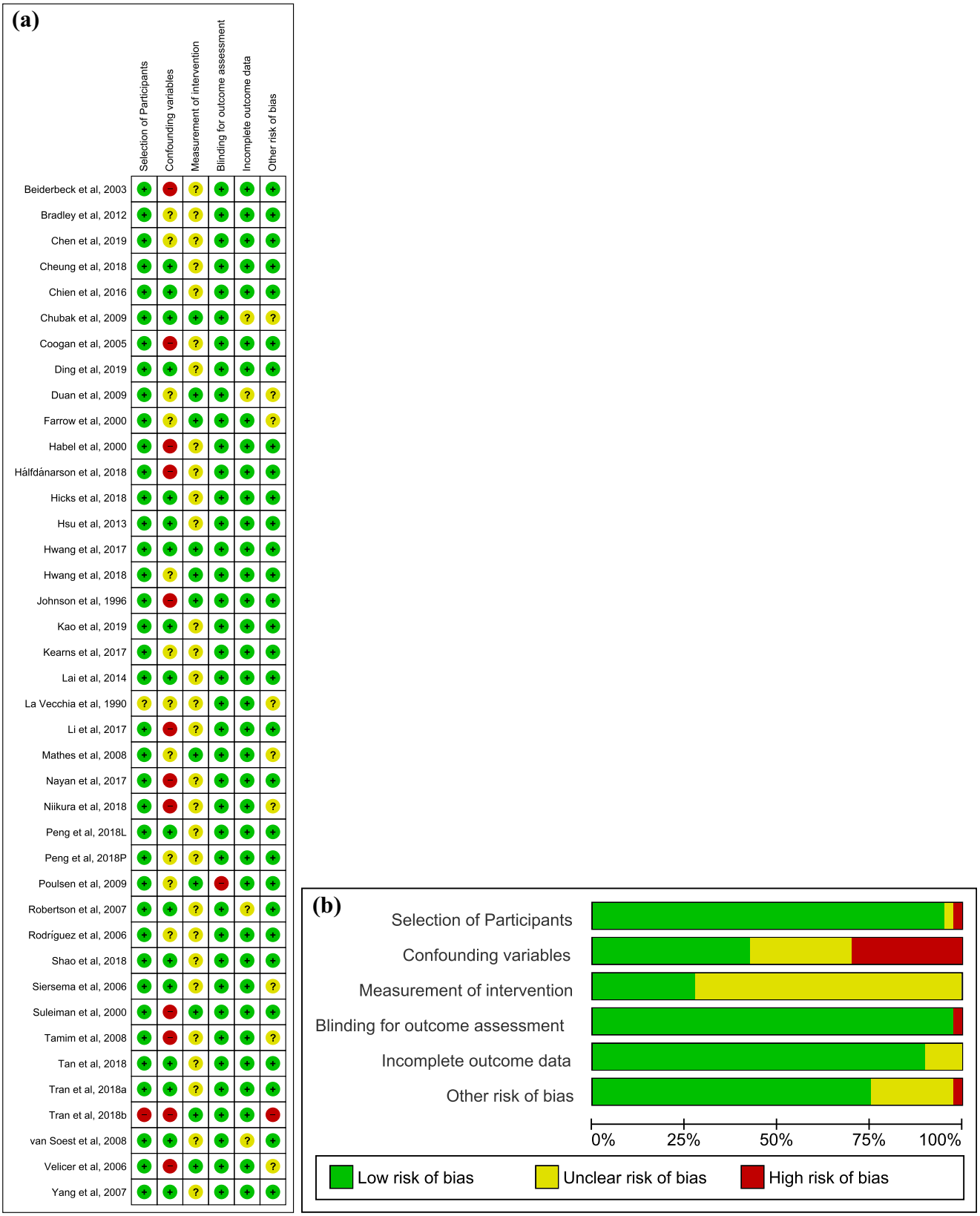

Fig. 2 Quality assessment of included studies using the Risk of Bias Assessment tool for Nonrandomized Studies (ROBANS): **a** ROBANS graph and **b** ROBANS summary. +: low risk of bias; ?: unclear risk of bias; −: high risk of bias

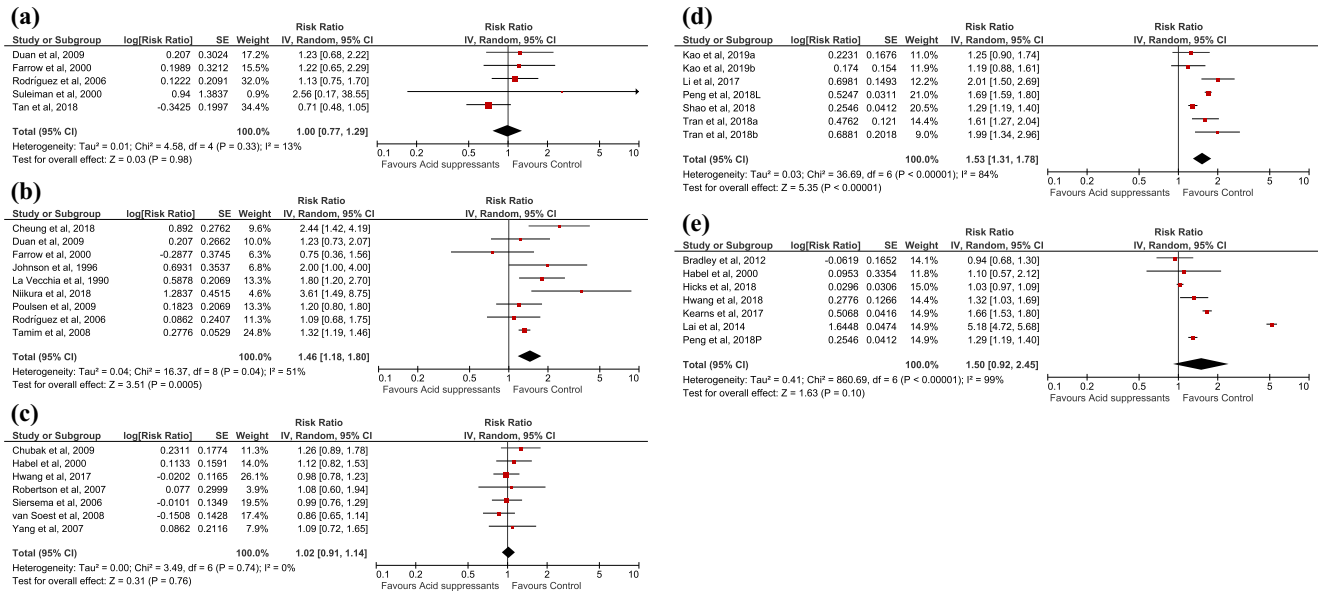

Fig. 3 The association between acid-suppressive agent use and the risk of cancer: **a** esophageal cancer, **b** gastric cancer, **c** colorectal cancer, **d** liver cancer, and **e** pancreatic cancer

Acid-suppressive agents and prostate cancer

Three studies including 84,522 individuals investigated the association between ASAs and prostate cancer. We did not find a significant association between the risk of prostate cancer and ASA use (RR, 1.09; 95% CI, 0.99–1.20); no heterogeneity was found (I^2 = 0%, P = 0.72) (Fig. 5b).

Acid-suppressive agents and other cancers

Two studies on lung cancer and two studies of melanoma were also included in the systematic review. ASA use was not significantly associated with the risk of lung cancer or melanoma compared with nonuse with no significant heterogeneity (RR, 1.07; 95% CI, 0.91–1.27; I^2 = 43%, P = 0.18 for lung cancer and RR, 0.86; 95% CI, 0.72–1.02; I^2 = 0%, P = 0.73 for melanoma).

One study reported kidney cancer, non-Hodgkin lymphoma, periampullary cancer, and all types of cancer. There was no significant association between PPIs and kidney cancer (OR, 0.99; 95% CI, 0.88–0.91) in the study by Nayan et al. and between H_2RA and non-Hodgkin lymphoma (aOR, 0.68; 95% CI, 0.41–1.41) in Beiderbeck et al.'s study. Chien et al. reported that PPI use increased the risk of periampullary cancer compared with nonuse (aOR, 1.35; 95% CI, 1.16–1.17). Habel et al. studied the association between cimetidine use and all types of cancer and reported no significant association for uterine, ovarian, and kidney/bladder cancers and lymphoma/myeloma/leukemia (Table 1).

Discussion

This systematic review assessed the association between ASA use and the risk of development of each cancer. We found that ASA use was associated with a 46% increase in the risk of gastric cancer and a 53% increase in the risk of liver cancer, but it was not significantly associated with other cancers, including esophageal, colorectal, pancreatic, breast, and prostate cancer. In particular, the increase in the risk of gastric and liver cancer with PPI use was higher than that with H_2RA use.

The results of our meta-analysis were similar to previous studies [10, 12]. Previous systematic review reported that long-term PPI use (at least 3 months) was significantly associated with a 78% increase in the risk of gastric cancer compared with nonuse [10], which is slightly higher than our results (36%). It may be because Islam et al. investigated the risk of gastric cancer with long-term PPI, while our study included ever use of PPIs or H_2RAs. Another meta-analysis found that PPIs and H_2RAs were associated with a 39% and 40% increase in gastric cancer risk [12]. In our subgroup analysis, the risk of gastric cancer in PPI users was higher than H_2RA users (39% vs. 26%) when compared with nonusers. The mechanism by which ASAs relate an increased risk of gastric cancer is unknown; however, several pathways have been suggested [12]. Researchers have speculated that cancer may arise from bacterial overgrowth and nitrosamine formation caused by the suppression of gastric acid formation [61–65]. In contrast to this theory, other researchers have proposed that acid-suppressing medications cause hypergastrinemia, which ultimately is related to gastric polyps and carcinomas [66–77].

Table 2 Subgroup analysis of the association between acid-suppressive agent use and the risk of cancer

Subgroup	Studies, *n*	Acid-suppressant users, *n*	Nonusers, *n*	Random effects, risk ratio [95% CI]	Effect, *P* value	I^2 (%)	Heterogeneity, *P* value
Esophageal cancer							
Type of acid suppressants							
PPI	2	1440	8629	0.75 [0.55, 1.03]	0.08	0	0.62
H_2RA	4	1263	10,169	0.98 [0.72, 1.32]	0.88	30	0.23
Drug uptake duration							
Less than 1 year	4	695	9774	0.87 [0.46, 1.64]	0.66	60	0.06
1 year or more	5	1069	10,475	1.22 [0.73, 2.05]	0.45	67	0.02
Type of esophageal cancer							
Adenocarcinoma	5	2409	10,455	1.00 [0.77, 1.29]	0.98	13	0.33
Squamous cell carcinoma	1	113	679	0.23 [0.05, 1.06]	0.06	–	–
Studies of low risk of bias of measurement of intervention	3	153	2043	1.25 [0.81, 1.91]	0.31	0	0.87
Gastric cancer							
Type of acid suppressants							
PPI[a]	5	20,620	34,383	1.53 [1.13, 2.07]	0.01	61	0.04
H_2RA	7	20,226	38,023	1.32 [1.08, 1.60]	0.01	26	0.23
Drug uptake duration							
Less than 1 year	2	609	9613	1.06 [0.49, 2.31]	0.88	70	0.07
1 year or more[a]	3	456	10,323	1.21 [0.54, 2.72]	0.64	74	0.01
Type of gastric cancer							
Cardia[a]	4	1503	9159	1.10 [0.81, 1.50]	0.53	0	0.56
Noncardia[a]	3	1307	9094	1.54 [0.89, 2.67]	0.12	72	0.03
Patients with *Helicobacter pylori*	2	3389	60,541	2.71 [1.71, 4.31]	< 0.001	0	0.46
Studies of low risk of bias of measurement of intervention	4	19,112	18,895	1.23 [0.90, 1.66]	0.19	18	0.30
Colorectal cancer							
Type of acid suppressants							
PPI	6	8980	512,196	1.06 [0.96, 1.16]	0.26	0	0.47
H_2RA	2	4429	50,207	0.96 [0.78, 1.19]	0.71	38	0.21
Drug uptake duration							
Less than 1 year	2	2404	50,428	1.36 [0.48, 3.92]	0.56	96	< 0.001
1 year or more	3	477	108,254	1.00 [0.75, 1.33]	1.00	0	0.65
Cumulative defined daily dose (DDD)							
< 60 DDDs	2	44,069	409,370	0.96 [0.88, 1.05]	0.34	0	0.93
≥ 60 DDDs	2	5884	409,370	0.97 [0.79, 1.19]	0.77	0	0.83
Studies of low risk of bias of measurement of intervention	2	5777	402,949	1.07 [0.85, 1.36]	0.56	29	0.24
Liver cancer[b]							
Type of acid suppressants							
PPI[c]	7	27,188	330,426	1.53 [1.31, 1.78]	< 0.001	84	< 0.001
H_2RA[c]	3	4322	2801	1.07 [0.86, 1.32]	0.54	42	0.18
Cumulative defined daily dose (DDD)							
< 365 DDDs[d]	5	3520	323,092	1.56 [0.99, 2.45]	0.06	86	< 0.001
≥ 365 DDDs[d]	4	2550	9399	1.41 [0.96, 2.08]	0.08	76	0.006
Type of liver cancer							
Hepatocellular carcinoma[c]	5	23,532	326,959	1.40 [1.17, 1.68]	< 0.001	57	0.06
Intrahepatic bile duct carcinoma[c, e]	2	–	–	1.90 [0.81, 4.50]	0.14	88	0.004
Patients with hepatitis B or C virus	3	13,244	13,266	1.45 [1.03, 2.03]	0.03	72	0.03
	2	812	473,576	1.70 [1.39, 2.09]	< 0.001	0	0.37

Table 2 (continued)

Subgroup	Studies, *n*	Acid-suppressant users, *n*	Nonusers, *n*	Random effects, risk ratio [95% CI]	Effect, *P* value	I^2 (%)	Heterogeneity, *P* value
Studies of low risk of bias of measurement of intervention							
Pancreatic cancer							
Type of acid suppressants							
PPI	6	22,375	460,936	1.56 [0.93, 2.64]	0.09	99	< 0.001
H_2RA	4	9688	38,464	1.22 [0.90, 1.65]	0.21	86	< 0.001
Drug uptake duration							
Less than 1 year	2	544	9181	1.14 [0.82, 1.59]	0.42	73	0.05
1 year or more	1	326	7781	0.94 [0.68, 1.30]	0.37	–	–
Cumulative defined daily dose (DDD)							
< 365 DDDs	4	50,148	443,814	1.10 [0.89, 1.35]	0.39	91	< 0.001
≥ 365 DDDs	2	1155	38,588	1.01 [0.87, 1.18]	0.89	0	0.69
Studies of low risk of bias of measurement of intervention	1	5710	403,826	1.32 [1.03, 1.69]	0.03	–	–
Breast cancer							
Type of acid suppressants							
PPI	3	22,441	134,832	0.78 [0.61, 1.00]	0.05	93	< 0.001
H_2RA	3	4750	45,821	0.95 [0.89, 1.01]	0.09	0	0.58
Drug uptake duration							
Less than 2 years	3	3095	29,989	1.03 [0.93, 1.13]	0.59	0	0.75
2 years or more	3	1069	29,989	0.98 [0.85, 1.14]	0.82	0	0.54
Cumulative defined daily dose (DDD)							
< 365 DDDs	2	6390	129,994	0.92 [0.79, 1.08]	0.32	79	0.03
≥ 365 DDDs	1	1110	133,97	1.00 [0.81, 1.23]	1.00	–	–
Studies of low risk of bias of measurement of intervention	1	455	2075	0.94 [0.88, 1.00]	0.07	–	–

PPI proton pump inhibitor, *H_2RA* histamine 2-receptor antagonist, *DDD* defined daily dose

[a] Cheng et al. did not report the number of patients in each group, so we could not include the number of patients from their study

[b] Kao et al. and Tran et al. presented each result from two different cohorts, so we included 5 studies and 7 cohorts for liver cancer

[c] Tran et al. did not report the number of patients in each group of the UK biobank cohort used

[d] Li et al. did not report the number of patients in each group

[e] Peng et al. did not report the number of patients in each group

A previous meta-analysis reported that PPI use did not show a significant association with hepatocellular carcinoma [78], but they mentioned that their meta-analysis lacked sufficient evidence to confirm the association. On the other hand, we found a statistically significant association between ASA use and liver cancer or hepatocellular carcinoma. The risk of liver cancer was associated with PPI use, but not H_2RA use. The exact pathway through which PPIs associate with an increasing risk of liver cancer is unknown; however, several mechanisms have been suggested [79]. Long-term PPI use and the associated hypergastrinemia have been implicated in carcinogenic effects on liver cells [80]. Other speculated mechanisms include the possibility that bacterial overgrowth due to decreased acid secretion in the stomach causes the transformation of primary bile acids to secondary bile acids, which subsequently exert deleterious effects on the liver, possibly leading to liver cancer [81–83]. In addition, it should be noted that exposure of mouse models to PPIs has been demonstrated to promote liver tumors, the progression of alcoholic liver disease, nonalcoholic fatty liver disease, and nonalcoholic steatohepatitis [84, 85]. Tran et al. explained that H_2RA use generally results in weaker acid suppression and lower effects on gastrin [79, 86].

Hu et al. showed that PPI use was not associated with the risk of esophageal adenocarcinoma and/or high-grade dysplasia in patients with Barrett's esophagus [87]. We also did not find a significant association between ASAs and esophageal cancer. This result was similar for both PPIs and H_2RAs. Theoretically, PPIs and H_2RAs decrease esophageal acid and bile refluxate exposure of the esophagus, thereby

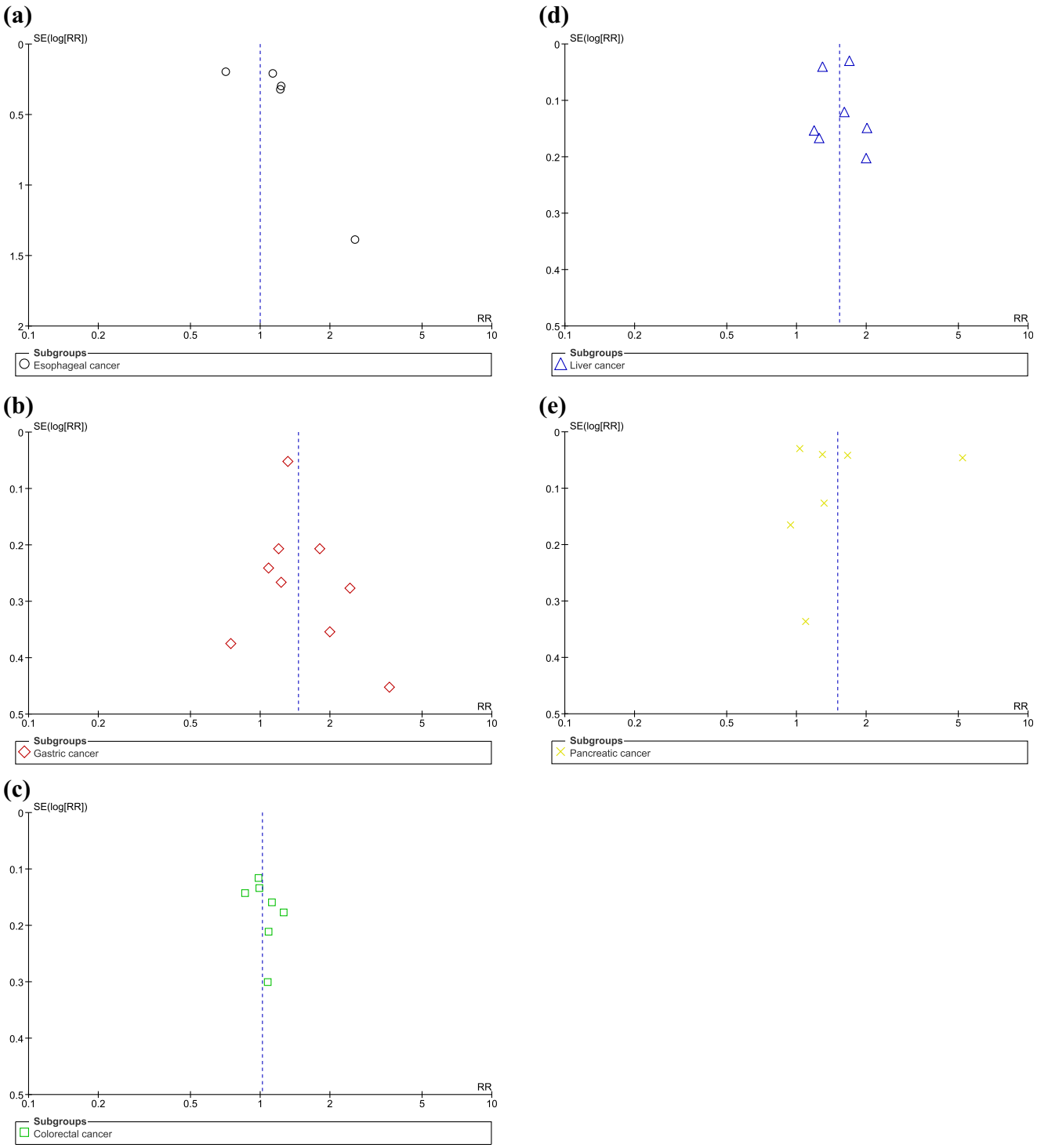

Fig. 4 Funnel plot of included studies: **a** esophageal cancer, **b** gastric cancer, **c** colorectal cancer, **d** liver cancer, and **e** pancreatic cancer

promoting mucosal healing and acting as a potential chemoprotective modality to mitigate esophageal cancers [87]. However, the guidelines for GERD recommend the use of ASAs for symptom control and not specifically for the prevention of esophageal adenocarcinoma [88]. It is important to note that reflux symptoms are poorly correlated with the actual amount of esophageal refluxate in patients with GERD; thus, PPI exposure may not be correlated with the incidence of esophageal cancers [89].

When Islam et al. pooled the ORs of colorectal and pancreatic cancers in PPI users and compared these values to those of nonusers, no significant association was observed [10]. These results were similar to our results: the RRs of ASAs for the risk of colorectal cancer and pancreatic cancer

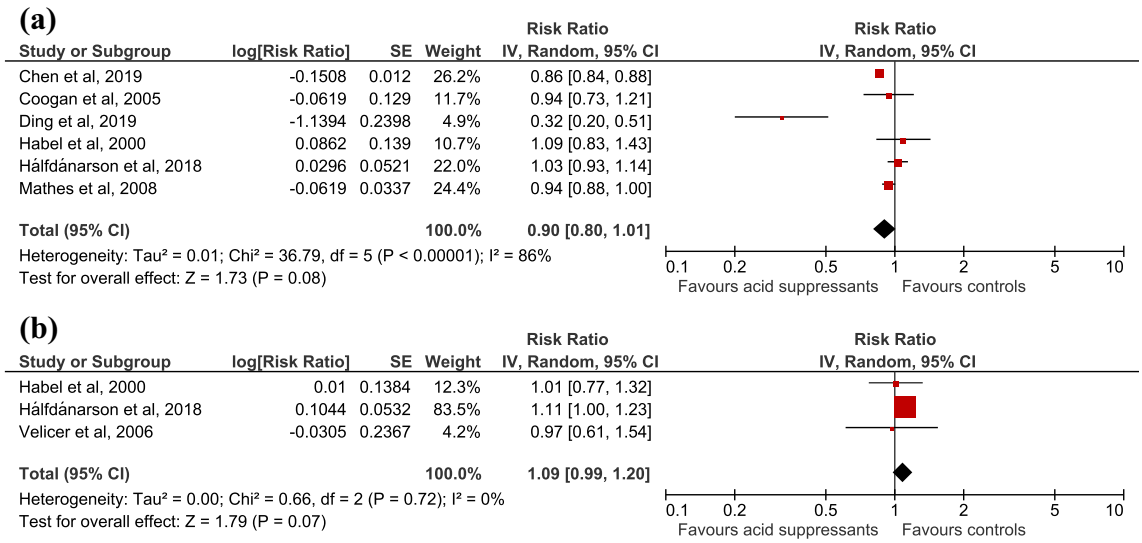

Fig. 5 The association between acid-suppressive agent use and the risk of cancer: **a** breast cancer and **b** prostate cancer

were 1.02 (95% CI, 0.91–1.14) and 1.50 (95% CI, 0.92–2.45). We could not find the previous systematic reviews of lung, breast, and prostate cancers and ASAs.

The results of the present study should be interpreted while considering some limitations. First, cohort and case–control studies were included in the final meta-analysis. Owing to the study designs of the included studies, we could not show a causal relationship between ASAs and cancers. However, we can describe a plausible mechanism and relative. Second, the results may include potential confounders, as the meta-analysis pooled studies that reported crude relative outcomes or adjusted outcomes with insufficient covariates. Third, ASAs can be bought OTC without a physician's prescription in most countries, so interventions may have been misclassified. We conducted the subgroup analysis for studies including both prescription medication and OTCs and the results remained consistent. Some results changed but we could not suggest them due to the small number of studies included in the subgroup analysis.

Despite these limitations, to the best of our knowledge, this is the first systematic review and meta-analysis for the association between ASA use and multiple types of cancer. We found that the increased risk of gastric and liver cancers was associated when ASAs were used, but there was no significant association between ASA use and other cancers. Although a limited number of studies were included in this meta-analysis, the results can be the best available evidence. In particular, low heterogeneity and a consistent direction were shown in esophageal cancer and colorectal cancer. We also conducted subgroup analyses according to PPI/H_2RA, duration of drug uptake, subtypes of cancer, and cumulative daily drug dose; these subgroup results can provide comprehensive and detailed information. Notably, our results showed that PPI use was associated with liver cancer, whereas H_2RA use was not.

Conclusions

The results of our meta-analysis suggests that ASA use was associated with an increased risk of gastric and liver cancer, but we did not find it to be significantly associated with esophageal or colorectal cancer. There was no strong evidence for the association of lung, breast, prostate, and kidney cancer; melanoma; and lymphoma risk with ASA use. The prescription of ASAs should be carefully considered under the potential risk of gastric and liver cancer until further well-designed studies with large sample cohorts confirm the results.

Acknowledgments We would like to thank Caitlin E. Kantner for proofreading the manuscript.

Author contributions HJS was involved in the study concept and design, literature search, study selection, quality assessment, data extraction, data analysis, data interpretation, and manuscript writing. NJ was involved in the literature search, study selection, quality assessment, data extraction, and manuscript writing. PS was involved in the study selection, quality assessment, and manuscript writing. All authors reviewed and approved the final version.

Funding information This work was supported by the Postdoctoral Research Program of Sungkyunkwan University (2017).

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

References

1. Antony Q (2009) Preventing stress ulcers with acid suppression. Pharmacy Times. https://www.pharmacytimes.com/publications/issue/2009/2009-05/hspstressulcers-0509.

2. Modlin IM, Sandor A (1997) An analysis of 8305 cases of carcinoid tumors. Cancer 79:813–829. https://doi.org/10.1002/(sici)1097-0142(19970215)79:4<813::aid-cncr19>3.0.co;2-2
3. Thorburn CM, Friedman GD, Dickinson CJ, Vogelman JH, Orentreich N, Parsonnet J (1998) Gastrin and colorectal cancer: a prospective study. Gastroenterology 115:275–280. https://doi.org/10.1016/s0016-5085(98)70193-3
4. Smith JP, Nadella S, Osborne N (2017) Gastrin and gastric cancer. Cell Mol Gastroenterol Hepatol 4:75–83. https://doi.org/10.1016/j.jcmgh.2017.03.004
5. Dacha S, Razvi M, Massaad J, Cai Q, Wehbi M (2015) Hypergastrinemia. Gastroenterol Rep (Oxf) 3:201–208. https://doi.org/10.1093/gastro/gov004
6. Rosen R, Amirault J, Liu H, Mitchell P, Hu L, Khatwa U, Onderdonk A (2014) Changes in gastric and lung microflora with acid suppression: acid suppression and bacterial growth. JAMA Pediatr 168:932–937. https://doi.org/10.1001/jamapediatrics.2014.696
7. Bajaj JS (2019) Alcohol, liver disease and the gut microbiota. Nat Rev Gastroenterol Hepatol 16:235–246. https://doi.org/10.1038/s41575-018-0099-1
8. Bajaj JS, Heuman DM, Hylemon PB, Sanyal AJ, White MB, Monteith P, Noble NA, Unser AB, Daita K, Fisher AR, Sikaroodi M, Gillevet PM (2014) Altered profile of human gut microbiome is associated with cirrhosis and its complications. J Hepatol 60:940–947. https://doi.org/10.1016/j.jhep.2013.12.019
9. Li M, Yuan J, Wen S, Chen J (2018) Alteration of gut microbiome in lung cancer patients. J Thorac Oncol 13:S947. https://doi.org/10.1016/j.jtho.2018.08.1772
10. Islam MM, Poly TN, Walther BA, Dubey NK, Anggraini Ningrum DN, Shabbir SA, Jack Li YC (2018) Adverse outcomes of long-term use of proton pump inhibitors: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol 30:1395–1405. https://doi.org/10.1097/MEG.0000000000001198
11. Tran-Duy A, Spaetgens B, Hoes AW, de Wit NJ, Stehouwer CD (2016) Use of proton pump inhibitors and risks of fundic gland polyps and gastric cancer: systematic review and meta-analysis. Clin Gastroenterol Hepatol 14:1706–1719.e5. https://doi.org/10.1016/j.cgh.2016.05.018
12. Ahn JS, Eom CS, Jeon CY, Park SM (2013) Acid suppressive drugs and gastric cancer: a meta-analysis of observational studies. World J Gastroenterol 19:2560–2568. https://doi.org/10.3748/wjg.v19.i16.2560
13. Qiu T, Zhou J, Zhang C (2018) Acid-suppressive drugs and risk of kidney disease: a systematic review and meta-analysis. J Gastroenterol Hepatol 33:1566–1573. https://doi.org/10.1111/jgh.14157
14. Lambert AA, Lam JO, Paik JJ, Ugarte-Gil C, Drummond MB, Crowell TA (2015) Risk of community-acquired pneumonia with outpatient proton-pump inhibitor therapy: a systematic review and meta-analysis. PLoS One 10:e0128004. https://doi.org/10.1371/journal.pone.0128004
15. Trifan A, Stanciu C, Girleanu I, Stoica OC, Singeap AM, Maxim R, Chiriac SA, Ciobica A, Boiculese L (2017) Proton pump inhibitors therapy and risk of *Clostridium difficile* infection: systematic review and meta-analysis. World J Gastroenterol 23:6500–6515. https://doi.org/10.3748/wjg.v23.i35.6500
16. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 151:W65–W94. https://doi.org/10.1016/j.jclinepi.2009.06.006
17. Kim SY, Park JE, Lee YJ, Seo HJ, Sheen SS, Hahn S, Jang BH, Son HJ (2013) Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. J Clin Epidemiol 66:408–414. https://doi.org/10.1016/j.jclinepi.2012.09.016
18. Davies HT, Crombie IK, Tavakoli M (1998) When can odds ratios mislead? BMJ 316:989–991. https://doi.org/10.1136/bmj.316.7136.989
19. Stare J, Maucort-Boulch D (2016) Odds ratio, hazard ratio and relative risk. Metodoloski zvezki 13:59–67
20. Zhang J, Yu KF (1998) What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA 280:1690–1691. https://doi.org/10.1001/jama.280.19.1690
21. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327:557–560. https://doi.org/10.1136/bmj.327.7414.557
22. Suleiman UL, Harrison M, Britton A, McPherson K, Bates T (2000) H2-receptor antagonists may increase the risk of cardio-oesophageal adenocarcinoma: a case-control study. Eur J Cancer Prev 9:185–191
23. Tan MC, El-Serag HB, Yu X, Thrift AP (2018) Acid suppression medications reduce risk of oesophageal adenocarcinoma in Barrett's oesophagus: a nested case-control study in US male veterans. Aliment Pharmacol Ther 48:469–477. https://doi.org/10.1111/apt.14895
24. Duan L, Wu AH, Sullivan-Halley J, Bernstein L (2009) Antacid drug use and risk of esophageal and gastric adenocarcinomas in Los Angeles County. Cancer Epidemiol Biomark Prev 18:526–533. https://doi.org/10.1158/1055-9965.EPI-08-0764
25. Farrow DC, Vaughan TL, Sweeney C, Gammon MD, Chow WH, Risch HA, Stanford JL, Hansten PD, Mayne ST, Schoenberg JB, Rotterdam H, Ahsan H, West AB, Dubrow R, Raumeni JF Jr, Blot WJ (2000) Gastroesophageal reflux disease, use of H2 receptor antagonists, and risk of esophageal and gastric cancer. Cancer Causes Control 11:231–238. https://doi.org/10.1023/a:1008913828105
26. Habel LA, Levin TR, Friedman GD (2000) Cimetidine use and risk of breast, prostate, and other cancers. Pharmacoepidemiol Drug Saf 9:149–155. https://doi.org/10.1002/(SICI)1099-1557(200003/04)9:2<149::AID-PDS481>3.0.CO;2-1
27. García Rodríguez LA, Lagergren J, Lindblad M (2006) Gastric acid suppression and risk of oesophageal and gastric adenocarcinoma: a nested case control study in the UK. Gut 55:1538–1544. https://doi.org/10.1136/gut.2005.086579
28. Cheung KS, Chan EW, Wong AYS, Chen L, Wong ICK, Leung WK (2018) Long-term proton pump inhibitors and risk of gastric cancer development after treatment for *Helicobacter pylori*: a population-based study. Gut 67:28–35. https://doi.org/10.1136/gutjnl-2017-314605
29. Johnson AG, Jick SS, Perera DR, Jick H (1996) Histamine-2 receptor antagonists and gastric cancer. Epidemiology 7:434–436. https://doi.org/10.1097/00001648-199607000-00016
30. La Vecchia C, Negri E, D'Avanzo B, Franceschi S (1990) Histamine-2-receptor antagonists and gastric cancer risk. Lancet 336:355–357. https://doi.org/10.1016/0140-6736(90)91888-h
31. Niikura R, Hayakawa Y, Hirata Y, Yamada A, Fujishiro M, Koike K (2018) Long-term proton pump inhibitor use is a risk factor of gastric cancer after treatment for *Helicobacter pylori*: a retrospective cohort analysis. Gut 67:1908–1910. https://doi.org/10.1136/gutjnl-2017-315710
32. Poulsen AH, Christensen S, McLaughlin JK, Thomsen RW, Sørensen HT, Olsen JH, Friis S (2009) Proton pump inhibitors and risk of gastric cancer: a population-based cohort study. Br J Cancer 100:1503–1507. https://doi.org/10.1038/sj.bjc.6605024
33. Tamim H, Duranceau A, Chen LQ, Lelorier J (2008) Association between use of acid-suppressive drugs and risk of gastric cancer. A nested case-control study. Drug Saf 31:675–684. https://doi.org/10.2165/00002018-200831080-00004

34. Chubak J, Boudreau DM, Rulyak SJ, Mandelson MT (2009) Colorectal cancer risk in relation to use of acid suppressive medications. Pharmacoepidemiol Drug Saf 18:540–544. https://doi.org/10.1002/pds.1749
35. Hwang IC, Chang J, Park SM (2017) Emerging hazard effects of proton pump inhibitor on the risk of colorectal cancer in low-risk populations: a Korean nationwide prospective cohort study. PLoS One 12:e0189114. https://doi.org/10.1371/journal.pone.0189114
36. Robertson DJ, Larsson H, Friis S, Pedersen L, Baron JA, Sørensen HT (2007) Proton pump inhibitor use and risk of colorectal cancer: a population-based, case-control study. Gastroenterology 133:755–760. https://doi.org/10.1053/j.gastro.2007.06.014
37. Siersema PD, Yu S, Sahbaie P, Steyerberg EW, Simpson PW, Kuipers EJ, Triadafilopoulos G (2006) Colorectal neoplasia in veterans is associated with Barrett's esophagus but not with proton-pump inhibitor or aspirin/NSAID use. Gastrointest Endosc 63:581–586. https://doi.org/10.1016/j.gie.2005.08.043
38. Yang YX, Hennessy S, Propert K, Hwang WT, Sedarat A, Lewis JD (2007) Chronic proton pump inhibitor therapy and the risk of colorectal cancer. Gastroenterology 133:748–754. https://doi.org/10.1053/j.gastro.2007.06.022
39. van Soest EM, van Rossum LG, Dieleman JP, van Oijen MG, Siersema PD, Sturkenboom MC, Kuipers EJ (2008) Proton pump inhibitors and the risk of colorectal cancer. Am J Gastroenterol 103:966–973. https://doi.org/10.1111/j.1572-0241.2007.01665.x
40. Kao WY, Su CW, Chia-Hui Tan E, Lee PC, Chen PH, Tang JH, Huang YH, Huo TI, Chang CC, Hou MC, Lin HC, Wu JC (2019) Proton pump inhibitors and risk of hepatocellular carcinoma in patients with chronic hepatitis B or C. Hepatology 69:1151–1164. https://doi.org/10.1002/hep.30247
41. Li DK, Yan P, Abou-Samra AB, Chung RT, Butt AA (2018) Proton pump inhibitors are associated with accelerated development of cirrhosis, hepatic decompensation and hepatocellular carcinoma in noncirrhotic patients with chronic hepatitis C infection: results from ERCHIVES. Aliment Pharmacol Ther 47:246–258. https://doi.org/10.1111/apt.14391
42. Peng YC, Lin CL, Hsu WY, Chow WK, Lee SW, Yeh HZ, Chen CC, Kao CH (2018) Association between cholangiocarcinoma and proton pump inhibitors use: a nested case-control study. Front Pharmacol 9:718. https://doi.org/10.3389/fphar.2018.00718
43. Shao YJ, Chan TS, Tsai K, Wu SY (2018) Association between proton pump inhibitors and the risk of hepatocellular carcinoma. Aliment Pharmacol Ther 48:460–468. https://doi.org/10.1111/apt.14835
44. Tran KT, McMenamin ÚC, Hicks B, Murchie P, Thrift AP, Coleman HG, Iversen L, Johnston BT, Lee AJ, Cardwell CR (2018) Proton pump inhibitor and histamine-2 receptor antagonist use and risk of liver cancer in two population-based studies. Aliment Pharmacol Ther 48:55–64. https://doi.org/10.1111/apt.14796
45. Bradley MC, Murray LJ, Cantwell MM, Hughes CM (2012) Proton pump inhibitors and histamine-2-receptor antagonists and pancreatic cancer risk: a nested case-control study. Br J Cancer 106:233–239. https://doi.org/10.1038/bjc.2011.511
46. Hicks B, Friis S, Pottegård A (2018) Use of proton pump inhibitors and risk of pancreatic cancer. Pharmacoepidemiol Drug Saf 27:926–930. https://doi.org/10.1002/pds.4576
47. Hwang IC, Chang J, Park SM (2018) Association between proton pump inhibitor use and the risk of pancreatic cancer: a Korean nationwide cohort study. PLoS One 13:e0203918. https://doi.org/10.1371/journal.pone.0203918
48. Kearns MD, Boursi B, Yang YX (2017) Proton pump inhibitors on pancreatic cancer risk and survival. Cancer Epidemiol 46:80–84. https://doi.org/10.1016/j.canep.2016.12.006
49. Lai SW, Sung FC, Lin CL, Liao KF (2014) Use of proton pump inhibitors correlates with increased risk of pancreatic cancer: a case-control study in Taiwan. J Kuwait Med Assoc 46:44–48
50. Peng YC, Lin CL, Hsu WY, Lu IT, Yeh HZ, Chang CS, Kao CH (2018) Proton pump inhibitor use is associated with risk of pancreatic cancer: a nested case-control study. Dose-Response 16(4):1559325818803283. https://doi.org/10.1177/1559325818803283
51. Hsu CL, Chang CH, Lin JW, Wu LC, Chuang LM, Lai MS (2013) Histamine-2 receptor antagonists and risk of lung cancer in diabetic patients – an exploratory analysis. Pharmacoepidemiol Drug Saf 22:632–640. https://doi.org/10.1002/pds.3441
52. Chen CH, Lee CZ, Lin YC, Kao LT, Lin HC (2019) Negative association of proton pump inhibitors with subsequent development of breast cancer: a nationwide population-based study. J Clin Pharmacol 59:350–355. https://doi.org/10.1002/jcph.1329
53. Coogan PF, Zhang Y, Palmer JR, Strom BL, Rosenberg L (2005) Cimetidine and other histamine 2-receptor antagonist use in relation to risk of breast cancer. Cancer Epidemiol Biomark Prev 14:1012–1015. https://doi.org/10.1158/1055-9965.EPI-04-0547
54. Ding DC, Sung FC, Chen W, Wang JH, Lin SZ (2019) Proton pump inhibitors reduce breast cancer risk in gastric ulcer patients: a population-based cohort study. Breast J 26:474–478. https://doi.org/10.1111/tbj.13519
55. Hálfdánarson ÓÖ, Fall K, Ogmundsdottir MH, Lund SH, Steingrímsson E, Ogmundsdottir HM, Zoega H (2019) Proton pump inhibitor use and risk of breast cancer, prostate cancer, and malignant melanoma: an Icelandic population-based case-control study. Pharmacoepidemiol Drug Saf 28:471–478. https://doi.org/10.1002/pds.4702
56. Mathes RW, Malone KE, Daling JR, Porter PL, Li CI (2008) Relationship between histamine 2-receptor antagonist medications and risk of invasive breast cancer. Cancer Epidemiol Biomark Prev 17:67–72. https://doi.org/10.1158/1055-9965.EPI-07-0765
57. Velicer CM, Dublin S, White E (2006) Cimetidine use and the risk for prostate cancer: results from the VITAL cohort study. Ann Epidemiol 16:895–900. https://doi.org/10.1016/j.annepidem.2006.03.003
58. Nayan M, Juurlink DN, Austin PC, Macdonald EM, Finelli A, Kulkarni GS, Hamilton RJ (2017) Canadian Drug Safety and Effectiveness Research Network (CDSERN). Medication use and kidney cancer risk: a population-based study. Eur J Cancer 83:203–210. https://doi.org/10.1016/j.ejca.2017.07.001
59. Beiderbeck AB, Holly EA, Sturkenboom MC, Coebergh JW, Stricker BH, Leufkens HG (2003) Prescription medications associated with a decreased risk of non-Hodgkin's lymphoma. Am J Epidemiol 157:510–516. https://doi.org/10.1093/aje/kwg004
60. Chien LN, Huang YJ, Shao YH, Chang CJ, Chuang MT, Chiou HY, Yen Y (2016) Proton pump inhibitors and risk of periampullary cancers - a nested case-control study. Int J Cancer 138:1401–1409. https://doi.org/10.1002/ijc.29896
61. Langman MJ (1985) Antisecretory drugs and gastric cancer. Br Med J (Clin Res Ed) 290:1850–1852. https://doi.org/10.1136/bmj.290.6485.1850
62. Freston JW (1982) Cimetidine: II. Adverse reactions and patterns of use. Ann Intern Med 97:728–734. https://doi.org/10.7326/0003-4819-97-5-728
63. Stockbruegger RW (1985) Bacterial overgrowth as a consequence of reduced gastric acidity. Scand J Gastroenterol Suppl 111:7–16. https://doi.org/10.3109/00365528509093749
64. Stockbrugger RW, Cotton PB, Eugenides N, Bartholomew BA, Hill MJ, Walters CL (1982) Intragastric nitrites, nitrosamines, and bacterial overgrowth during cimetidine treatment. Gut 23:1048–1054. https://doi.org/10.1136/gut.23.12.1048
65. Rowland JR (1988) The toxicology of N-nitroso compounds. In: Hill MJ (ed) Nitrosamines-toxicology and microbiology. Ellis Horwood pp, London, pp 117–141

66. Klinkenberg-Knol EC, Festen HP, Jansen JB, Lamers CB, Nelis F, Snel P, Lückers A, Dekkers CP, Havu N, Meuwis-sen SG (1994) Long-term treatment with omeprazole for refractory reflux esophagitis: efficacy and safety. Ann Intern Med 121:161–167. https://doi.org/10.7326/0003-4819-121-3-199408010-00001
67. Lamberts R, Creutzfeldt W, Stöckmann F, Jacubaschke U, Maas S, Brunner G (1988) Long-term omeprazole treatment in man: effects on gastric endocrine cell populations. Digestion 39:126–135. https://doi.org/10.1159/000199615
68. Laine L, Ahnen D, McClain C, Solcia E, Walsh JH (2000) Review article: potential gastrointestinal effects of long-term acid suppression with proton pump inhibitors. Aliment Pharmacol Ther 14:651–668. https://doi.org/10.1046/j.1365-2036.2000.00768.x
69. Havu N (1986) Enterochromaffin-like cell carcinoids of gastric mucosa in rats after life-long inhibition of gastric secretion. Digestion 35:42–55. https://doi.org/10.1159/000199381
70. Smith JP, Wood JG, Solomon TE (1989) Elevated gastrin levels in patients with colon cancer or adenomatous polyps. Dig Dis Sci 34: 171–174. https://doi.org/10.1007/bf01536047
71. Seitz JF, Giovannini M, Gouvernet J, Gauthier AP (1991) Elevated serum gastrin levels in patients with colorectal neoplasia. J Clin Gastroenterol 13:541–545. https://doi.org/10.1097/00004836-199110000-00013
72. Singh P, Indaram A, Greenberg R, Visvalingam V, Bank S (2000) Long term omeprazole therapy for reflux esophagitis: follow up in serum gastrin levels, EC cell hyperplasia and neoplasia. World J Gastroenterol 6:789–792. https://doi.org/10.3748/wjg.v6.i6.789
73. Jalving M, Koornstra JJ, Wesseling J, Boezen HM, DE Jong S, Kleibeuker JH (2006) Increased risk of fundic gland polyps during long-term proton pump inhibitor therapy. Aliment Pharmacol Ther 24:1341–1348. https://doi.org/10.1111/j.1365-2036.2006.03127.x
74. Solcia E, Fiocca R, Havu N, Dalväg A, Carlsson R (1992) Gastric endocrine cells and gastritis in patients receiving long-term omeprazole treatment. Digestion 51:82–92. https://doi.org/10.1159/000200921
75. Pashankar DS, Israel DM (2002) Gastric polyps and nodules in children receiving long-term omeprazole therapy. J Pediatr Gastroenterol Nutr 35:658–662. https://doi.org/10.1097/00005176-200211000-00013
76. Cats A, Schenk BE, Bloemena E, Roosedaal R, Lindeman J, Biemond I, Klinkenberg-Knol EC, Meuwissen SG, Kuipers EJ (2000) Parietal cell protrusions and fundic gland cysts during omeprazole maintenance treatment. Hum Pathol 31:684–690. https://doi.org/10.1053/hupa.2000.7637
77. van Grieken NC, Meijer GA, Weiss MM, Bloemena E, Lindeman J, Baak JP, Meuwissen SG, Kuipers EJ (2001) Quantitative assessment of gastric corpus atrophy in subjects using omeprazole: a randomized follow-up study. Am J Gastroenterol 96:2882–2886. https://doi.org/10.1111/j.1572-0241.2001.04242.x
78. Zhao J, Hua L, Li N, An R, Liang C (2018) Letter: proton pump inhibitors use and risk of hepatocellular carcinoma: a meta-analysis of observational studies. Aliment Pharmacol Ther 48:886–888. https://doi.org/10.1111/apt.14962
79. Tran KT, McMenamin ÚC, Hicks B, Murchie P, Thrift AP, Coleman HG, Iversen L, Johnston BT, Lee AJ, Cardwell CR (2018) Proton pump inhibitor and histamine-2 receptor antagonist use and risk of liver cancer in two population-based studies. Aliment Pharmacol Ther 48:55–64. https://doi.org/10.1111/apt.14796
80. Caplin M, Khan K, Savage K, Rode J, Varro A, Michaeli D, Grimes S, Brett B, Pounder R, Dhillon A (1999) Expression and processing of gastrin in hepatocellular carcinoma, fibrolamellar carcinoma and cholangiocarcinoma. J Hepatol 30:519–526
81. Llorente C, Schnabl B (2015) The gut microbiota and liver disease. Cell Mol Gastroenterol Hepatol 1:275–284. https://doi.org/10.1016/j.jcmgh.2015.04.003
82. Jansen PLM (2007) Endogenous bile acids as carcinogens. J Hepatol 47:434–435. https://doi.org/10.1016/j.jhep.2007.06.001
83. Komichi D, Tazuma S, Nishioka T, Hyogo H, Chayama K (2005) Glycochenodeoxycholate plays a carcinogenic role in immortalized mouse cholangiocytes via oxidative DNA damage. Free Radic Biol Med 39:1418–1427. https://doi.org/10.1016/j.freeradbiomed.2005.07.005
84. Llorente C, Jepsen P, Inamine T, Wang L, Bluemel S, Wang HJ, Loomba R, Bajaj JS, Schubert ML, Sikaroodi M, Gillevet PM, Xu J, Kisseleva T, Ho SB, DePew J, Du X, Sørensen HT, Vilstrup H, Nelson KE, Brenner DA, Fouts DE, Schnabl B (2017) Gastric acid suppression promotes alcoholic liver disease by inducing overgrowth of intestinal Enterococcus. Nat Commun 8:1–14. https://doi.org/10.1038/s41467-017-00796-x
85. Hayashi H, Shimamoto K, Taniai E, Ishii Y, Morita R, Suzuki K, Shibutani M, Mitsumori K (2012) Liver tumor promoting effect of omeprazole in rats and its possible mechanism of action. J Toxicol Sci 37:491–501. https://doi.org/10.2131/jts.37.491
86. Dacha S, Razvi M, Massaad J, Cai Q. Wehbi M (2015) Hypergastrinemia. Gastroenterol Rep 3:201–208. https://doi.org/10.1093/gastro/gov004
87. Hu Q, Sun TT, Hong J, Fang JY, Xiong H, Meltzer SJ (2017) Proton pump inhibitors do not reduce the risk of esophageal adenocarcinoma in patients with Barrett's esophagus: a systematic review and meta-analysis. PLoS One 12:e0169691. https://doi.org/10.1371/journal.pone.0169691
88. Katz PO, Gerson LB, Vela MF (2013) Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol 108:308–328. https://doi.org/10.1038/ajg.2012.444
89. Kleiman DA, Sporn MJ, Beninato T, Metz Y, Crawford C, Fahey TJ 3rd, Zarnegar R (2013) Early referral for 24-h esophageal pH monitoring may prevent unnecessary treatment with acid-reducing medications. Surg Endosc 27:1302–1309. https://doi.org/10.1007/s00464-012-2602-z