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REVIEW

Proton pump inhibitors and the risk of colorectal cancer: a systematic review and meta-analysis of observational studies

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Abstract

Purpose The increased risk of colorectal cancer (CRC) associated with long-term use of proton pump inhibitors (PPIs) has attracted considerable attention; however, the conclusions of studies evaluating this correlation are inconsistent or even controversial. Therefore, we conducted a systematic review and meta-analysis to determine the association of PPI use with the risk of CRC.

Methods A systematic literature search was conducted in PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials to identify relevant studies. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) for the associations between PPI use and the risk of CRC were estimated with a fixed-effects or random-effects model.

Results We identified and included 9 observational studies (3 cohort studies and 6 case-control studies) comprising 1,036,438 participants. Overall, there was no statistically significant association between PPI use and the risk of CRC (pooled OR 1.26, 95% CI: 0.90–1.73; $p = 0.166$) when PPI exposure was assessed as a binary variable. However, a weak association between long-term use of PPIs and CRC was demonstrated (pooled OR 1.19, 95% CI: 1.09–1.31; $p < 0.001$) when the cumulative duration of PPI exposure was confined to > 5 years.

Conclusions Although the present meta-analysis suggests a weak association between long-term use (> 5 years) of PPIs and CRC, there is not enough statistical power to refute or confirm an association between the use of PPIs and CRC. More high-quality prospective cohort studies are needed to assess this correlation.

Keywords Colorectal cancer · Risk · Proton pump inhibitor · Systematic review · Meta-analysis

Introduction

Colorectal cancer (CRC) is the most commonly diagnosed digestive system cancer and the third most common cancer worldwide [1]. In 2018, there were 1.8 million CRC cases and 881,000 related deaths worldwide, accounting for one-tenth of cancer cases and deaths [2]. It is currently estimated that worldwide, 2.2 million CRC patients will be diagnosed every year in 2030 [3]. In addition, in contrast to the declining trend among the elderly population, the incidence of CRC among adults under 50 years of age continues to rise, and this early-onset CRC now accounts for 10–12% of all new CRC diagnoses [4]. Although the pathogenesis of CRC is still unclear, some related risk factors have been identified, including various environmental, genetic, and lifestyle factors [5, 6]. In addition, recent studies have shown that CRC is associated with many medicines, including aspirin, antibiotics, and proton pump inhibitors (PPIs) [7–9].

PPIs are one of the most commonly prescribed medicines in America [10]. Although PPIs are mainly recommended for short-term use in patients with peptic ulcer disease, they are increasingly used for long-term and often lifetime use for "gastroprotection" in patients taking non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, anticoagulants, or antiplatelet therapy [11, 12]. The proportion of inappropriate PPI use is estimated to be up to 50%, particularly among elderly patients [13]. PPIs were previously considered to be inherently safe, even for long-term use, but growing evidence for potential side effects associated with the long-term use of PPIs has caused concern among doctors and patients in the past decade [14]; these side effects include dementia,

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infection, micronutrient deficiency, kidney diseases, bone diseases, and a variety of digestive system cancers (gastric, liver, pancreatic, and colorectal cancer) [15–18].

The association between PPI use and the risk of CRC remains controversial, with conflicting results in the literature [8, 19, 20]. Several previous meta-analyses showed no statistically significant association between PPI use and the risk of CRC (odds ratio (OR) = 1.19, 95% confidence interval (CI) = 0.90–1.57; OR = 1.08, 95% CI = 0.96–1.20) [21, 22]. However, several new studies have been published since then [8, 18, 20, 23, 24], some of which offer the opposite view [8, 18]. Therefore, to achieve a more accurate and comprehensive assessment, we combined all the latest data in this meta-analysis to comprehensively investigate the relationship between PPI use and the risk of CRC.

Materials and methods

Search strategy

We conducted a systematic literature search in PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials from inception to 25 April 2020 to assess the association between PPIs and the risk of CRC, and the literature search was repeated on 17 June 2020. We used the following medical subject heading search terms in combination: ("proton pump inhibitor(s)" OR "PPI(s)" OR "pantoprazole" OR "omeprazole" OR "esomeprazole" OR "lansoprazole" OR "ilaprazole") and ("colon cancer" OR "colon neoplasm" OR "colon tumor" OR "rectal cancer" OR "rectal neoplasm" OR "rectal tumor" OR "colorectal cancer" OR "colorectal neoplasm" OR "colorectal tumor"). The search was not restricted by language. To ensure the integrity of the studies, we conducted a manual search of the reference lists of the retrieved articles as well as relevant reviews and meta-analyses to retrieve additional potential studies.

Study selection

The present meta-analysis followed the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines [25]. Based on the inclusion criteria established, we included (1) studies that reported the association between PPI use for any indication and the risk of CRC in adults; (2) cohort studies or case-control studies; (3) studies where PPI non-users were compared (as the control group) with PPI users (as the treatment group); and (4) studies that provided the corresponding risk estimates such as relative risk (RR), ORs or hazard ratios (HRs), and 95% CI, or sufficient data to estimate the OR, RR or HR, and 95% CI.

Data extraction and quality assessment

Two review authors conducted data extraction and quality assessment independently, and any disagreements were resolved by discussion with the third independent author. The following information was extracted from each eligible study: the first author's surname, year of publication, country, study period, study design, study participants, mean age, gender, data source, participants' characteristics, confounder adjustment and definition, and ascertainment of PPI exposure and CRC.

We assessed the methodological quality of the included case-control and cohort studies using the Newcastle–Ottawa scale (NOS) [26]. The NOS system judges the quality of observational studies based on three parameters of quality (selection (4 items), comparability (1 item), and exposure/outcome (3 items)) by a star system ranging from 0 to 9. A study with seven stars or more was considered a high-quality study.

Statistical analyses

The primary outcome of this meta-analysis was the pooled risk of CRC among PPI users. The method of inverse variance was applied for the study weights. The analysis was performed using the summary measure pooled OR and 95% CI. We considered the HR to approximate the RR and the RR to approximate the OR due to the low incidence (< 10%) of results of interest [27]. Whenever available, data analyses were conducted on adjusted ratios, unless only unadjusted data were available, in which case we used the unadjusted ratios. The heterogeneity among studies was confirmed with the Cochran Q statistic and quantified using the I^2 statistic [28]. $p < 0.10$ for the Q statistic indicated high heterogeneity. For I^2, a threshold of ≥ 25% indicates low heterogeneity, ≥ 50% indicates moderate heterogeneity, and ≥ 75% indicates high heterogeneity [28]. If there was a moderate heterogeneity or high heterogeneity, the random-effects model (DerSimonian–Laird method) [29] was used to pool the estimates; otherwise, the fixed-effects model (Mantel–Haenszel method) was applied. In the sensitivity analysis, the influence of a single study on the overall risk estimate was determined by excluding studies from the meta-analysis one by one. In addition, to further explore the potential sources of heterogeneity, subgroup analysis was performed according to different study features and clinical factors, including study design (case-control study, nested case-control study, cohort study), study region (Asia, Europe, America), NOS scores (NOS ≥ 7, NOS < 7), duration of PPI use (0–1, ≥ 1, > 5 years), sample size (≤ 10,000, > 10,000, > 50,000), and adjusted covariates/confounders (aspirin, statins, body mass index, colonoscopy, inflammatory bowel disease). We assessed funnel plot asymmetry visually and evaluated it with Egger's and Begg's tests ($p > 0.10$ was considered to indicate low publication bias) to

determine the presence of publication bias [30]. All statistical tests were two-tailed, and $p < 0.05$ (except for heterogeneity and publication bias) was considered to indicate statistical significance. All statistical analysis was performed using Stata 16.0 (Stata Corporation, College Station, TX, USA).

Results

Literature search

Figure 1 shows the PRISMA flow diagram of study selection. Our search strategy initially identified 325 articles for screening. First, we removed 77 duplicates, and then 219 articles were excluded after title and/or abstract screening by 2 independent reviewers. The references of the remaining 29 articles were searched manually, and no additional publications were identified. A full-text review of 29 articles was conducted, and 20 articles were further excluded: 2 non-human studies, 1 case series, 2 meta-analyses, 8 review articles, 2 study assessing the mortality of CRC patients as an outcome, 4 studies assessing colorectal polyps or adenomas as outcomes, and 1 study assessing CRC risk between pantoprazole and other PPIs. Finally, 9 articles published between 2007 and 2020 met the inclusion criteria [8, 18–20, 23, 24, 31–33] and were included in this systematic review and meta-analysis.

Study characteristics and quality assessment

Table 1 summarizes the characteristics of the included studies. Among the 9 eligible studies, there were 3 cohort studies (including 2 prospective cohort studies) [8, 23, 24], 2 case-control studies [32, 33], and 4 nested case-control studies [18–20, 31]. Three of the studies were from North America [20, 24, 33], 3 were from Europe [19, 31, 32], and 3 were from Asia [8, 18, 23]. The sample size of the studies ranged from 1282 to 451,284, and a total of 1,036,438 participants were included. The quality score based on the Newcastle–Ottawa quality assessment scale shows that each study was considered a high-quality study except the studies of Lai et al. [18] and Babic et al. [24].

Primary outcome

Nine studies could be used to assess the association between PPI use and CRC risk, each of which provided a multivariate adjusted OR. Yang et al. [19] presented data on the association between multiple durations (< 1 year, 1–2 years, 2–3 years, 3–4 years, > 5 years) of PPI use and the risk of CRC [19], but the overall effect of PPI use on CRC was not available. As colorectal carcinogenesis is estimated to take at least 10 years [19], we used data for > 5 years as routine long-term PPI usage to represent Yang's data in this analysis. The pooled risk showed that there was no significant association between PPI use and the risk of CRC (pooled OR 1.26, 95% CI: 0.91–1.73; $p = 0.166$; Fig. 2). Additionally, there was a significant heterogeneity based on the Q test, p value ($p < 0.001$), and I^2 index ($I^2 = 97.10\%$). Crude OR was available in 6 studies, but no significant change in the overall combined OR was observed when using unadjusted data (pooled OR 1.34, 95% CI: 0.75–2.39; $I^2 = 97.20\%$) (Table 2).

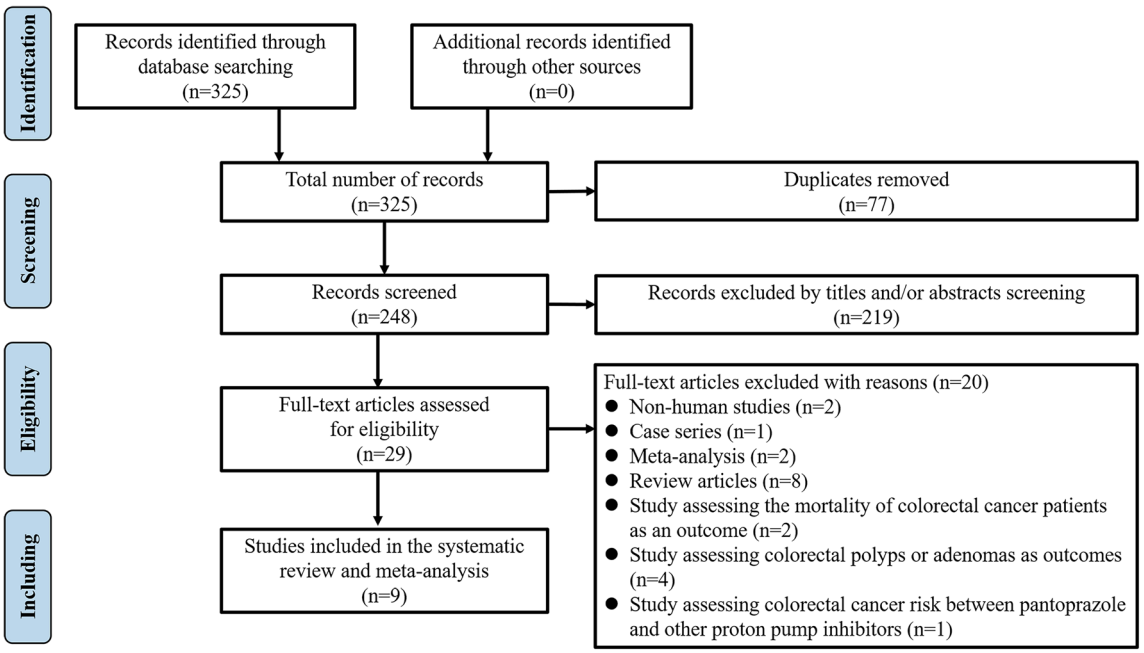

Fig. 1 PRISMA flow diagram of study selection

Table 1 Characteristics of the included studies

First author, year	Country	Study period	Study design	Study participants	Mean age (year) (SD)	Male	Data source/participant characteristics	Definition and ascertainment of PPI exposure	Definition and ascertainment of CRC	Confounder adjustment	Study quality (NOS)
Robertson, 2007 [31]	Denmark	1989–2005	Nested case--control study	5589 cases and 55,890 controls	71 (SD not reported)	50.2%	National Health Service/participants with no CRC diagnosis before the start of follow-up.	Exposed to PPIs for > 30 pills during the follow-up, and excluded cases with PPI exposure within 1 year of the index date.	Diagnosis of CRC was made according to ICD-8 or ICD-10 codes during the entire period of observation.	Sex, age, aspirin/NSAID use, H2RA use, antidiabetic use, statin use, history of cholecystectomy, and alcoholism	8
Yang, 2007 [19]	UK	1987–2002	Nested case--control study	4432 cases and 44,292 controls	Cases: 67.5 (8.9) Controls: 63.6 (9.1)	Cases: 54.5% Controls: 44.2%	General Practice Research Database (GPRD)/participants aged ≥ 50 years at the time of database enrolment with a total follow-up time of ≥ 5 years, and CRC was not diagnosed before follow-up or within the first 5 years of follow-up.	Exposed to PPIs with ≥ 1 year of cumulative use, and the last prescription was within 6 months before the index date.	Diagnosis of CRC was defined as an initial diagnosis of CRC after accumulating at least 5 years of CRC-free follow-up.	Sex, age, follow-up duration, general practice site, calendar periods, BMI, alcohol, smoking, H2RA use, HRT use, aspirin/NSAID use, history of colonoscopy or flexible sigmoidoscopy	9
van Soest, 2008 [32]	Netherlands	1996–2005	Case-control study	594 cases and 7790 controls	Cases: 69.5 (11.9) Controls: 69.3 (11.9)	Cases: 50.7% Controls: 51.8%	Integrated Primary Care Information (IPCI) database/participants with ≥ 1 year of valid database history and no CRC diagnosis before the start of follow-up.	Exposed to PPIs at least once during the follow-up, and excluded cases with PPI exposure in the year before the diagnosis date.	Diagnosis of CRC was defined according to ICPC code D75.1.	Sex, age, calendar time, follow-up duration, comorbidity	9
Chubak, 2009 [33]	USA	2000–2003	Case-control study	641 cases and 641 controls	70 (SD not reported)	48.4%	Group Health database/participants aged ≥ 40 years at diagnosis or reference date, with an enrolment period of ≥ 2 years, and participants with a previous diagnosis of	Two or more prescriptions for PPIs filled within a 6-month period, and excluded cases with PPI exposure in	Diagnosis of CRC was defined as the first primary diagnosis of CRC in the cancer registry between 1 January 2000 and 31 December 2003.	Sex, age, follow-up duration, calendar time	7

Table 1 (continued)

First author, year	Country	Study period	Study design	Study participants	Mean age (year) (SD)	Male	Data source/participant characteristics	Definition and ascertainment of PPI exposure	Definition and ascertainment of CRC	Confounder adjustment	Study quality (NOS)
							CRC or IBD were excluded.	the year before the diagnosis date.			
Lai, 2013 [18]	Taiwan	2000–2010	Nested case--control study	3989 cases and 15,956 controls	Cases: 65.8 (13.7) Controls: 65.2 (13.9)	Cases: 57.2% Controls: 57.2%	Taiwan National Health Insurance Program/participants aged ≥ 20 years excluding participants with a diagnosis of CRC or any other cancer before the index date.	NR	Diagnosis of CRC was defined according to ICD-9 codes.	Sex, age, alcoholism, diabetes mellitus, colorectal adenomas, IBD, H2RA use, statin use, aspirin/NSAID use	6
Hwang, 2017 [23]	Korea	2007–2013	Prospective cohort study	49,520 PPI users and 401,764 non--users	NR	PPI users: 54.3% Non-users: 53.4%	Korean National Health Insurance Corporation (NHIC)/participants aged ≥ 40 years excluding participants with a diagnosis of any cancer, patients who died, and patients who were missing any non-survey health check-up variables before the index date.	Exposed to PPIs ≥ 60 DDDs during the follow-up, and excluded participants who were prescribed PPIs in 2002.	Diagnosis of CRC was defined by ICD-10 codes, with ≥ 3 outpatient visits with the code, ≥ 3 days of admission with the code, a record of curative cancer treatments, or death from code-related causes, excluding cases with a CRC diagnosis within 1 year after the index date.	Sex, age, smoking, alcohol, BMI, consumption, physical activity, type 2 diabetes, CCI score, aspirin use, metformin use, stain use, socioeconomic status	8
Babic, 2020 [24]	USA	1988–2015	Prospective cohort study	13,205 PPI users and 162,654 non--users	PPI users: 60.8 (12.0) Non-users: 57.7 (11.6)	PPI users: 29.1% Non-users: 12.8%	Nurses' Health Study (NHS), Nurses' Health Study II (NHSII), and Health Professionals Follow-Up Study (HPFS)/participants were health professionals aged 25–75 years, excluding participants with a previous history of cancer, except IBD	Reported "regular use" of any PPIs in the baseline questionnaire.	Diagnosis of CRC was defined by biennial questionnaires and further confirmed by pathological reports and medical records.	Age, physical activity, BMI, family history of CRC, alcohol, 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	6

Table 1 (continued)

First author, year	Country	Study period	Study design	Study participants	Mean age (year) (SD)	Male	Data source/participant characteristics	Definition and ascertainment of PPI exposure	Definition and ascertainment of CRC	Confounder adjustment	Study quality (NOS)
							and non-melanoma skin cancer.				
Lee, 2020 [20]	USA	1996–2016	Nested case--control study	18,595 cases and 160,122 controls	Cases: 68.3 (12.9) Controls: 67.7 (12.9)	Cases: 51.2% Controls: 51.9%	Kaiser Permanente Northern California (KPNC)/participants aged ≥ 18 years with ≥ 1 year of continuous enrolment and ≥ 2 years of cumulative membership before the diagnosis date.	Two years or more cumulative PPI supply during the follow-up.	Diagnosis of CRC was defined by ICD codes, excluding cases for which PPI exposure was initiated ≤ 1 year before the diagnosis date.	Sex, age, race/ethnicity, primary medical facility at match date, enrolment duration, smoking, chronic alcohol consumption, BMI, IBD, history of colonoscopy, family history of CRC	8
Lei, 2020 [8]	Taiwan	1999–2011	Retrospective cohort study	45,382 PPI users and 45,382 non--users	PPI users: 46.7 (15.0) Non-users: 46.9 (14.9)	PPI users: 52.5% Non-users: 52.2%	Longitudinal Health Insurance Database (LHID)/participants aged ≥ 20 years with continuous enrolment since 1999; no history of celiac disease, colectomy, IBD, or CRC; and a lack of PPI prescriptions between 1999 and 2000.	Exposed to PPIs for 30 days or more during the follow-up.	Diagnosis of CRC was defined by ICD-9 codes and excluded cases within 1 year of the PPI prescription.	Sex, age, year of index date, diabetes, coronary artery disease, hypertension, dyslipidemia, COPD, cirrhosis, CCI, aspirin/NSAID use, statin use, metformin use	9

SD standard deviation, *NR* not reported, *PPI* proton pump inhibitor, *CRC* colorectal cancer, *NOS* Newcastle–Ottawa scale, *ICD* International Classification of Diseases, *NSAID* non-steroidal anti-inflammatory drug, *H2RA* histamine-2 receptor antagonists, *BMI* body mass index, *HRT* hormone replacement therapy, *ICPC* International Classification for Primary Care, *IBD* inflammatory bowel disease, *DDDs* daily defined doses, *CCI* Charlson comorbidity index, *COPD* chronic obstructive pulmonary disease

Subgroup analysis

To make the results more meaningful, we conducted a subgroup analysis by various study features and clinical factors. Five studies reported the correlation between different categories of cumulative duration of PPI use and CRC. We found that the overall pooled OR estimate (pooled OR 1.22, 95% CI: 0.89–1.66) of study participants whose cumulative duration of PPI use was ≥ 1 year was higher than the overall pooled OR estimate (pooled OR 1.09, 95% CI: 0.60–1.98) of study participants whose cumulative duration of PPI use was < 1 year, but neither difference reached statistical significance (Table 2). However, subgroup analysis pooling data for a more prolonged cumulative duration (> 5 years) showed that long-term use of PPIs was associated with a 19% increased risk of CRC (pooled OR 1.19, 95% CI: 1.09–1.31; Fig. 3), with statistical significance ($p < 0.001$) and low heterogeneity between studies ($I^2 = 48.00\%$; $p = 0.123$). In addition, when stratified according to the study design, study region, NOS scores, sample size, and adjusted covariates/confounders, the associated risks were no longer statistically significant (Table 2).

Sensitivity analysis

Because of the high heterogeneity ($I^2 = 97.10\%$; $p < 0.001$), a sensitivity analysis was performed. First, to evaluate the impact of 1 study on the primary results, we conducted a sensitivity analysis by excluding one study at a time; however, it did not substantially change the pooled effect or the level of heterogeneity (Table 3). We also excluded the following studies: (1) studies

Table 2 Primary analysis and subgroup analysis of proton pump inhibitor use and the risk of colorectal cancer

	No. of studies	Pooled effect estimate		*p* value	Assessment of heterogeneity	
		OR	(95% CI)		I^2 (%)	*p* value
Primary analysis						
Adjusted	9	1.26	0.91–1.73	0.166	97.10%	< 0.001
Unadjusted	6	1.34	0.75–2.39	0.325	97.20%	< 0.001
Subgroup analyses						
Study design						
Case-control study	2	1.08	0.57–2.07	0.809	59.90%	0.114
Nested case-control study	4	1.36	0.81–2.28	0.247	98.80%	< 0.001
Cohort study	3	1.21	0.74–1.96	0.454	92.00%	< 0.001
Region						
Asia	3	1.72	0.96–3.09	0.067	96.40%	< 0.001
Europe	3	1.06	0.94–1.20	0.304	19.20%	0.290
America	3	1.04	0.98–1.10	0.185	39.70%	0.190
NOS						
NOS ≥ 7	7	1.15	0.97–1.37	0.105	78.30%	< 0.001
NOS < 7	2	1.51	0.54–4.22	0.431	98.60%	< 0.001
Duration of PPI use						
0–1 year	2	1.09	0.6–1.98	0.787	50.60%	0.155
≥ 1 year	4	1.22	0.89–1.66	0.213	90.40%	< 0.001
> 5 years	4	1.19	1.09–1.31	< 0.001	48.00%	0.123
Sample size						
≤ 10000	2	1.08	0.57–2.07	0.809	59.90%	0.114
> 10000	7	1.29	0.90–1.85	0.166	97.80%	< 0.001
> 50000	5	1.14	0.95–1.37	0.167	85.10%	< 0.001
Adjusted covariates/confounders						
Use of aspirin	6	1.34	0.87–2.07	0.191	97.00%	< 0.001
Use of statins	4	1.54	0.92–2.59	0.102	97.70%	< 0.001
Body mass index	4	1.04	0.98–1.10	0.235	0.00%	0.539
Colonoscopy	3	1.04	0.98–1.10	0.204	0.00%	0.380
Inflammatory bowel disease	2	1.63	0.69–3.88	0.268	99.60%	< 0.001

OR odds ratio, *CI* confidence interval, *NOS* Newcastle–Ottawa scale, *PPI* proton pump inhibitor

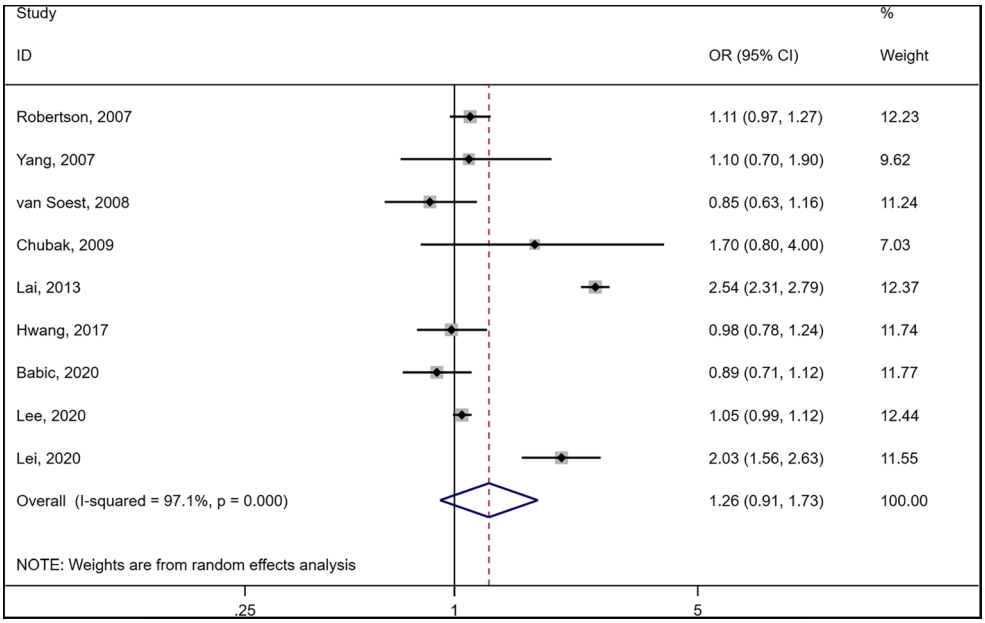

Fig. 2 Forest plot of the association between proton pump inhibitor use and the risk of colorectal cancer. Data are presented as adjusted risk ratios

without lag time analysis [18, 19, 24]; (2) studies in which PPI use duration data were not available [18, 23, 33]; and (3) studies that included patients with IBD, but unadjusted IBD as a confounder [19, 23, 31, 32]. However, the correlation was still nonsignificant (Table 3).

Publication bias

We did not draw funnel plots to assess publication bias because the use of this approach for less than 10 studies can lead to a reduction in its evaluating ability and reliability [34]. The results of Egger's test and Begg's test were statistically nonsignificant ($p = 0.993$ and $p = 0.466$, respectively).

Discussion

A meta-analysis based on nine observational studies showed that there was no significant correlation between PPI use and the risk of CRC when PPI exposure was assessed as a binary variable. However, when we stratified according to the cumulative duration of PPI use, we found that long-term use (> 5 years) of PPIs could slightly increase the risk of CRC. However, considering the small number of studies focusing on the association between the long-term use of PPIs and CRC, and the fact that some risk factors for CRC have not been fully adjusted, this result should be interpreted with caution. The preliminary results of our study are consistent with those of the meta-analysis of Ahn et al. [21], that is, the overall use of PPIs is not associated with the risk of CRC. However,

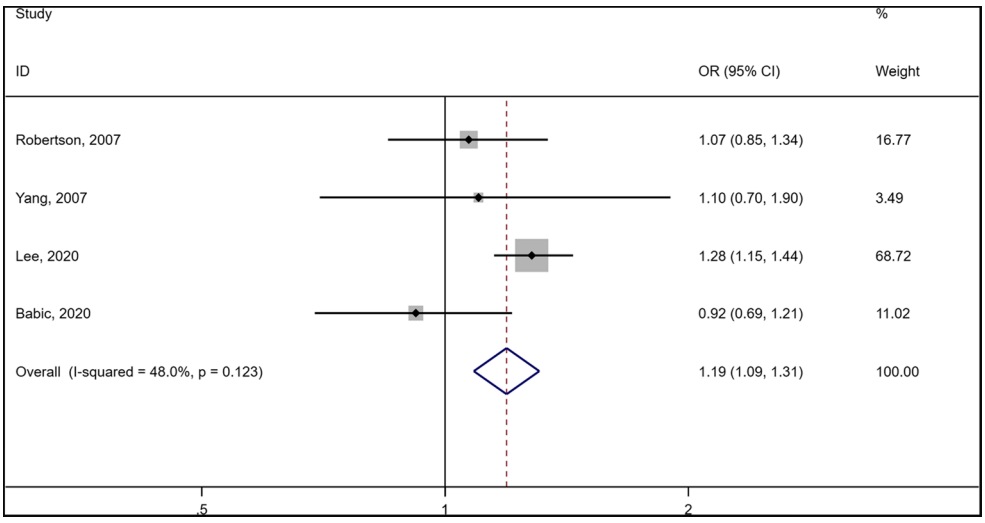

Fig. 3 Forest plot of the association between prolonged proton pump inhibitor use (> 5 years) and the risk of colorectal cancer. Data are presented as adjusted risk ratios

Table 3 Sensitivity analysis of the studies

Included studies	Pooled effect estimate		*p* value	Assessment of heterogeneity	
	OR	(95% CI)		I^2 (%)	*p* value
All	1.26	0.91–1.73	0.166	97.10%	< 0.001
Exclude study of Robertson	1.28	0.87–1.87	0.206	97.50%	< 0.001
Exclude study of Yang	1.27	0.90–1.79	0.166	97.50%	< 0.001
Exclude study of van Soest	1.32	0.93–1.87	0.116	97.40%	< 0.001
Exclude study of Chubak	1.23	0.88–1.72	0.232	97.50%	< 0.001
Exclude study of Lai	1.11	0.95–1.30	0.185	76.90%	< 0.001
Exclude study of Hwang	1.30	0.91–1.85	0.147	97.50%	< 0.001
Exclude study of Babic	1.32	0.93–1.87	0.125	97.40%	< 0.001
Exclude study of Lee	1.29	0.88–1.90	0.198	96.20%	< 0.001
Exclude study of Lei	1.18	0.83–1.67	0.349	97.40%	< 0.001
Exclude studies without lag time analysis	1.16	0.96–1.40	0.118	81.90%	< 0.001
Exclude studies in which PPI use duration data are not available	1.12	0.93–1.34	0.233	82.40%	< 0.001
Exclude studies in which included participants with IBD or studies unadjusted IBD as a confounder	1.51	0.90–2.53	0.117	98.50%	< 0.001

OR odds ratio, *CI* confidence interval, *PPI* proton pump inhibitor, *IBD* inflammatory bowel disease

the study of Ahn et al. [21] suggested that even if the duration of PPI use is limited to more than 5 years, PPIs are still not associated with CRC risk, which is contrary to our conclusion.

Although we use adjusted estimates and random-effects models that take into account variability and confounding factors for pooled estimates, there is still a significant heterogeneity between the studies. Because relatively few studies are available for each determinant, meta-regression is not suitable to explore the source of heterogeneity, so we conducted a subgroup analysis. Subgroup analysis showed that differences in study design, study region, cumulative duration of PPI use, and partially adjusted covariates/confounders could partly explain this heterogeneity, but the results of most subgroup analyses were still highly heterogeneous. This may be due to differences in how PPI exposure and CRC were characterized, differences in characteristics among different study populations, and some unmeasured confounders.

Of the 9 studies included in this systematic review, only 2 studies [8, 18] found a correlation between exposure to PPIs and CRC. The studies by Lai et al. [18] and Lei et al. [8] showed that the use of PPIs can increase the risk of CRC by more than 2-fold. In addition, in the study of Lai et al., the average duration of exposure to PPIs was 75 days, which obviously could not lead to CRC, a disease with a long induction period. We considered that some occult CRC patients were treated with PPIs because of vague symptoms of the upper digestive tract associated with undiagnosed CRC, resulting in a false association between PPIs and CRC. Lag time analysis of drug exposure can avoid this protopathic bias to some extent, and the 6 included studies [8, 20, 23, 31–33] used a 1-year lag time analysis, so we conducted a sensitivity analysis based on these studies; the results remained the same. The results of Lei et al. [8] show that the risk of CRC continues to increase with more frequent use of PPIs. Unfortunately, although some studies have reported defined daily doses, the cutoff ranges varied, so the dose–response relationship could not be demonstrated. In addition, the lead time bias should not be ignored in this study. The development of CRC is expected to take at least 10 years before clinical testing [19], but most cases with PPI exposure before the diagnosis date were followed up for less than 10 years. Therefore, a longer follow-up time is required to identify any causative links. In addition, a prospective cohort study [24] followed up for 26 years showed that no increase in CRC risk was observed even after a 10-year lag in drug use.

Although the relationship between the use of PPIs and CRC is uncertain, several possible pathophysiological mechanisms have been proposed. Studies have shown that lansoprazole and ilaprazole, novel and specific T-lymphokine–activated killer cell–originated protein kinase (TOPK) inhibitors, can directly inhibit the anchorage-independent growth of colorectal cancer cells with high TOPK levels in vitro and in vivo [35, 36]. However, more evidence is needed for this potential targeting effect. Another study showed that omeprazole inhibited the proliferation and carcinogenesis of colon cancer cell lines in a rat azomethane (AOM) model [37].

An indirect mechanism of PPIs in the development of CRC seems more likely. First, long-term use of PPIs will cause an increase in serum gastrin levels in most individuals, although there is a great variability [38]. In addition, two prospective studies have shown a statistical association between

hypergastrinemia and colorectal cancer or colorectal adenoma [39, 40]. Previous studies have suggested that gastrin, a peptide hormone with mitogen function, has tumorigenic nutritional effects [41] and fosters the tumor microenvironment [42]. The growth-promoting effect of hypergastrinemia caused by PPIs on CRC cells has been confirmed in a mouse model [43]. However, it is worth noting that some studies suggest that PPIs can block the nutritional effect of gastrin on colonic epithelial cells in vivo and in vitro [44, 45]. It has also been reported that gastrin inhibits the growth of colon cancer by inhibiting the EGR1/anion exchanger-2/P16/P-ERK signaling pathway [46]. Thus, the available evidence suggests that PPIs can affect tumor development via gastrin, but it is hard to determine whether it is promoted or inhibited.

Second, long-term use of PPIs significantly reduces the abundance and microbial diversity of intestinal symbiotic bacteria [47]. This intestinal dysbiosis is related to the occurrence of CRC [48]. Moreover, PPIs have been shown to promote the reproduction of certain bacteria (e.g., *Escherichia coli*, *Enterococcus*, *Streptococcus*) associated with the pathogenesis of CRC [49, 50]. These bacteria themselves, their derived virulence factors, and/or metabolites formed by fermentation by-products can drive the host's pro-inflammatory or anti-inflammatory immune response and influence the composition of the tumor microenvironment [51]. In addition, a rodent experiment demonstrated that PPIs could increase *Clostridium perfringens* abundance and promote the production of *Clostridium perfringens* enterotoxin to further activate yes-associated protein to enhance the progression of CRC [43]. Third, the use of PPIs has been shown to be associated with microscopic colitis [52]. Although the mechanism is unclear, microscopic colitis has been found to be negatively correlated with the risk of colorectal cancer and adenoma by multiple studies, including a prospective study [53, 54]. In contrast, several studies have reported that a systemic chronic inflammatory state is one of the causes of CRC [55], and the levels of circulating inflammatory biomarkers (such as C-reactive protein) have been related to the progression of CRC [56]. Long-term use of aspirin as an anti-inflammatory drug has been shown to prevent CRC [7]. Moreover, a cross-sectional study among subjects referred for colonoscopy found that the use of PPIs was associated with elevated fecal levels of calcitonin [57], which is a neutrophil degradation product related to intestinal inflammation and is regarded as a sensitive noninvasive marker of CRC [58].

This meta-analysis has several strengths. Compared with the previous meta-analysis, our study includes a larger sample size (n = 1,036,438), more studies (n = 9), and the latest studies, including three cohort studies [8, 23, 24], which makes our study more statistically powerful. We also analyzed the correlations between different exposure durations of PPI and colorectal cancer. In addition, we used adjusted OR values to minimize the impact of confounders.

However, there are also some limitations of our meta-analysis. First, all the included studies were observational studies. Although some studies included sophisticated methods, such as propensity score analysis [8], inherent bias and selection bias cannot be avoided. Therefore, we cannot confirm the existence of causality. Second, all but 2 of the included studies [23, 24] defined PPI exposure based on a prescription database, and some people may use over-the-counter drugs or fail to follow prescriptions, which will lead to misclassification of exposure status. In addition, the study of Babic et al. [24] used questionnaires to ask about the "regular use" of drugs, which is highly volatile. Third, due to the lack of original data, there is no subgroup analysis based on the individual type of PPIs. Lei et al. [8] found that the use of lansoprazole, omeprazole, and esomeprazole increased the risk of CRC, but the use of pantoprazole and rabeprazole was not associated with an increased risk of CRC. This is similar to the conclusion of another study that compared the incidence of CRC among users of pantoprazole and other PPIs [59]. We are also unable to analyze the association based on the tumor site due to the lack of sufficient data. Therefore, further studies are needed to evaluate the correlations between different types of PPIs and different tumor sites while controlling for other confounding factors. Finally, some important covariates/confounders related to cancer risk have not been reported or well-adjusted in the included study, including several known risk factors for CRC, such as diet, physical activity, body mass index, history of colonoscopy, *Helicobacter pylori* infection, use of aspirin/NSAIDs, inflammatory bowel disease, hereditary cancer syndrome, and family history of CRC. Future studies should adjust for as many confounders as possible to provide a more realistic illustration of the relationship between PPIs and the risk of CRC.

Conclusion

Our results show that although there may be a weak association between the long-term use of PPIs (> 5 years) and the risk of CRC, this conclusion was drawn based on limited observational studies, many potential confounders, and different definitions of exposure duration. Therefore, we do not have enough statistical power to refute or confirm an association between the use of PPIs and CRC. Further prospective cohort studies with large sample sizes, high quality, and long follow-up periods are needed to assess the correlation between PPI use and the risk of CRC. PPIs should be given for the shortest possible time with the lowest effective dose for an appropriate indication before clear conclusions can be drawn.

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Authors' contributions Tianyi Ma contributed to the study design, statistical analysis, and manuscript writing; Meng Wu and Shengnan Jia conducted literature retrieval and data collection; and Lanlan Yang viewed and revised the manuscript. All authors read and approved the final version of the manuscript.

Data availability All data are available upon request.

Compliance with ethical standards

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

Ethics approval This systematic review and meta-analysis used previously published data and did not use any unpublished data. Therefore, ethical approval for the analysis was not applicable.

Consent to participate Not applicable.

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