Proton pump inhibitors and risk of gastrointestinal cancer: A meta-analysis of cohort studies

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Abstract. Although proton pump inhibitors (PPIs) are widely used in the treatment of various acid-related disorders, observational studies have raised concern about an association between PPI use and the risk of gastrointestinal cancer. The present study aimed to investigate the association between them using a meta-analysis of cohort studies. PubMed and Excerpta Medica dataBASE were searched from inception to December 2022 to identify relevant cohort studies. The primary outcome was the risk of gastrointestinal cancer among PPI users, expressed as a pooled odds ratio (OR), relative risk (RR) or hazard ratio (HR) and its 95% CI based on a random-effects model. A total of 25 cohort studies from 23 articles were included in the final analysis. In the meta-analysis of all studies, an increased risk of gastrointestinal cancer following the use of PPIs was observed (OR/RR/HR, 2.09; 95% CI, 1.78-2.46). Subgroup analyses by type of cancer also revealed an association between PPI use and the risk of esophageal, gastric, liver and pancreatic cancer, whereas there was no association for colorectal cancer. The increased risk of gastrointestinal cancer was also observed in individuals who had used PPIs for <1 year (OR/RR/HR, 5.23; 95% CI, 2.96-9.24) as well as individuals who had used PPIs for up to 3 years. The present meta-analysis revealed that the use of PPIs was associated with an increased risk of gastrointestinal cancer.

Introduction

Since the first approval of proton pump inhibitors (PPIs) in 1989, they have proven to be an effective first-line treatment for gastrointestinal disorders including symptomatic peptic ulcer disease, gastresophageal reflux disease, and Zollinger-Ellison syndrome, as well as for the prevention of gastrointestinal bleeding in patients receiving antiplatelet therapy (1-7). PPIs are also one of the standard treatments for *Helicobacter pylori* infection, along with antibiotics (1). Their popularity has steadily grown, and they are now one of the most prescribed drug classes worldwide, both in the outpatient and inpatient clinical settings (8). In the United States, the consumption of PPIs in non-hospitalized patients doubled from 1999 to 2012 (9). In England, over 50 million prescriptions that contained PPIs were prescribed in 2015 (10). Due to the effectiveness of PPIs in prevention and treatment of gastrointestinal disorders, physicians tend to prescribe PPIs in the long term for specific conditions such as Barrett's esophagus, chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) with high to moderate bleeding risk, severe oesophagitis, and Zollinger-Ellison syndrome, and patients usually take these medications for longer than needed (11-14). In England, amongst new users of PPIs in a cohort study from 1990 to 2014, 26.7% of them continued taking PPIs for more than one year.15 Sixty percent of the long-term PPI users did not make an attempt to step down or discontinue PPI therapy (15), and approximately 30% of the PPI users were not appropriately prescribed for the long-term treatment (16,17).

The long-term use of PPIs has raised concerns about infection (18,19), dementia (20), osteoporosis, fracture (21), and cancer (22). Specifically, the risk of gastrointestinal cancers has been a major concern to both patients and physicians. Previous laboratory and animal studies have reported that PPIs can suppress gastric acid secretion and interfere with bacterial growth and nitrosamine formation (23,24). Furthermore, PPIs have been linked to hypergastrinemia, which has been identified as a possible risk factor for cancer progression (25,26).

Meanwhile, observational epidemiological studies have reported inconsistent findings on whether PPIs increase the risk of gastrointestinal cancers (27-49). Fourteen cohort studies reported a significant increased risk of gastrointestinal cancers by the use of PPIs (29,30,32-37,40,42-45,47), while 10 cohort studies did no association between them (27,28,31,38,39,41,46,48,49).

Several meta-analyses of retrospective cohort studies and case-control studies have reported the associations between

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the use of PPIs and a specific type of gastrointestinal cancers such as gastric cancer, colorectal cancer, and pancreatic cancer (50-54). However, no comprehensive meta-analysis of cohort studies for all types of gastrointestinal cancers including esophageal cancer, liver cancer, and biliary cancer has been reported up to date.

Thus, the current study aimed to investigate the association between the use of PPIs and the risk of gastrointestinal cancers using a comprehensive meta-analysis of cohort studies.

Materials and methods

Literature search strategy. This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (55). A literature search in both PubMed and Excerpta Medica dataBASE (EMBASE) databases was conducted up to December 2022. This search used a combination of the National Library of Medicine (NLM) Medical Subject Headings (MeSH) terms with a wide range of free-text terms as search terms to identify as many relevant articles as possible. A PICO framework was used to determine search terms related with the topic of this study as follows: P for population is 'general population'; I for intervention (exposure in this study) is 'use of PPIs'; C for comparison is 'no use of PPIs'; and O for outcome is 'incidence of cancer'. Study design of included studies was restricted to cohort study for the current meta-analysis. Thus, using Boolean operators for all the determined MeSH and free-text terms, a combination of search terms was created as follows: (proton pump inhibitors or omeprazole or esomeprazole or pantoprazole or lansoprazole or dexlansoprazole or rabeprazole) and cancer and cohort study. Data S1 shows the final search strategy for the PubMed example. Additionally, the reference lists of the identified articles were examined to identify relevant studies that were not detected through the initial search strategy.

Eligibility criteria. Observational epidemiological studies were included in the final meta-analysis based on the following criteria: i) an original prospective or retrospective cohort study; ii) investigated the association between the use of PPIs and any types of gastrointestinal cancers; iii) reported outcome measures with an adjusted relative risk (RR), odds ratio (OR) or hazard ratios (HR) and its 95% confidence intervals (CI); iv) publication in English. If data were reported in multiple publications from the same study, the study presenting the most comprehensive data was included. Studies that were not published in peer-reviewed journals or only presented in academic conferences were excluded.

Selection of relevant studies. Two authors (Tran HT and Trinh TKT) independently selected all studies retrieved from the databases. Discrepancies in study selection were resolved by reaching a consensus with a senior author (Myung SK). The extraction process encompassed the collection of year of publication and first author's name, type of study, country, year of the enrollment of participants, population (number of participants, gender, and baseline age range), type of cancer, definition of PPI exposure and a control group, adjusted OR/RR/HR with 95% CI, and adjusted variables.

Assessment of methodological quality. The methodological quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) for assessing the quality of cohort studies in the meta-analyses (56). The NOS score system ranges from 0 to 9 representing the three subscales of the study quality dimensions: study selection, comparability, and exposure assessment. Given the absence of established cutoff criteria for designating a study as high- or low-quality, studies scoring above the average were categorized as high-quality.

Main and subgroup analyses. The main meta-analysis investigated the association between the use of PPIs and the risk of gastrointestinal cancers. Subsequently, subgroup meta-analyses were conducted, categorized by type of cancer (esophageal, gastric, pancreatic, colorectal, liver, gallbladder, or bile duct cancer), sex (male or female), age (over 50 years old), obesity (yes or no), smoking status (yes or no), type of PPIs (omeprazole, lansoprazole, esomeprazole, pantoprazole, or rabeprazole), duration of PPI use (within 1 year, 1-3 years, 3-5 years, or over 5 years), concurrent medications (aspirin or statins), geographical region, study design (retrospective or prospective cohort study), and methodological quality of study (high or low quality).

Statistical analysis. A pooled OR/RR/HR with its 95% CI was calculated using the adjusted OR/RR/HR and its respective 95% CI from each study reporting the association between the use of PPIs and the risk of gastrointestinal cancers. Additionally, an evaluation of heterogeneity across the studies was performed using Higgins I^2, which measures the percentage of total variation across the studies (57). The I^2 value is calculated as follows:

$$I^2 = 100\% \times (Q - df)/Q,$$

where Q is Cochran's heterogeneity statistic, and df indicates the degrees of freedom. Negative values of the I^2 were set at zero; the I^2 ranges from 0% (no observed heterogeneity) to 100% (maximal heterogeneity) (57). An I^2 value greater than 50% indicates substantial heterogeneity (57).

The pooled estimate was computed using the DerSimonian and Laird method (58). A random-effects model was used due to the diverse geographical contexts and varying populations in which the identified studies were conducted.

Publication bias was assessed utilizing the Begg's funnel plot and Egger's test (59). Publication bias exists when the Begg's funnel plot shows asymmetry or when the P-value of the Egger's test is less than 0.05 (59). Further, sensitivity analyses were conducted to explore the influence of each study on the pooled estimate by omitting a study one by one and re-analyzing. Stata SE version 16.1 statistical software package (StataCorp, College Station, Texas, USA) was used for all the meta-analyses.

Results

Identification of relevant studies. Fig. 1 shows a flow diagram of the selection process for the current study. A total of 1,934 articles were identified by searching two electronic databases, PubMed and EMBASE. After removing 195 duplicate

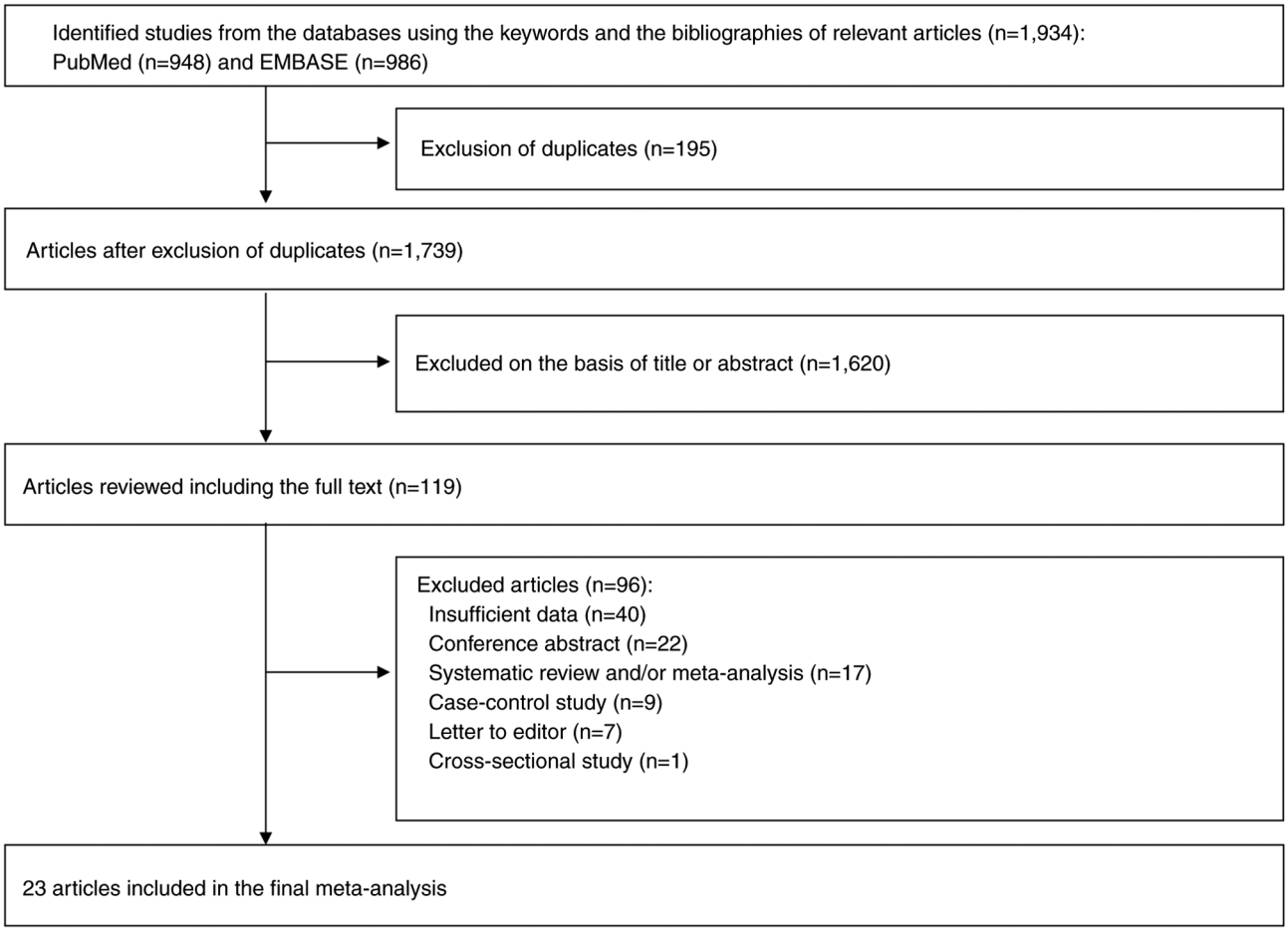

Figure 1. Flow diagram of identification of relevant studies.

articles, an additional 1,620 articles were excluded based on the predetermined selection criteria. A thorough review was conducted on the remaining 119 articles. Among these, 96 articles were excluded for the following reasons: insufficient data (n=40); conference abstract (n=22); systematic review or/and meta-analysis (n=17); case-control studies (n=9); letters to editor (n=7); and cross-sectional studies (n=1). The remaining 23 articles (27-49) were included in the final analysis. The result of the assessment with Cohen's kappa in the selecting studies was 0.97, suggesting an almost perfect agreement between the two authors.

Characteristics of studies included in the final meta-analysis. This meta-analysis included 25 cohort studies from 23 articles that had a total of 10,309,227 participants. Table I shows the general characteristics of the studies included in the final meta-analysis. Types of cancers were as follows: esophageal, gastric, pancreatic, liver, colorectal, gallbladder, and bile duct cancer. Of the 23 articles, 13 articles are prospective cohort studies, and 10 articles are retrospective cohort studies. Publication dates ranged from 2009 to 2022. Eleven studies were conducted in Europe, nine studies in Asia, and three studies in North America.

Methodological quality of studies. The quality scores by the NOS for the individual studies ranged from 6 to 9; the average score was 8.4. In this meta-analysis, a study scored 9 was considered to possess high level of quality. Thus thirteen studies were rated as high-quality studies (Table II).

Use of PPIs and risk of gastrointestinal cancers. As shown in Fig. 2, PPI use was significantly associated with a significantly increased risk of gastrointestinal cancer (OR/RR/HR=2.09; 95% CI 1.78-2.46). In the subgroup meta-analyses by type of cancer, the use of PPIs was associated with a significantly increased risk of esophageal cancer (OR/RR/HR=2.44; 95% CI 1.61-3.70; n=2), gastric cancer (OR/RR/HR=2.88; 95% CI 2.29-3.61; n=11), pancreatic cancer (OR/RR/HR=1.80; 95% CI 1.34-2.42; n=3), and liver cancer (OR/RR/HR=1.55; 95% CI 1.17-2.06; n=3), while no association was found in the risk of colorectal cancer (OR/RR/HR=1.15; 95% CI 0.85-1.54; n=4) (Table III).

Use of PPIs and risk of gastrointestinal cancers by various factors. Table III shows findings from the subgroup meta-analyses stratified by baseline characteristics (sex, age over 50 years old, obesity, and smoking status), type of PPIs, duration of PPI use, concurrent medications, geographical region of studies, study design, and methodological quality of study. In the subgroup meta-analyses by duration of PPI use, a significantly increased risk was observed in people using PPIs within 1 year and from 1 to 3 years. No significant association was found in the subgroup meta-analyses by type of PPIs.

Table I. Characteristics of the studies included in the final meta-analysis (n=23).

First author/s, year	Type of study	Country	Study period	Population (sex and age)	Type of cancer	Definition of PPI exposure	OR/RR/HR (95% CI)	Adjusted variables	(Refs.)
Nguyen *et al*, 2009	Retrospective cohort study	USA	1982-2005	344 individuals (men and women; mean age, 61 years)	Esophageal cancer	Received a dispensed prescription for PPIs vs. non-users	0.40 (0.16-0.97)	Sex, age, Barrett's esophagus length and NSAIDs/COX-2/ aspirin	(27)
Poulsen *et al*, 2009	Retrospective cohort study	Denmark	1990-2003	18,790 individuals	Gastric cancer	Patients who received ≥2 PPI prescriptions during the study period vs. non-users	1.20 (0.80-2.00)	Calendar period, sex, age, history of *H. pylori* eradication therapy, gastroscopy, COPD, alcohol-related admission or therapy and ever using NSAIDs	(28)
Boursi *et al*, 2017	Retrospective cohort study	UK	1995-2013	19,146 individuals	Pancreatic cancer	PPI users vs. non-users	1.89 (1.52-2.36)	Age, smoking, insulin, oral hypoglycemics, metformin, HbA1C, Hb, total cholesterol, creatinine and alkaline phosphatase	(29)
Brusselaers *et al*, 2017	Prospective cohort study	Sweden	2005-2012	797,067 individuals	Gastric cancer	PPI users vs. non-users	3.38 (3.25-3.53)	Age, sex, calendar and categories	(30)
Hwang *et al*, 2017	Prospective cohort study	South Korea	2002-2013	451,284 individuals (men and women aged ≥40 years)	Colorectal cancer	Patients who consumed >60 DDDs of PPIs vs. non-users	0.98 (0.78-1.24)	Age, male sex, obesity, current smoking, frequent drinking, low physical activity, comorbid conditions (including type 2 diabetes), concurrent drug use, (aspirin, metformin, statin) and low socioeconomic status	(31)
Wennerström *et al*, 2017	Retrospective cohort study	Denmark	1995-2011	1,563,860 individuals	Gastric cancer	PPI users vs. non-users	2.51 (2.26-2.79)	Age, sex and municipality	(32)
Cheung *et al*, 2018	Retrospective cohort study	Hong Kong	2003-2012	63,397 individuals (≥18-year-old male and female patients)	Gastric cancer	PPI users vs. non-users	2.44 (1.42-4.20)	Age of receiving *H. pylori* eradication therapy, sex, smoking, alcohol use, comorbidities and concomitant medications	(33)
Hwang *et al*, 2018	Prospective cohort study	South Korea	2002-2013	453,655 individuals (men and women aged ≥40 years)	Pancreatic cancer	Patients who consumed >60 DDDs of PPIs vs. non-users	1.32 (1.03-1.70)	Age, male sex, obesity, current smoking, frequent drinking, low physical activity, comorbid conditions	(34)

Table I. Continued.

First author/s, year	Type of study	Country	Study period	Population (sex and age)	Type of cancer	Definition of PPI exposure	OR/RR/HR (95% CI)	Adjusted variables	(Refs.)
								(type 2 diabetes, chronic pancreatitis), Charlson Comorbidity Index score and low socioeconomic status	
Li *et al*, 2018	Prospective cohort study	USA	2001-2015	11,526 individuals (men and women; median age, 53 years)	Liver cancer	PPI users vs. non-users	2.01 (1.50-2.70)	Age, sex, ethnicity, smoking history, alcohol abuse history, body mass index, diabetes, baseline FIB-4 score, gastro-esophageal reflux disease, HCV genotype, past completed anti-HCV treatment and attainment of SVR	(35)
Tran *et al*, 2018	Prospective cohort study	UK	1991-2004	475,768 individuals	Liver cancer	PPI users vs. non-users	1.99 (1.34-2.94)	Age, sex, deprivation, BMI, alcohol, smoking, comorbidities (including GORD, peptic ulcer disease, cirrhosis, hepatitis and diabetes) and other medication use (statins, aspirin)	(36)
Brusselaers *et al*, 2019	Prospective cohort study	Sweden	2005-2012	796,492 individuals (≥18-year-old male and female patients)	Gastric cancer; esophageal cancer	≥180 days of accumulated use of PPIs vs. non-users	2.97 (2.83-3.10); 3.93 (3.63-4.24)	Age and calendar categories	(37)
Kao *et al*, 2019	Retrospective cohort study	Taiwan	2003-2013	14,984 individuals	Liver cancer	PPI users vs. non-users	HBV cohort, 1.25 (0.90-1.73) HCV cohort, 1.19 (0.88-1.61)	Age, sex, year of cohort entry, comorbidities (cirrhosis, nonalcoholic liver disease, alcoholic liver disease, hypertension, chronic kidney disease, hyperlipidemia, diabetes) and concomitant medication (interferon/nucleos(t)ides, nonaspirin NSAIDs,	(38)

Table I. Continued.

First author/s, year	Type of study	Country	Study period	Population (sex and age)	Type of cancer	Definition of PPI exposure	OR/RR/HR (95% CI)	Adjusted variables	(Refs.)
								histamine 2 receptor antagonist, aspirin, statin, fibrate, insulin, metformin)	
Babic *et al*, 2020	Prospective cohort study	USA	1988-2015	175,871 individuals (female nurses aged 25-55 years; male health professionals aged 40-75 years)	Colorectal cancer	PPI users vs. non-users	1.12 (0.78-1.59)	Age, BMI, physical activity, family history of colorectal cancer, alcohol intake, pack-years of smoking, history of lower endoscopy, caloric intake, vitamin D, calcium intake, regular aspirin use, folate intake, menopausal hormone therapy use and red meat as main dish	(39)
Brusselaers *et al*, 2020	Prospective cohort study	Sweden	2005-2012	796,492 individuals (≥18-year-old male and female patients)	Pancreatic cancer	PPI users vs. non-users	2.22 (2.12-2.32)	Age, sex and calendar period	(40)
Liu *et al*, 2020	Prospective cohort study	UK	2006-2014	471,779 individuals	Gastric cancer	PPI users vs. non-users	1.28 (0.86-1.90)	Age, sex, socioeconomic status, alcohol, smoking, BMI, comorbidities (diabetes, GORD, oesophagitis and peptic ulcer) and other medication uses (statins and aspirin)	(41)
Kamal *et al*, 2021	Prospective cohort study	Sweden	2005-2012	738,881 individuals	Gallbladder cancer; extrahepatic bile ducts cancer; intrahepatic bile ducts cancer	PPI users vs. non-users	1.58 (1.37-1.81); 1.77 (1.56-2.00); 1.88 (1.57-2.23)	Sex, age group and calendar period	(42)
Lei *et al*, 2021	Retrospective cohort study	Taiwan	1999-2011	90,764 individuals (men and women) non-users	Colorectal cancer	Patients who used PPIs ≥30 days vs. CVD, CAD, COPD,	2.03 (1.56-2.63)	Age, sex, comorbidities (hypertension, diabetes,	(43)

Table I. Continued.

First author/s, year	Type of study	Country	Study period	Population (sex and age)	Type of cancer	Definition of PPI exposure	OR/RR/HR (95% CI)	Adjusted variables	(Refs.)
								dyslipidemia, liver cirrhosis), and baseline medication (aspirin, NSAIDs, statin and metformin)	
Ng *et al*, 2021	Retrospective cohort study	Hong Kong	2004-2017	13,476 individuals (men and women)	Gastric cancer	Patients who used PPIs for ≥30 days vs. non-users (exposed to PPIs <14 days)	2.38 (1.20-4.76)	Age, sex, comorbidities and baseline medication	(44)
Seo *et al*, 2021	Retrospective cohort study	South Korea	2002-2013	23,482 individuals (men and women; age ≥19 years)	Gastric cancer	Patients who used PPIs for ≥30 consecutive days vs. non-users	General population cohort, 2.44 (1.17-5.16) Post *H. pylori* eradication cohort, 2.22 (1.05-4.67)	Age, sex, smoking, alcohol, comorbidities and baseline medication	(45)
Shin *et al*, 2021	Retrospective cohort study	South Korea	2004-2015	39,799 individuals (men and women; age ≥40 years)	Gastric cancer	PPI users vs. H2RA users	1.01 (0.88-1.16)	Age, sex, calendar period of prescription, time from medication start to 180 cDDD-days (months), socioeconomic characteristics (income, smoking and alcohol use), indication for drug use (gastresophageal reflux disease or peptic ulcer), Charlson Comorbidity Index, *Helicobacter pylori* eradication and use of other medications (aspirin, metformin and statin)	(46)
Abrahami *et al*, 2022	Prospective cohort study	UK	1990-2018	973,281 individuals (men and women; mean age, 60.4 years)	Gastric cancer	PPI users vs. H2RA users	1.45 (1.06-1.98)	Age, sex, alcohol-related disorders, smoking status, BMI, comorbidities and baseline medication	(47)

Table I. Continued.

First author/s, year	Type of study	Country	Study period	Population (sex and age)	Type of cancer	Definition of PPI exposure	OR/RR/HR (95% CI)	Adjusted variables	(Refs.)
Abrahami *et al*, 2022	Prospective cohort study	UK	1990-2018	1,293,749 individuals (men and women; mean age, 52.6 years)	Colorectal cancer	PPI users vs. H2RA users	1.02 (0.92-1.14)	Age, sex, alcohol-related disorders smoking status, BMI, comorbidities, baseline medication, mammographic screening, prostate-specific antigen testing, colorectal cancer screening and influenza vaccination	(48)
Gong *et al*, 2022	Prospective cohort study	South Korea	2002-2013	1,025,340 individuals (men and women; age ≥20 years)	Gastric cancer	PPI users vs. H2RA users	1.30 (0.75-2.27)	Age, sex, residential area, household income and comorbidities	(49)

NSAID, Non-steroidal anti-inflammatory drug; COX-2, cyclooxygenase-2; H2RAs, H-2 receptor antagonists; COPD, chronic obstructive pulmonary disease; GORD, gastro-esophageal reflux disease; OR, odds ratio; RR, relative ratio; CVD, cerebrovascular disease; CAD, coronary artery disease; HBV, hepatitis B virus; HCV, hepatitis C virus; SVR, sustained virologic response; FIB-4, fibrosis-4; cDDD, cumulative defined daily dose; DDD, defined daily dose; PPI, proton pump inhibitor; HR, hazard ratio; HbA1C, hemoglobin A1C; Hb, hemoglobin.

Table II. Methodological quality of studies included in the final analysis based on the Newcastle-Ottawa Scale[a] for assessing the quality of cohort studies (n=23).

	Selection				Comparability	Outcome				
First author/s, year (n=23)	Represent-ativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Control for important factor or additional factor	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total	(Refs.)
Nguyen *et al*, 2009	0	0	1	1	2	1	1	1	7	(27)
Poulsen *et al*, 2009	1	1	1	1	2	1	1	1	9	(28)
Boursi *et al*, 2017	0	0	1	1	1	1	1	1	6	(29)
Brusselaers *et al*, 2017	1	1	1	1	1	1	1	1	8	(30)
Hwang *et al*, 2017	1	1	1	1	2	1	1	1	9	(31)
Wennerström *et al*, 2017	1	1	1	1	1	1	1	1	8	(32)
Cheung *et al*, 2018	1	1	1	1	2	1	1	1	9	(33)
Hwang *et al*, 2018	1	1	1	1	2	1	1	1	9	(34)
Li *et al*, 2018	0	1	1	1	2	1	1	1	8	(35)
Tran *et al*, 2018	1	1	1	1	2	1	1	1	9	(36)
Brusselaers *et al*, 2019	1	1	1	1	1	1	1	1	8	(37)
Kao *et al*, 2019	0	1	1	1	2	1	1	1	8	(38)
Babic *et al*, 2020	0	1	1	1	2	1	1	1	8	(39)
Brusselaers *et al*, 2020	1	1	1	1	1	1	1	1	8	(40)
Liu *et al*, 2020	1	1	1	1	2	1	1	1	9	(41)
Kamal *et al*, 2021	1	1	1	1	1	1	1	1	8	(42)
Lei *et al*, 2021	1	1	1	1	2	1	1	1	9	(43)
Ng *et al*, 2021	1	1	1	1	2	1	1	1	9	(44)
Seo *et al*, 2021	1	1	1	1	2	1	1	1	9	(45)
Shin *et al*, 2021	1	1	1	1	2	1	1	1	9	(46)
Abrahami *et al*, 2022	1	1	1	1	2	1	1	1	9	(47)
Abrahami *et al*, 2022	1	1	1	1	2	1	1	1	9	(48)
Gong *et al*, 2022	1	1	1	1	2	1	1	1	9	(49)

[a]Each study can be awarded a maximum of one point for each item within the selection and exposure categories, while a maximum of two points can be given for the comparability category. Mean score, 8.4.

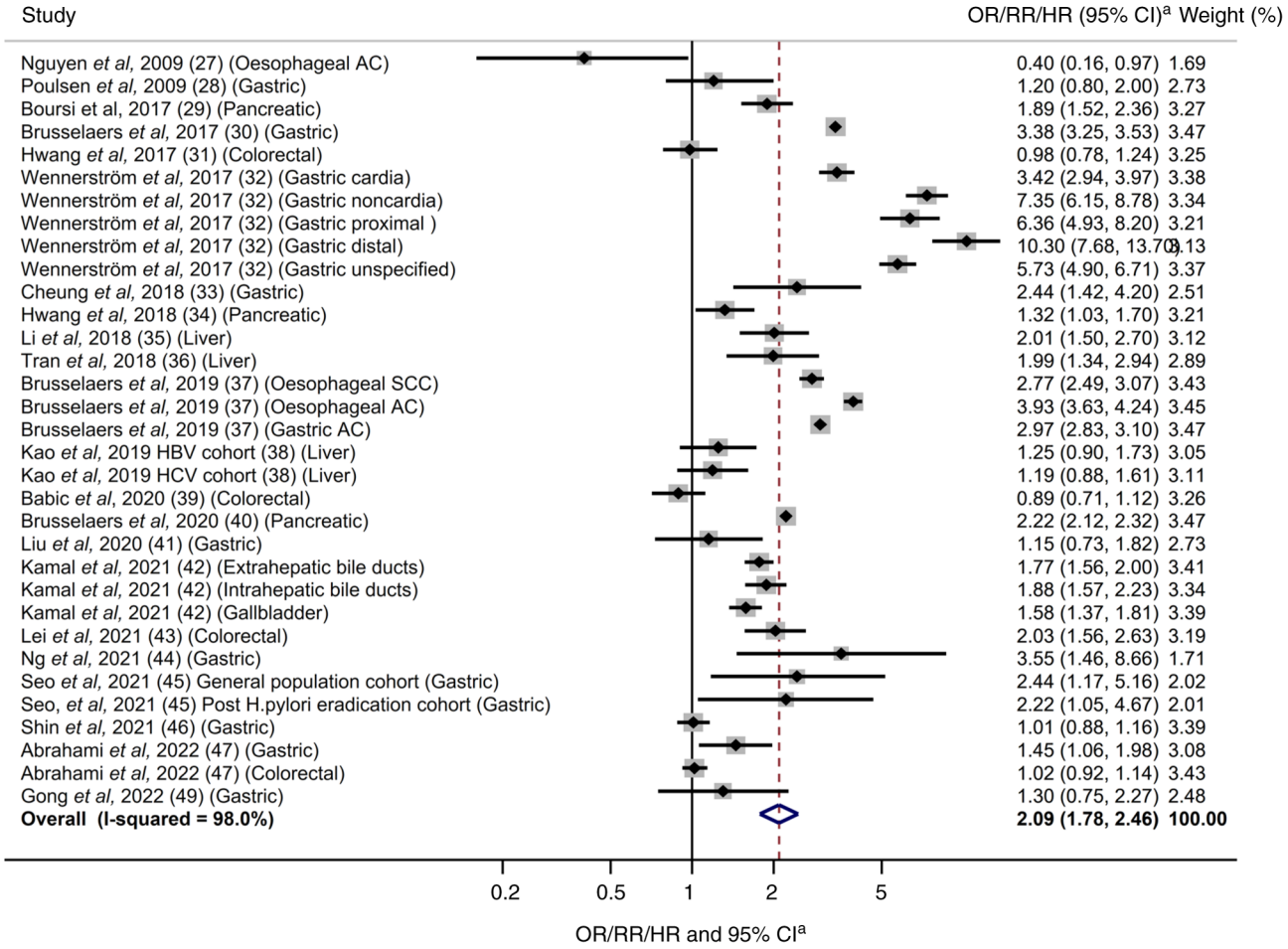

Figure 2. Association between proton pump inhibitor use and risk of gastrointestinal cancer in a random-effects model meta-analysis of cohort studies. [a]Random-effects model. OR, odds ratio; RR, relative risk; HR, hazard ratio; AC, adenocarcinoma; SCC, squamous cell carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus.

Heterogeneity, publication bias, and sensitivity analysis. Statistical heterogeneity was observed (I^2=85.7%) in the meta-analysis of all the studies. Publication bias was not observed in both the Begg's funnel plot (Fig. 3) and Egger's test (P=0.105). Sensitivity analysis to discern the influence of each study did not show any substantial change in the pooled estimate of the effect size and statistical significance (data not shown in figure).

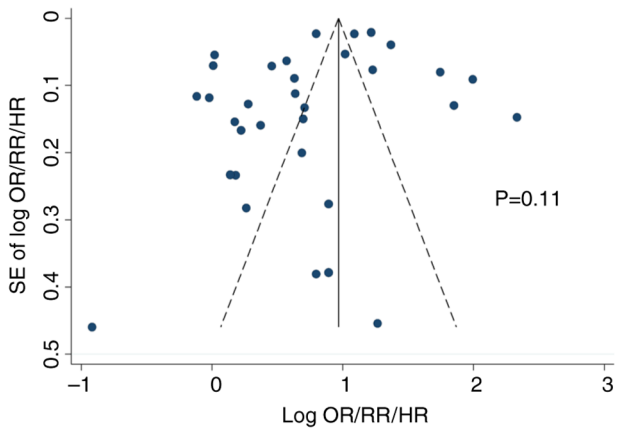

Figure 3. Begg's funnel plot and Egger's test to identify publication bias in the meta-analysis of cohort studies. OR, odds ratio; RR, relative risk; HR, hazard ratio; SE, standard error.

Discussion

In this meta-analysis of cohort studies, a significant association was observed between the use of PPIs and an increased risk of gastrointestinal cancers. In the subgroup meta-analysis by type of gastrointestinal cancers, the use of PPIs was significantly associated with the increased risk of gastric cancer, liver cancer, pancreatic cancer, and esophageal cancer, whereas there was no association for colorectal cancer. The increased risk of gastrointestinal cancers was also observed in people who had used PPIs within 1 year as well as up to 3 years.

Possible biological mechanisms for the increased risk of gastrointestinal cancers by the use of PPIs can be explained by previous *in vitro* and *in vivo* studies (60-62). First, PPIs reduce gastric acid secretion by blocking the H+/K+ ATPase of parietal cells (63), which can induce an increase of gastrin secretion from G-cells (64). Gastrin has long been suspected to be a potential risk factor of gastric cancer by causing hypergastrinemia (25). Hypergastrinemia also could lead to the development of gastrointestinal cancers, including

Table III. Association between PPIs and risk of gastrointestinal cancer in subgroup meta-analyses using a random-effects model.

Factors	No. of studies	Summary OR/RR/HR (95% CI)	Heterogeneity, I^2 (%)	(Refs.)
All studies	23	2.09 (1.78-2.46)	98.0	(27-49)
Type of cancer				
Esophageal cancer	2	2.44 (1.61-3.70)	49.6	(27,37)
Gastric cancer	11	2.88 (2.29-3.61)	97.4	(28,30,32,33,37,41,44-47,49)
Pancreatic cancer	3	1.80 (1.34-2.42)	88.6	(34,40)
Colorectal cancer	4	1.15 (0.85-1.54)	88.9	(31,39,43,48)
Liver cancer	3	1.55 (1.17-2.06)	67.2	(35,36,38)
Gallbladder cancer	1	1.58 (1.37-1.81)	N/A	(42)
Extrahepatic bile ducts cancer	1	1.17 (1.56-2.00)	N/A	(42)
Intrahepatic bile ducts cancer	1	1.88 (1.57-2.33)	N/A	(42)
Sex				
Male	11	1.70 (1.36-2.12)	98.1	(30,31,34,35,38,40,41,42,46-48)
Female	10	1.84 (1.55-2.19)	96.1	(30,31,34,38,40,41,42,46-48)
Age (≥50 years)	7	1.76 (1.41-2.20)	97.7	(30,31,34,38,40,42,46)
Obesity	3	1.14 (1.01-1.27)	0	(31,34,35)
Smoking	4	1.11 (0.98-1.27)	65.8	(31,34,35,47)
Type of PPIs				
Omeprazole	4	1.32 (0.96-1.80)	69.4	(41,43,47,48)
Lansoprazole	4	1.42 (0.99-2.06)	81.1	(41,43,47,48)
Pantoprazole	3	1.08 (0.91-1.28)	0	(43,47,48)
Esomeprazole	3	1.17 (0.70-1.96)	72.6	(43,47,48)
Rabeprazole	3	1.09 (0.77-1.56)	51.6	(43,47,48)
Duration of PPI use				
≤1 year	4	5.23 (2.96-9.24)	99.6	(30,37,40,42)
1-3 years	10	1.72 (1.44-2.07)	86.8	(30,33,37,40,42,43-45,47,48)
3-5 years	6	1.17 (0.96-1.43)	79.5	(27,30,33,37,40,43)
>5 years	4	1.16 (0.74-1.84)	96.6	(30,37,40,42)
Concurrent medication				
Aspirin	3	1.09 (1.01-1.18)	0	(31,38,47)
Statins	4	0.85 (0.69-1.06)	56.5	(31,35,38,47)
Region				
America	3	1.09 (0.55-2.17)	86.3	(27,35,39)
Asia	9	1.45 (1.17-1.80)	79.8	(31,33,34,38,43-46,49)
Europe	11	1.93 (1.51-2.45)	98.3	(28-30,32,36,37,40-42,47,48)
Study design				
Retrospective cohort	10	2.60 (1.88-3.60)	97.6	(27,28,30,32,33,38,43-46)
Prospective cohort	13	1.71 (1.41-2.08)	97.9	(29,31,34-37,39-42,47-49)
Methodological quality				
High quality	13	1.43 (1.20-1.70)	78.2	(28,31,33,34,36,41,43-49)
Low quality	10	2.61 (2.20-3.09)	98.0	(27,29,30,32,35,37-40,42)

PPI, proton pump inhibitor; OR, odds ratio; RR, relative risk; HR, hazard ratio.

esophagus, stomach, pancreatic, and liver cancers (25). Second, PPIs might contribute to increased bacterial colonisation and a larger number of bacteria that are able to produce nitrosamines (23,24). Nitrosamines and gut microbiome alterations could lead to an increased risk of gastrointestinal cancers (23,65,66). Third, PPIs might increase the production of enterochromaffin-like cells (ECL cells) by inducing hypoacidity (67). ECL cells are the key target cells of gastrin in the oxyntic mucosa and are associated with the expression of cholecystokinin-2 (CCK-2) receptors, which might consequently lead to the formation of neuroendocrine tumors (NETs), such as pancreatic cancer (67).

Some preclinical studies have reported a preventive effect of PPIs against the development of colorectal cancer (68,69). Pantoprazole was identified to be a potential T-cell-originated protein kinase (TOPK) inhibitors and blocked the anchorage-independent proliferation of colorectal cancer cells with high TOPK levels in an in vitro cancer cell line study and an in vivo mouse study (68). Also, a rat azoxymethane (AOM) model study showed that omeprazole suppressed the proliferation and carcinogenesis of colon cancer cell lines (69). On the other hand, a transgenic APC genes (APCMin-/+) mouse model study reported that omeprazole-induced hypergastrinemia lead to a significant increase in the proliferation of colorectal adenomas. Thus, there are some inconsistencies regarding the effect of PPI use on the colorectal cancer risk.

The findings of this meta-analysis are in line with previous meta-analyses that investigated the association between the use of PPIs and the risk of gastric cancer (50,51,70). Jiang *et al* (71) found that long-term use of PPIs may possibly increase the risk of gastric cancer (OR 2.50; 95% CI: 1.74-3.85). Nevertheless, they were unable to assess publication bias due to the small number of studies, and all studies were retrospective in design. Tran-Duy *et al* (51) assessed the effects of PPI therapy on the risk of gastric cancer by including a cohort and 3 case-control studies. They concluded that PPI therapy was positively associated with an increased risk of gastric cancer (51). Nonetheless, there were too few studies included in their analysis to confirm the association. Segna *et al* (50) conducted a meta-analysis including 5 retrospective cohort and 8 case-control studies. They found that PPI use had a 1.94-fold higher risk of gastric cancer compared with the non-PPI group (50). They also included retrospective studies only.

Regarding the risk of pancreatic cancer, the finding of this meta-analysis is consistent with two previous meta-analyses, which also included only a few studies. Laoveeravat *et al* (53) and Alkhushaym *et al* (54) included one and two cohort studies, respectively. They also found that PPIs use could significantly increase the risk of pancreatic cancer. Regarding the risk of colorectal cancer, the finding of this meta-analysis is consistent with that of Ma *et al*'s (52) meta-analysis of 3 cohort studies, which reported that there was no statistically significant association between PPI use and the risk of colorectal cancer.

To the best of current knowledge, this is the most comprehensive meta-analysis of cohort studies on this topic. Although a recent meta-analysis of observational epidemiological studies regarding this topic was published in 2021 (50), it included only case-control and retrospective cohort studies and revealed no clear duration-dependent risk increase among PPI users. This meta-analysis included a total of 23 cohort studies with 13 prospective cohort studies as well as 10 retrospective studies and reported the evidence of the gastrointestinal cancers risk with long-term use of PPIs. In addition, this meta-analysis provided information regarding the types of PPI and the risk of gastrointestinal cancers. This meta-analysis also assessed the risk of gastrointestinal cancers by providing various subgroup analyses that might help to minimize potential confounding factors.

This study has several limitations. This meta-analysis only included cohort studies. In terms of evidence-based medicine, it is important to emphasize that while randomised controlled trials (RCTs) offer a higher level of evidence compared to cohort studies, they pose ethical and practical challenges when investigating the association between PPI use and cancer risk. Nevertheless, it would be possible to conduct a meta-analysis of RCTs using secondary outcomes from the original trials. Second, the stratification of gastrointestinal cancer risk based on PPI dosage was hindered by the limited availability of relevant data from individual studies. Lastly, it was not feasible to confirm the effect of PPI use on the risk of gallbladder and bile duct cancers because only one study for each type of cancer was included in the current study. Further studies are warranted.

This meta-analysis of cohort studies suggested a significant association between the use of PPIs and the increased risk of gastrointestinal cancers. This finding was observed in people using PPIs for less than 1 year as well as up to 3 years. These findings should be confirmed by RCTs that provide a higher level of evidence than cohort studies.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable requests.

Authors' contributions

SKM and THT conceptualized the present study, conducted the investigation, and were involved in data curation. THT and TTKT analyzed and interpreted data. THT wrote the original draft. SKM, THT, and TTKT wrote, reviewed and edited the manuscript. THT and SKM confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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