Original research

Proton pump inhibitors and risk of colorectal cancer

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ABSTRACT

Objective To determine whether proton pump inhibitors (PPIs) are associated with an increased risk of colorectal cancer, compared with histamine-2 receptor antagonists (H2RAs).

Design The United Kingdom Clinical Practice Research Datalink was used to identify initiators of PPIs and H2RA from 1990 to 2018, with follow-up until 2019. Cox proportional hazards models were fit to estimate marginal HRs and 95% CIs of colorectal cancer. The models were weighted using standardised mortality ratio weights using calendar time-specific propensity scores. Prespecified secondary analyses assessed associations with cumulative duration, cumulative dose and time since treatment initiation. The number needed to harm was calculated at five and 10 years of follow-up.

Results The cohort included 1 293 749 and 292 387 initiators of PPIs and H2RAs, respectively, followed for a median duration of 4.9 years. While the use of PPIs was not associated with an overall increased risk of colorectal cancer (HR: 1.02, 95% CI 0.92 to 1.14), HRs increased with cumulative duration of PPI use (<2 years, HR: 0.93, 95% CI 0.83 to 1.04; 2–4 years, HR: 1.45, 95% CI 1.28 to 1.60; ≥4 years, HR: 1.60, 95% CI 1.42 to 1.80). Similar patterns were observed with cumulative dose and time since treatment initiation. The number needed to harm was 5343 and 792 for five and 10 years of follow-up, respectively.

Conclusion While any use of PPIs was not associated with an increased risk of colorectal cancer compared with H2RAs, prolonged use may be associated with a modest increased risk of this malignancy.

Summary box

What is already known about this subject?
- Previous observational studies present conflicting evidence regarding the association between proton pump inhibitor use and colorectal cancer incidence.
- Previous studies have been limited by small sample sizes, short durations of follow-up, and other methodological shortcomings.

What are the new findings?
- The results of this study suggest that any use of proton pump inhibitors is not associated with an increased risk of colorectal cancer.
- However, prolonged durations of use of proton pump inhibitors may be associated with a modest increased risk of colorectal cancer.

How might it impact on clinical practice in the foreseeable future?
- Given that proton pump inhibitors are commonly overprescribed for inappropriately long durations, this study highlights the need to reassess the need for ongoing treatment regularly.

INTRODUCTION

Proton pump inhibitors (PPIs) are commonly prescribed drugs indicated for several gastric conditions, including peptic ulcer disease, GORD and Barrett's oesophagus.[1 2] Histamine-2 receptor antagonists (H2RAs), an alternative class of acid suppressant drugs, are indicated for similar conditions, although they are less effective at lowering stomach acid levels compared with PPIs.[1] Recent evidence suggests that PPIs are commonly overprescribed, either in patients without an evidence-based indication for use or longer durations than necessary.[3] This is particularly relevant as several observational studies have associated the use of PPIs with different adverse health outcomes, including GI malignancies such as colorectal cancer.[4–13]

Hypergastrinaemia may be induced by prolonged use of PPIs,[14] which in turn, may be associated with the development of colorectal cancer, as hypergastrinaemia has been shown to promote the proliferation of both normal and malignant colonic and rectal cancer cells in vitro.[15–20] While animal models suggest that hypergastrinaemia leads to adenoma progression, an important precursor to colorectal cancer,[21] the association between PPI use and adenomatous polyps has not been shown consistently in humans.[22] To date, several observational studies that investigated the association between PPI use and colorectal cancer have generated conflicting findings (relative risks ranging from 0.85 to 2.54) and had important methodological shortcomings.[4–13] Major sources of bias in the existing literature include confounding by indication, the inclusion of prevalent users, and latency bias.[23–25] These conclusion-altering biases can lead to spurious and exaggerated associations in both directions, limiting the conclusions drawn from these studies.

Given the conflicting observational evidence, it remains unclear whether the use of PPIs is associated with the incidence of colorectal cancer, a leading cause of cancer death with an increasing incidence among younger adults.[26 27] Additional studies are needed to better inform the safety profile of this widely prescribed drug class. Thus, the objective of

this large population-based cohort study is to determine whether the use of PPIs, when compared with the use of H2RAs, is associated with an increased risk of colorectal cancer.

METHODS

Data source

We used data from the UK Clinical Practice Research Datalink (CPRD), a large, computerised database of longitudinal primary care records of over 15 million patients.[28 29] The CPRD contains information on medical diagnoses and procedures, prescription details including dose and quantity, laboratory values and lifestyle characteristics, including smoking and body mass index (BMI). The data have been extensively validated, generating high-positive predictive values and high sensitivities for various diagnoses, including colorectal cancer.[30–36] Indeed, the sensitivity, specificity and positive predictive value of colorectal cancer have been estimated at above 90% in several studies.[33–35] Moreover, when assessing the validity of 183 different diagnoses, a median of 89% of cases were confirmed using additional internal or external data.[36]

Study population

We used a new-user, active comparator design to compare patients newly treated with PPIs (including all available in the UK: esomeprazole, lansoprazole, omeprazole, pantoprazole, or rabeprazole; online supplemental table 1) with patients newly treated with H2RAs (including all available in the UK: cimetidine, famotidine, nizatidine, or ranitidine; online supplemental table 2). We selected H2RAs as the comparator group because they represent a clinically relevant group used in similar indications as PPIs and thus should minimise confounding by indication. Cohort entry was defined as the date of this first prescription of either a PPI or H2RA from 1 January 1990, through 30 April 2018. To be included in the cohort, patients were required to be at least 18 years of age and have at least 1 year of medical information in the CPRD before cohort entry; the latter served as a washout period to ensure new use of PPIs and H2RAs. We excluded patients for whom a PPI and an H2RA were prescribed concomitantly at cohort entry and those with a history of Zollinger-Ellison syndrome (a rare indication for PPI use)[1] or cystic fibrosis, which is known to increase the risk of early-onset colorectal cancer,[37] at any time on or before cohort entry. We also excluded patients with a history of colorectal cancer (ie, to exclude prevalent cases) or rare inherited cancer syndromes (familial adenomatous polyposis, Lynch syndrome, Li Fraumeni syndrome, Peutz-Jeghers syndrome, or Cowden syndrome),[38–41] at any time on or before cohort entry. Finally, to allow for a sufficient latency period and minimise detection bias and reverse causality, the cohort was restricted to patients with at least 1 year of follow-up after cohort entry (ie, 1-year lag period).[42]

Exposure definition

Patients were considered continuously exposed to their cohort entry drug (ie, first of either PPI or H2RA prescription) starting 1 year after cohort entry until the end of follow-up. This exposure definition, which does not consider treatment termination, aligns with the hypothesised biological mechanism (ie, adenoma progression from prolonged PPI use would progress even following treatment discontinuation). Thus, patients were followed starting 1 year after cohort entry until an incident diagnosis of colorectal cancer (identified using Read codes, online supplemental table 3), 1 year after switching between the study drug classes (ie, switch from PPI to H2RA or vice versa to account for the 1 year lag period, with person-time during the lag period attributed to initial exposure), death from any cause, end of registration with the general practice, or end of the study period (30 April 2019), whichever occurred first. Online supplemental figure 1 illustrates a schematic of this exposure definition.

Potential confounders

We considered the following potential confounders, all measured on or before cohort entry: age (modelled as a continuous variable using a cubic spline model to account for a possible non-linear relation with the outcome),[43] sex, alcohol-related disorders, smoking status (current, former, never), BMI, type 2 diabetes, hypertension, coronary artery disease, chronic obstructive pulmonary disease, cancer (other than non-melanoma skin cancer), Crohn's disease, UC, other IBD, GI polyps, cholecystectomy and solid organ transplant. We also considered the indication for acid suppressant drug use (approved indications: peptic ulcer disease, GORD, dyspepsia, *Helicobacter pylori* infection, and Barrett's oesophagus; off-label indications: gastritis/duodenitis and stomach pain). We also included the following drugs previously associated with colorectal cancer incidence, measured at any time before cohort entry: hormone replacement therapy, aspirin, other non-steroidal anti-inflammatory drugs, statins, bisphosphonates, and use of synthetic prostaglandin analogues, which are older drugs used to manage gastric conditions.[1] Finally, we included measures of health-seeking behaviours, such as mammographic screening, prostate-specific antigen testing, colorectal cancer screening, and influenza vaccination.

Statistical analysis

We used calendar time-specific propensity scores to reweigh our study population.[44] Using multivariable logistic regression, we estimated propensity scores within 5-year calendar bands at cohort entry (1990–1994, 1995–1999, 2000–2004, 2005–2009, 2010–2018) as the predicted probability of receiving a PPI versus an H2RA conditional on the covariates listed above. Calendar time-specific propensity scores were chosen to account for temporal changes in the prescribing of acid suppressants and colorectal cancer incidence during the study period.[3 45] Patients in non-overlapping regions of the propensity score distributions were trimmed from the analysis. Using the propensity scores, treatment weights were assigned using standardised mortality ratio weights. Thus, PPI initiators were given a weight of 1, while H2RA initiators were given a weight of the odds of the treatment probability (propensity score/(1-propensity score)).[46] This weight functions to upweight the comparator patients (ie, H2RA users) to represent the treated population (ie, PPI users). We assessed covariate balance using standardised differences, with differences of less than 0.10 considered acceptable.[47]

Incident rates of colorectal cancer, with 95% CIs based on the Poisson distribution, were calculated for each exposure group. Weighted Kaplan-Meier curves were plotted to display the cumulative incidence of colorectal cancer over the follow-up period for PPI and H2RA users. Weighted Cox proportional hazards models were fit to estimate marginal HRs of colorectal cancer with 95% CIs using robust variance estimators. This marginal HR is a population-level estimate that described the average treatment effect in the treated; the average causal effect of treatment in the PPI cohort.[46 48] Finally, we calculated the number needed to harm at five and 10 years of follow-up using the Kaplan-Meier method.[49]

Secondary analyses

We performed five secondary analyses. The first analysis assessed duration–response and dose–response relations according to cumulative duration of use, cumulative omeprazole equivalents, and time since treatment initiation. Cumulative duration was defined by summing the durations of each PPI prescription from cohort entry until the time of the event defining risk set. Given the different potencies of various PPIs, cumulative dose was defined using defined daily doses, a standardised unit of drug consumption defined by the WHO (online supplemental table 4).[50] Individual PPI molecules were converted to omeprazole equivalents, and the cumulative dose was calculated by summing the dose of each prescription from cohort entry until the risk set. According to the defined daily dose, a patient prescribed a 30-day course of 30 mg of esomeprazole has equivalent usage to a patient prescribed a 30-day course of 20 mg omeprazole. Finally, time since treatment initiation was defined as the time between cohort entry and the risk set. HRs for these secondary exposures were estimated using time-dependent Cox proportional hazards models using predefined categories (<2 years, 2–4 years and ≥4 years), and cumulative duration and dose were also modelled flexibly using restricted cubic spline models.[43] Second, we stratified by type of PPI (omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole or combinations) to determine whether there were any molecule-specific effects. Third, to determine if the association varies by cancer type, we repeated the primary analysis by stratifying on colon versus rectal cancer. Fourth, we considered whether there is effect measure modification by sex, age (<40, 40–59, and ≥60 years), history of IBD (including UC and Crohn's disease), GI polyps and aspirin use. Age, sex, IBD and GI polyp history are strong nonmodifiable risk factors for colorectal cancer, while aspirin use has been associated with a decreased risk of colorectal cancer.[51–56] For these analyses, we included an interaction term in the primary model between exposure status and these variables. Finally, we calculated HRs according to the most common approved indications at baseline (GORD, peptic ulcer disease and dyspepsia).

Sensitivity analyses

We conducted six sensitivity analyses to assess the robustness of our findings. First, we repeated the primary analysis by increasing the exposure lag period to 3, 5 and 10 years, as there are uncertainties regarding the optimal length of the latency window. These analyses were restricted to patients with at least 3, 5 and 10 years of follow-up, respectively. Second, to address the impact of informative censoring, we did not censor patients who switched between drug classes (ie, an intention-to-treat exposure definition). Third, as an alternative method to investigate the impact of informative censoring, we used stabilised inverse probability of censoring weights to account for censoring from switching between drug classes during follow-up,[57 58] and to account for the competing risk of death from any cause.[59] Censoring weights were calculated using two separate logistic regression models within 1-year intervals, with one estimating the probability of remaining uncensored from a drug switch and the other estimating the probability of not dying (online supplemental method 1). Fourth, as certain H2RAs have recently been found to be contaminated with a probable carcinogen (N-nitrosodimethylamine (NDMA)),[60] we repeated the analysis with follow-up truncated on 31 December 2017, which is before the time NDMA contaminants were found.[60] Fifth, to investigate the impact of residual confounding, we repeated the analysis using the high-dimensional propensity score (HD-PS) approach to calculate treatment weights (online supplemental method 2).[61] For this analysis, we considered all predefined covariates listed above, along with 200 empirically selected covariates from the HD-PS algorithm. Finally, we investigated the potential impact of detection bias from differential screening uptake using inverse probability of screening weighting, estimated within 2-year intervals (online supplemental method 3).[62] All analyses were conducted with SAS V.9.4 (SAS Institute) and R V.4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Patient and public involvement

We did not include patients as study participants as our study involved the use of secondary data. Patients were not involved in the design or implementation of the study. We do not plan to involve patients in the dissemination of results, nor will we disseminate results directly to patients.

RESULTS

The cohort included 1 293 749 and 292 387 initiators of PPIs and H2RAs, respectively (figure 1). Over a median duration of 4.9 years of follow-up (including the 1-year postcohort entry latency period), there were 6759 incident colorectal cancer events among PPI users versus 1264 events among H2RA users. The corresponding crude incidence rates of colorectal cancer were 105.5 (95% CI 103.0 to 108.0) and 87.7 (95% CI 82.9 to 92.7) per 100 000 person years among PPI and H2RA users, respectively.

Table 1 shows the baseline characteristics of PPI and H2RA users before and after weighting. Before weighting, the exposure groups were similar in age, sex, history of IBD and cancer. PPI users were more likely to be former smokers, obese, use nonsteroidal anti-inflammatory drugs and statins, and have type 2 diabetes and hypertension, but were less likely to have dyspepsia compared with H2RA users. PPI users were also more likely to be screened for colorectal cancer and have a history of prostate-specific antigen testing. After weighting, the exposure groups were well balanced on all study covariates, with all standardised differences below 0.10. During the follow-up period, 52.8% of H2RA users added-on or switched to PPIs, while 7.7% of PPI users added-on or switched to H2RAs.

Table 2 shows the results of the primary and secondary analyses. After adjusting for treatment weights, any use of PPIs was not associated with colorectal cancer incidence, compared with the use of H2RAs (HR: 1.02, 95% CI 0.92 to 1.14). The cumulative incidence of colorectal cancer was similar in both exposure groups (online supplemental figure 2). In secondary analyses, there was a gradual increase in risk with increasing cumulative duration of use, cumulative omeprazole equivalents, and time since treatment initiation (table 2). The risk was most elevated in the highest categories of use for all exposure definitions (≥4 years cumulative duration, HR: 1.60, 95% CI 1.42 to 1.80; ≥29 200 mg omeprazole dose equivalents, HR: 1.58, 95% CI 1.39 to 1.78; ≥4 years since treatment initiation, HR: 1.19, 95% CI 1.03 to 1.34) and consistently elevated in the restricted cubic spline models (online supplemental figures 34). The number needed to harm at five years of follow-up was 5343 patients, and at 10 years of follow-up was 792 patients. There was no evidence of molecule-specific effects (online supplemental table 5), and there was no difference in risk when stratifying by colon versus rectal cancer (online supplemental table 6). The association between PPI use and colorectal cancer was modified by sex (male HR: 0.90, 95% CI 0.78 to 1.04; female HR: 1.22, 95% CI 1.04 to 1.45, online supplemental table 7), but was not

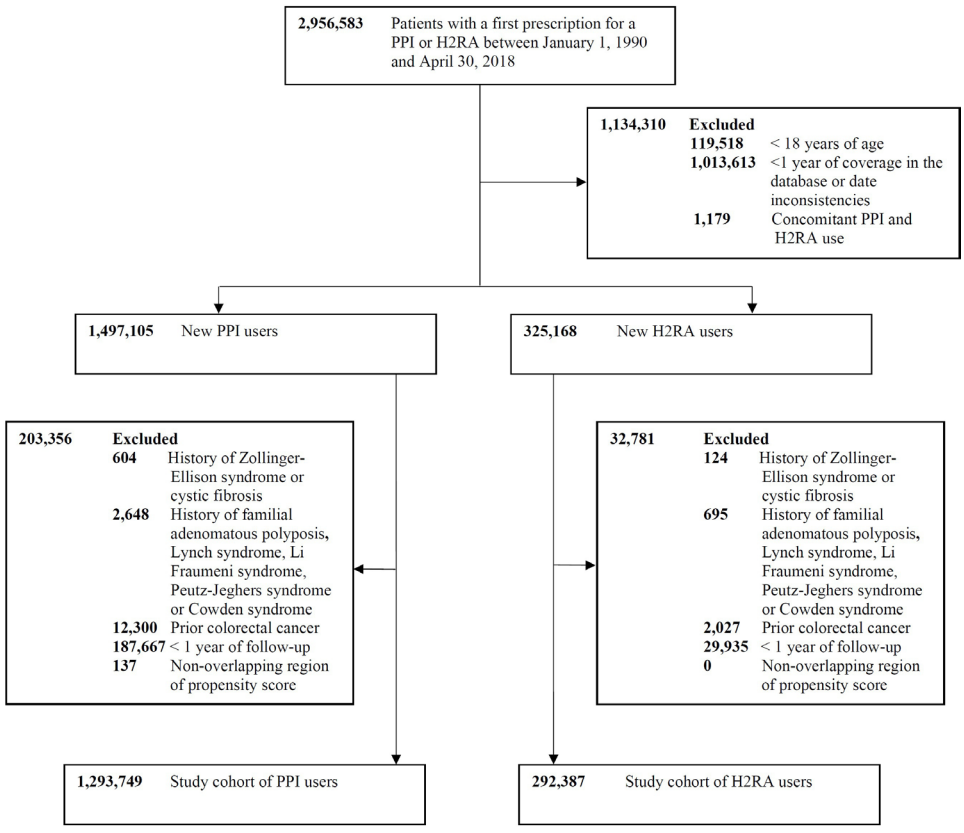

Figure 1 Study flow chart illustrating the construction of the proton pump inhibitor (PPI) and histamine-2 receptor antagonist cohorts (H2RA).

modified by age, history of IBD, GI polyps or aspirin use (online supplemental tables 8–10). The HR was slightly elevated among patients with dyspepsia at baseline, although the CIs across indications largely overlapped (online supplemental table 12).

The sensitivity analyses generated highly consistent results (figure 2, online supplemental tables 13 to 18). Overall, the HRs ranged from 0.97 for the intention-to-treat exposure definition to 1.24 for the screening analysis. The screening rate in the PPI and H2RA cohorts was 55.4 and 20.0 per 1000 person years, respectively.

DISCUSSION

Principal findings

In this large population-based cohort study, we assessed whether initiators of PPIs are at an increased risk of colorectal cancer compared with initiators of H2RAs (figure 3). While any use of PPIs was not associated with an increased risk of colorectal cancer, there was evidence of a duration–response relation, with elevated relative risks with increasing duration, dose and time since initiation. The number needed to harm was 5343 and 792 for five and 10 years of follow-up, respectively. The association was modified by sex, with female PPI initiators at an increased risk of colorectal cancer compared with males. The results remained largely consistent across several sensitivity analyses, although adjustment for screening led to a slight increase in the HR, as colorectal screening is an interventional procedure that decreases the risk of colorectal cancer.[63]

Comparison with previous studies

The existing evidence on the association between the use of PPIs and overall colorectal cancer risk has been inconsistent, with relative risks ranging from 0.85 to 2.54 (online supplemental table 19).[4–13] While the overall results of our study are in line with some of the previous studies,[4 5 8–12] few studies found evidence of duration–response relation.[5 11 13] However, there are important methodological differences between our study and the previous literature, which may explain some of the discrepant findings. First, while some studies assessed the effect of H2RAs on colorectal cancer risk (relative risks ranging from 0.80 to 2.10),[6 7 12] no study used H2RAs as an active comparator. Comparing PPI users to the general population may lead to spurious associations from confounding by indication.[23] The previous studies were also limited by other important biases, such as the inclusion of prevalent users, time-related biases like time-window and immortal-time bias, and failure to account for cancer latency.[24 25 64 65] In light of these conclusion-altering biases, it is difficult to interpret the existing literature.

The existing biological evidence on the association between PPI use and colorectal cancer is limited. Indeed, chronic suppression of acid through PPI use can induce hypergastrinaemia,[14] which has been associated with increased proliferation of normal and malignant colonic and rectal cancer cells in vitro.[15–20] However, our findings suggest that for most PPI users who are using PPIs as a short-term treatment, this does not amount to a meaningful increase in the risk of colorectal cancer. Moreover, there is no consensus in the literature as to whether hypergastrinaemia leads to adenoma progression.[21 22] While we did not find an increased risk of colorectal cancer from any PPI use, our findings do support the aforementioned biological hypothesis, in that there was a modest increased risk of colorectal cancer among patients prescribed PPIs for increasing durations. Thus, it remains possible that

Table 1 Baseline characteristics of proton pump inhibitor and histamine-2 receptor antagonist users before and after weighting

	Before weighting			After weighting*		
Characteristic	**PPI**	**H2RA**	**ASD**	**PPI**	**H2RA**	**ASD**
Total	1 293 749	292 387		1 293 749	1 294 713	
Age (mean, SD)	52.6 (17.6)	50.3 (18.3)	0.12	52.6 (17.6)	52.6 (37.3)	0.00
Male	583 401 (45.1)	125 897 (43.1)	0.04	583 401 (45.1)	589 773 (45.6)	0.01
Alcohol related disorders	72 658 (5.6)	11 746 (4.0)	0.07	72 658 (5.6)	73 068 (5.6)	0.00
Smoking Status						
Current	286 577 (22.2)	72 347 (24.7)	0.06	286 577 (22.2)	289 184 (22.3)	0.00
Former	366 403 (28.3)	51 301 (17.6)	0.27	366 403 (28.3)	365 923 (28.3)	0.00
Never	593 370 (45.9)	130 113 (44.5)	0.03	593 370 (45.9)	592 021 (45.7)	0.00
Missing	47 399 (3.7)	38 626 (13.2)	0.35	47 399 (3.7)	47 585 (3.7)	0.00
Body mass index						
<25 kg/m^2	428 551 (33.1)	99 667 (34.1)	0.02	428 551 (33.1)	431 364 (33.3)	0.00
25–29.9 kg/m^2	399 316 (30.9)	78 045 (26.7)	0.09	399 316 (30.9)	396 685 (30.6)	0.00
≥30 kg/m^2	290 289 (22.4)	45 218 (15.4)	0.18	290 289 (22.4)	289 311 (22.4)	0.00
Missing	175 593 (13.6)	69 457 (23.8)	0.26	175 593 (13.6)	177 353 (13.7)	0.00
Type 2 diabetes	76 125 (5.9)	9429 (3.2)	0.13	76 125 (5.9)	76 388 (5.9)	0.00
Hypertension	315 352 (24.4)	53 032 (18.1)	0.15	315 352 (24.4)	316 400 (24.4)	0.00
Coronary artery disease	136 300 (10.5)	32 677 (11.2)	0.02	136 300 (10.5)	137 106 (10.6)	0.00
Chronic obstructive pulmonary disorder	88 909 (6.9)	25 219 (8.6)	0.07	88 909 (6.9)	89 933 (7.0)	0.00
Cancer	77 844 (6.0)	13 209 (4.5)	0.07	77 844 (6.0)	79 864 (6.2)	0.01
Crohn's disease	5115 (0.4)	885 (0.3)	0.02	5115 (0.4)	5404 (0.4)	0.00
UC	7865 (0.6)	1484 (0.5)	0.01	7865 (0.6)	8336 (0.6)	0.00
Other IBD	2349 (0.2)	394 (0.1)	0.01	2349 (0.2)	2492 (0.2)	0.00
GI polyps	16 170 (1.3)	2068 (0.7)	0.06	16 170 (1.3)	16 034 (1.2)	0.00
Cholecystectomy	35 359 (2.7)	7716 (2.6)	0.01	35 359 (2.7)	36 162 (2.8)	0.00
Solid organ transplant	1191 (0.1)	698 (0.2)	0.04	1191 (0.1)	1272 (0.1)	0.00
Peptic ulcer disease	31 715 (2.5)	9978 (3.4)	0.06	31 715 (2.5)	32 459 (2.5)	0.00
GORD	115 880 (9.0)	24 378 (8.3)	0.02	115 880 (9.0)	119 752 (9.3)	0.01
Dyspepsia	232 197 (18.0)	89 299 (30.5)	0.30	232 197 (18.0)	239 284 (18.5)	0.01
Helicobacter pylori infection	29 269 (2.3)	1606 (0.6)	0.15	29 269 (2.3)	30 665 (2.4)	0.01
Barrett's oesophagus	2923 (0.2)	86 (0.0)	0.06	2923 (0.2)	3305 (0.3)	0.01
Gastritis/duodenitis	58 373 (4.5)	18 877 (6.5)	0.09	58 373 (4.5)	59 573 (4.6)	0.00
Stomach pain	405 117 (31.3)	95 561 (32.7)	0.03	405 117 (31.3)	413 004 (31.9)	0.01
Hormone replacement therapy	158 233 (12.2)	33 504 (11.5)	0.02	158 233 (12.2)	158 046 (12.2)	0.00
Aspirin	234 232 (18.1)	40 567 (13.9)	0.12	234 232 (18.1)	233 410 (18.0)	0.00
Other non-steroidal anti-inflammatory drugs	882 495 (68.2)	170 674 (58.4)	0.21	882 495 (68.2)	878 900 (67.9)	0.01
Statins	247 703 (19.2)	24 229 (8.3)	0.32	247 703 (19.2)	248 201 (19.2)	0.00
Bisphosphonates	42 257 (3.3)	3644 (1.3)	0.14	42 257 (3.3)	43 548 (3.4)	0.01
Prostaglandin analogues	1595 (0.1)	1153 (0.4)	0.05	1595 (0.1)	1710 (0.1)	0.00
Mammographic screening	296 749 (22.9)	45 178 (15.5)	0.19	296 749 (22.9)	298 034 (23.0)	0.00
Prostate-specific antigen test	113 480 (8.8)	9807 (3.4)	0.23	113 480 (8.8)	113 427 (8.8)	0.00
Colorectal cancer screening	116 028 (9.0)	9384 (3.2)	0.24	116 028 (9.0)	117 518 (9.1)	0.00
Influenza vaccination	502 581 (38.9)	86 798 (29.7)	0.19	502 581 (38.9)	506 735 (39.1)	0.01
Year of cohort entry						
1990–1994	9318 (0.7)	44 492 (15.2)	0.56	9318 (0.7)	9331 (0.7)	0.00
1995–1999	45 318 (3.5)	69 634 (23.8)	0.62	45 318 (3.5)	45 395 (3.5)	0.00
2000–2004	189 891 (14.7)	92 139 (31.5)	0.41	189 891 (14.7)	189 804 (14.7)	0.00
2005–2009	426 895 (33.0)	48 367 (16.6)	0.39	426 895 (33.0)	427 304 (33.0)	0.00
2010–2018	622 327 (48.1)	37 755 (12.9)	0.83	622 327 (48.1)	622 881 (48.1)	0.00

Before weighting: counts (percentages), unless otherwise stated; after weighting: count, rounded to the nearest whole number, (percentages), unless otherwise stated.
*Pseudopopulation created by applying standardised mortality ratio weights.
ASD, absolute standardised difference; PPI, proton pump inhibitor; H2RA, histamine-2 receptor antagonist.;

prolonged hypergastrinaemia over an extended period may lead to increased colorectal cancer risk among long-term PPI users. This association may also be explained by changes to the gut microbiome induced through PPI use,[66 67] which can alter colorectal cancer susceptibility and progression.[68]

Strengths and limitations of this study

This study has several strengths. First, to our knowledge, this is the largest study with the longest potential follow-up conducted to date. Second, contrary to previous studies, we used an active comparator for our analyses, minimising confounding by

Table 2 Crude and adjusted HRs for the association between the use of proton pump inhibitors and colorectal cancer compared with the use of histamine-2 receptor antagonists

	Events	Person years	Crude incidence rate (95% CI) *	Crude HR	Marginal HR (95% CI) †
Histamine-2 receptor antagonist (n=292 387)	1264	1 440 977	87.7 (82.9 to 92.7)	1.00	1.00 (reference)
Proton pump inhibitor (n=1 293 749)	6759	6 406 425	105.5 (103.0 to 108.0)	1.23	1.02 (0.92 to 1.14)
Cumulative duration of proton pump inhibitors					
<2 years	4961	5 248 111	94.5 (91.9 to 97.2)	1.09	0.93 (0.83 to 1.04)
2–4 years	836	574 744	145.5 (135.8 to 155.7)	1.72	1.45 (1.28 to 1.65)
≥4 years	962	583 570	164.8 (154.6 to 175.6)	1.85	1.60 (1.42 to 1.80)
Cumulative omeprazole dose equivalents					
<14 600 mg	5120	5 356 848	95.6 (93.0 to 98.2)	1.11	0.94 (0.84 to 1.05)
14 600–29 200 mg	839	556 726	150.7 (140.7 to 161.3)	1.77	1.50 (1.32 to 1.70)
≥29 200 mg	800	492 851	162.3 (151.3 to 174.0)	1.80	1.58 (1.39 to 1.78)
Time since proton pump inhibitor initiation					
<2 years	1206	1 182 062	102.0 (96.3 to 108.0)	1.13	0.87 (0.69 to 1.10)
2–4 years	1795	1 844 488	97.3 (92.9 to 102.0)	1.15	0.92 (0.74 to 1.13)
≥4 years	3758	3 379 875	111.2 (107.7 to 114.8)	1.30	1.19 (1.03 to 1.34)

*Per 100 000 person years.
†Weighted using standardised mortality ratio weights.

indication and presenting a clinically meaningful comparison. Third, our new-user study design eliminated the biases associated with the inclusion of prevalent users, such as survival bias and confounding. This active comparator new-user study design also minimises the possibility of immortal time bias, as person time at risk starts after the initiation of treatment.[69] Fourth, we used propensity score-weighted models, which ensured that baseline confounders were well balanced between our study groups. Finally, we present measures of absolute risk, which are important in understanding the potential burden of colorectal cancer in patients using PPIs.

This study has certain limitations that need to be considered. First, there may be some exposure misclassification, as the CPRD captures prescriptions issued by general practitioners and does not contain data on specialist prescriptions or over-the-counter use. However, in the UK, general practitioners are responsible for the long-term care of gastric disorders,[70] and patients with underlying disease, for whom moderate-to-long-term treatment is indicated, are financially incentivised to receive prescriptions from their general practitioner rather than from over-the-counter. Nonetheless, we expect any potential exposure misclassification to be non-differential between the exposure groups. It was also not possible to measure treatment adherence, although this is unlikely to be differential between the exposure groups. Second, we were unable to stratify the outcome according to cancer stage or tumour site (colon vs rectal or left-sided vs right-sided colon), as these variables are not available in the CPRD. This would have been useful to understand whether any observed increased risk of colorectal cancer was a result of increased detection. Third, the prevalence of screening may be underestimated in this cohort.[71] Finally, as with all observational studies, residual confounding from unknown or unmeasured confounders is possible, including family history, diet, or ethnicity. We attempted to minimise the impact of residual confounding using an active comparator and a wide variety of potential confounders in our propensity score models. Moreover, the results from the HD-PS analysis, which included an additional 200 covariates, which may be proxies for unknown or unmeasured confounders,[61] generated highly consistent findings.

In summary, the results of this study suggest that while any use of PPIs is not associated with an increased risk of colorectal cancer compared with the use of H2RAs, prolonged use might be associated with an increased risk of this malignancy. Though the

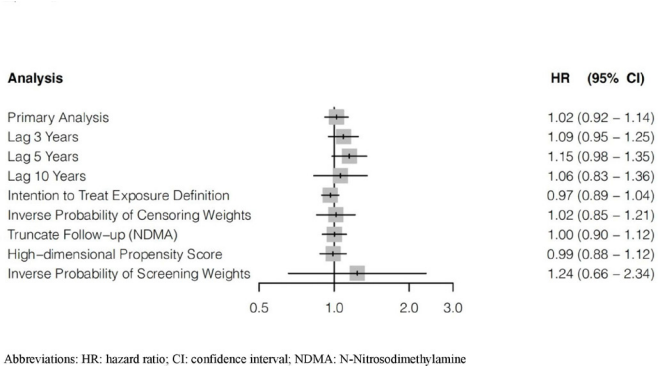

Figure 2 Forest plot summarising the results of the primary and sensitivity analyses, with weighted HRs and 95% CIs for the association between use of proton pump inhibitors and colorectal cancer, compared with the use of histamine-2 receptor antagonists.

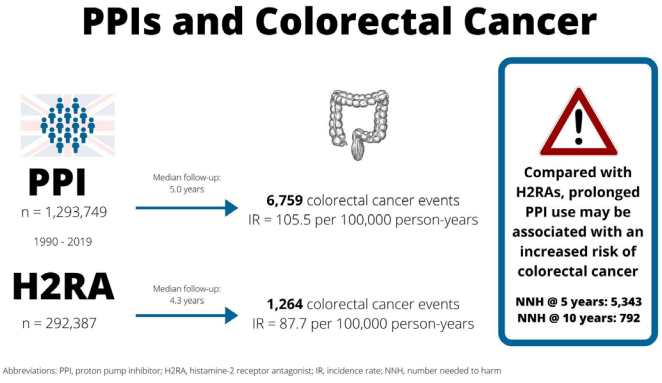

Figure 3 Graphical summary: graphical summary highlighting the main findings of the association between the use of proton pump inhibitors and colorectal cancer, compared with the use of histamine-2 receptor antagonists.

absolute risk of colorectal cancer is low at the individual level, given the high prevalence of PPI use, this increased risk could translate to a significant excess number of colorectal cancer cases at the population level. In light of this risk, PPIs should be deprescribed in patients for whom treatment is no longer indicated, and physicians should closely monitor patients that require long-term PPI treatment.

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Contributors All authors conceived and designed the study. LA acquired the data. DA and LA did the statistical analyses. MES and SS provided statistical expertise. All authors analysed and interpreted the data. EGM and ANB provided clinical expertise. DA wrote the manuscript, and all authors critically revised the manuscript. LA supervised the study and is the guarantor. All authors approved the final version of the manuscript and agree to be accountable for the accuracy of the work.

Competing interests SS participated in advisory meetings or as a guest speaker for Atara Biotherapeutics, Boehringer-Ingelheim, Bristol-Myers-Squibb, Merck and Pfizer, all unrelated to this study. LA served as a consultant for Janssen and Pfizer for work unrelated to this study. The other authors have no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Supplementary Table 1. List of British National Formulary Codes for Proton Pump Inhibitors

British National Formulary Code	British National Formulary Header
01030500/05010103	Proton Pump Inhibitors/Broad-spectrum Penicillins
01030500/10010100	Proton Pump Inhibitors/Non-steroidal Anti-inflammatory Drugs
01030500/05010500	Proton Pump Inhibitors/Macrolides
1030500	Proton Pump Inhibitors

Supplementary Table 2. List of British National Formulary Codes for Histamine-2 Receptor Antagonists

British National Formulary Code	British National Formulary Header
1030100	H2 receptor antagonists
01030100/01010201	H2 receptor antagonists/Alginate preparations
01030300/01030100	Chelates and complexes/H2 receptor antagonists
01030300/01030100	Chelates and complexes/H2 receptor antagonists
01030100/01010202	H2 receptor antagonists/Indigestion remedies
01010201/01030100	Compound Alginate Preparations/H2-Receptor Antagonists
01010202/01030100	Indigestion Preparations/H2-Receptor Antagonists

Abbreviations: H2, Histamine-2

Supplementary Table 3. Colorectal Cancer Read Codes Used to Define Events

Read Code	Read Term
B13..00	Malignant neoplasm of colon
B141.00	Malignant neoplasm of rectum
B133.00	Malignant neoplasm of sigmoid colon
B134.00	Malignant neoplasm of caecum
B141.12	Rectal carcinoma
B131.00	Malignant neoplasm of transverse colon
B141.11	Carcinoma of rectum
B130.00	Malignant neoplasm of hepatic flexure of colon
B13z.11	Colonic cancer
B132.00	Malignant neoplasm of descending colon
B136.00	Malignant neoplasm of ascending colon
B902500	Neoplasm of uncertain behaviour of rectum
B137.00	Malignant neoplasm of splenic flexure of colon
B902400	Neoplasm of uncertain behaviour of colon
B134.11	Carcinoma of caecum
B140.00	Malignant neoplasm of rectosigmoid junction
B13z.00	Malignant neoplasm of colon NOS
B14..00	Malignant neoplasm of rectum, rectosigmoid junction and anus
B13y.00	Malignant neoplasm of other specified sites of colon
B14z.00	Malignant neoplasm rectum,rectosigmoid junction and anus NOS
B14y.00	Malig neop other site rectum, rectosigmoid junction and anus
B138.00	Malignant neoplasm, overlapping lesion of colon
B1z0.11	Cancer of bowel
BB5N100	[M]Adenocarcinoma in adenomatous polposis coli
BB5N.00	[M]Adenomatous and adenocarcinomatous polyps of colon
BB5L100	[M]Adenocarcinoma in adenomatous polyp
BB5L.00	[M]Adenomatous and adenocarcinomatous polyps
BB5L300	[M]Adenocarcinoma in multiple adenomatous polyps

Abbreviations: NOS, not otherwise specified.

Supplementary Table 4. Defined Daily Dose of Proton Pump Inhibitors

Proton Pump Inhibitor Type	Defined Daily Dose*
Omeprazole	20 mg
Esomeprazole	30 mg
Rabeprazole	20 mg
Lansoprazole	30 mg
Pantoprazole	40 mg

*All doses are equivalent to 1 Defined Daily Dose

The dose of each PPI prescription was defined according to the World Health Organization defined daily dose and converted into omeprazole equivalents.[1] This allows for PPIs with different potencies to be compared. According to the defined daily dose, a patient prescribed a 30-day course of 30-mg of esomeprazole is equivalent to a patient prescribed a 30-day course of 20-mg omeprazole.

Supplementary Table 5. Crude and Adjusted HRs for the Association Between the Use of Specific Types of Proton Pump Inhibitors and Colorectal Cancer Compared to the Use of Histamine-2 Receptor Antagonists

	Events	Person-years	Crude incidence rate (95% CI) *	Crude HR	Marginal HR (95% CI) †
Histamine-2 receptor antagonist	1,264	1,440,977	87.7 (82.9 to 92.7)	1.00	1.00 [Reference]
Proton pump inhibitor type					
Esomeprazole	94	103,912	90.5 (73.1 to 110.7)	1.02	0.81 (0.64 to 1.01)
Lansoprazole	2,407	2,174,265	110.7 (106.3 to 115.2)	1.28	1.04 (0.93 to 1.15)
Omeprazole	3,878	3,791,049	102.3 (99.1 to 105.6)	1.20	1.03 (0.91 to 1.15)
Pantoprazole	161	134,210	120.0 (102.1 to 140.0)	1.34	1.06 (0.88 to 1.27)
Rabeprazole	214	199,263	107.4 (93.5 to 122.8)	1.21	0.92 (0.78 to 1.08)
Combinations	5	3,726	134.2 (43.6 to 313.2)	1.53	1.24 (0.51 to 2.99)

Abbreviations: CI, confidence interval; HR, hazard ratio

* Per 100,000 person-years

† Weighted using standardized mortality ratio weights

Supplementary Table 6. Crude and Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Colorectal Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Stratified by Colorectal Cancer Type)

Cancer Type *	Events	Person-years	Crude incidence rate (95% CI) †	Crude HR	Marginal HR (95% CI) ‡
Colon					
Histamine-2 receptor antagonists	852	1,440,977	59.1 (55.2 to 63.2)	1.00	1.00 [Reference]
Proton pump inhibitor	4,895	6,406,425	76.4 (74.3 to 78.6)	1.32	1.00 (0.88 to 1.14)
Rectal					
Histamine-2 receptor antagonists	408	1,440,977	28.3 (25.6 to 31.2)	1.00	1.00 [Reference]
Proton pump inhibitor	1,834	6,406,425	28.6 (27.3 to 30.0)	1.03	1.07 (0.87 to 1.30)

Abbreviations: CI, confidence interval; HR, hazard ratio; H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor

* Other colorectal cancer types generated 33 events

† Per 100,000 person-years

‡Weighted using standardized mortality ratio weights

Supplementary Table 7. Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Colorectal Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Interaction with Sex)

	Male	**Female**
Events	4,338	3,685
Person-Years	3,526,065	4,321,337
Crude Incidence Rate (95% CI) *	123.0 (119.4 to 126.7)	85.3 (82.5 to 88.1)
Crude HR		
Histamine-2 receptor antagonists	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	1.19	1.27
		p-interaction: 0.28
Adjusted HR (95% CI) †		
Histamine-2 receptor antagonists	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	0.90 (0.78 to 1.04)	1.22 (1.04 to 1.45)
		p-interaction: 0.01

Abbreviations: HR, hazard ratio; CI, confidence interval
* Per 100,000 person-years
† Weighted using standardized mortality ratio weights

Supplementary Table 8. Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Colorectal Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Interaction with Age)

	Age < 40	**Age 40-59**	**Age ≥ 60**
Events	151	1,806	6,066
Person-Years	2,074,653	3,128,625	2,644,124
Crude Incidence Rate (95% CI) *	7.3 (6.2 to 8.5)	57.7 (55.1 to 60.5)	229.4 (223.7 to 235.3)
Crude HR			
Histamine-2 receptor antagonists	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	1.08	1.22	1.01 p-interaction: 0.05
Adjusted HR (95% CI) †			
Histamine-2 receptor antagonists	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	0.77 (0.40 to 1.48)	1.08 (0.84 to 1.40)	0.97 (0.85 to 1.09) p-interaction: 0.56

Abbreviations: HR, hazard ratio; CI, confidence interval
* Per 100,000 person-years
†Weighted using standardized mortality ratio weights

Supplementary Table 9. Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Colorectal Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Interaction with Gastrointestinal Polyps)

	Gastrointestinal Polyps	No Gastrointestinal Polyps
Events	176	7,847
Person-Years	80,435	7,766,967
Crude Incidence Rate (95% CI) *	218.8 (187.7 to 253.6)	101.0 (98.8 to 103.3)
Crude HR		
Histamine-2 receptor antagonists	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	0.91	1.23
		p-interaction: 0.20
Adjusted HR (95% CI) †		
Histamine-2 receptor antagonists	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	1.22 (0.59 to 2.54)	1.02 (0.91 to 1.14)
		p-interaction: 0.63

Abbreviations: HR, hazard ratio; CI, confidence interval

* Per 100,000 person-years

† Weighted using standardized mortality ratio weights

Supplementary Table 10. Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Colorectal Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Interaction with Inflammatory Bowel Disease)

	Inflammatory Bowel Disease	**No Inflammatory Bowel Disease Inflammatory Bowel Disease**
Events	92	7,931
Person-Years	78,948	7,768,454
Crude Incidence Rate (95% CI) *	116.5 (93.9 to 142.9)	102.1 (99.9 to 104.4)
Crude HR		
Histamine-2 receptor antagonists	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	0.98	1.23
		p-interaction: 0.44
Adjusted HR (95% CI) †		
Histamine-2 receptor antagonists	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	1.06 (0.26 to 4.29)	1.02 (0.92 to 1.14)
		p-interaction: 0.96

Abbreviations: HR, hazard ratio; CI, confidence interval
* Per 100,000 person-years
† Weighted using standardized mortality ratio weights

Supplementary Table 11. Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Colorectal Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Interaction with Aspirin Use)

	Aspirin History	**No Aspirin History**
Events	2,491	5,532
Person-Years	1,249,495	6,597,907
Crude Incidence Rate (95% CI) *	199.4 (191.6 to 207.3)	83.8 (81.7 to 86.1)
Crude HR		
Histamine-2 receptor antagonists	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	1.19	1.14
		p-interaction: 0.58
Adjusted HR (95% CI) †		
Histamine-2 receptor antagonists	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitors	1.10 (0.91 to 1.34)	0.98 (0.86 to 1.12)
		p-interaction: 0.33

Abbreviations: HR, hazard ratio; CI, confidence interval
* Per 100,000 person-years
† Weighted using standardized mortality ratio weights

Supplementary Table 12. Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Colorectal Cancer Compared to the Use of Histamine-2 Receptor Antagonists Stratified by Approved Indication at Baseline

Indication *	Events	Person-years	Crude incidence rate (95% CI) †	Crude HR	Marginal HR (95% CI) ‡
Gastroesophageal reflux disease					
Histamine-2 receptor antagonists	114	110,811	102.9 (84.9 to 123.6)	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitor	687	626,438	109.7 (101.6 to 118.2)	1.08	0.95 (0.66 to 1.36)
Peptic ulcer disease					
Histamine-2 receptor antagonists	90	48,255	186.5 (150.0 to 229.3)	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitor	320	176,638	181.2 (161.9 to 202.1)	0.98	0.91 (0.57 to 1.46)
Dyspepsia					
Histamine-2 receptor antagonists	378	446,774	84.6 (76.3 to 93.6)	1.00 [Reference]	1.00 [Reference]
Proton pump inhibitor	1,316	1,284,222	102.5 (97.0 to 108.2)	1.24	1.27 (1.03 to 1.57)

Abbreviations: HR, hazard ratio; CI, confidence interval

* Barrett's esophagus and *H. pylori* generated few events with unstable estimates

† Per 100,000 person-years

‡ Weighted using standardized mortality ratio weights

Supplementary Table 13. Crude and Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Colorectal Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Different Lag Periods)

Length of lag period	Events	Person-years	Crude incidence rate (95% CI) *	Crude HR	Marginal HR (95% CI) †
3 years					
Histamine-2 receptor antagonist	882	1,000,052	88.2 (82.5 to 94.2)	1.00	1.00 [Reference]
Proton pump inhibitor	4,598	4,224,388	108.8 (105.7 to 112.0)	1.27	1.09 (0.95 to 1.25)
5 years					
Histamine-2 receptor antagonist	623	691,325	90.1 (83.2 to 97.5)	1.00	1.00 [Reference]
Proton pump inhibitor	3,069	2,671,337	114.9 (110.9 to 119.0)	1.31	1.15 (0.98 to 1.35)
10 years					
Histamine-2 receptor antagonist	257	242,346	106.0 (93.5 to 119.8)	1.00	1.00 [Reference]
Proton pump inhibitor	858	647,821	132.4 (123.7 to 141.6)	1.25	1.06 (0.83 to 1.36)

Abbreviations: CI, confidence interval; HR, hazard ratio
* Per 100,000 person-years
† Weighted using standardized mortality ratio weights

Supplementary Table 14. Crude and Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Colorectal Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Intention to Treat Exposure Definition) *

Analysis	Events	Person-years	Crude incidence rate (95% CI) †	Crude HR	Marginal HR (95% CI) ‡
Histamine-2 receptor antagonist	2,589	2,565,103	100.9 (97.1 to 104.9)	1.00	1.00 [Reference]
Proton pump inhibitor	7,322	6,912,360	105.9 (103.5 to 108.4)	1.12	0.97 (0.89 to 1.04)

Abbreviations: CI, confidence interval; HR, hazard ratio
* Did not censor on switch between drug classes
† Per 100,000 person-years
‡ Weighted using standardized mortality ratio weights

Supplementary Table 15. Crude and Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Colorectal Cancer Compared to the Use of Histamine-2 Receptor Antagonists (IPCW)

	Events	Person-years	Crude incidence rate (95% CI) *	Crude HR	Marginal HR (95% CI) †
Histamine-2 receptor antagonist	1,264	1,892,953	66.8 (63.1 to 70.6)	1.00	1.00 [Reference]
Proton pump inhibitor	6,759	8,365,632	80.8 (78.9 to 82.7)	1.23	1.02 (0.85 to 1.21)

Abbreviations: CI, confidence interval; HR, hazard ratio

* Per 100,000 person-years

† Weighted using standardized mortality ratio weights and stabilized inverse probability of censoring weights for death and switching

Supplementary Table 16. Crude and Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Colorectal Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Truncate Follow-up for Possible NDMA Contaminant) *

	Events	Person-years	Crude incidence rate (95% CI) †	Crude HR	Marginal HR (95% CI) ‡
Histamine-2 receptor antagonist	1,245	1,438,394	86.6 (81.8 to 91.5)	1.00	1.00 [Reference]
Proton pump inhibitor	6,269	6,372,752	98.4 (96.0 to 100.8)	1.15	1.00 (0.90 to 1.12)

Abbreviations: CI, confidence interval; HR, hazard ratio
* Follow-up truncated on December 31, 2017
† Per 100,000 person-years
‡ Weighted using standardized mortality ratio weights

Supplementary Table 17. Crude and Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Colorectal Cancer Compared to the Use of Histamine-2 Receptor Antagonists (High-dimensional Propensity Score) *

	Events	Person-years	Crude incidence rate (95% CI) †	Crude HR	Marginal HR (95% CI) ‡
Histamine-2 receptor antagonist	1,264	1,440,924	87.7 (83.0 to 92.7)	1.00	1.00 [Reference]
Proton pump inhibitor	6,758	6,406,237	105.5 (103.0 to 108.0)	1.23	0.99 (0.88 to 1.12)

Abbreviations: CI, confidence interval; HR, hazard ratio

* Treatment weights created using predefined covariates listed in the manuscript and 200 empirically selected covariates from the high-dimensional propensity score algorithm

† Per 100,000 person-years

‡ Weighted using standardized mortality ratio weights

Supplementary Table 18. Crude and Adjusted HRs for the Association Between the Use of Proton Pump Inhibitors and Colorectal Cancer Compared to the Use of Histamine-2 Receptor Antagonists (Inverse Probability of Screening Weights) *

	Events	Person-intervals	Crude incidence rate (95% CI) †	Crude HR	Marginal HR (95% CI) ‡
Histamine-2 receptor antagonist	1,264	1,005,714	125.7 (118.8 to 132.8)	1.00	1.00 [Reference]
Proton pump inhibitor	6,759	4,478,253	150.9 (147.4 to 154.6)	1.20	1.24 (0.66 to 2.34)

Abbreviations: CI, confidence interval; HR, hazard ratio
* Screening weights calculated within 2-year intervals
† Per 100,000 person-intervals
‡ Weighted using standardized mortality ratio weights and stabilized inverse probability of screening rates for colorectal screening

Supplementary Table 19. Summary of observational studies assessing the association between PPIs and colorectal cancer

First Author (Year)	Study Design	Study Size	Effect estimate (95% CI)	Main Limitation
Yang (2007)	Nested case-control	48,724	OR: 1.1 (0.7 to 1.9)	Confounding by indication Latency bias Prevalent users
Robertson (2007)	Nested case-control	61,479	OR: 1.11 (0.97 to 1.27)	Confounding by indication Prevalent users Time-window bias
Van Soest (2008)	Nested case-control	8,384	OR: 0.85 (0.63 to 1.16)	Confounding by indication Prevalent users
Chubak (2009)	Case-control	1,282	OR: 1.7 (0.8 to 4.0)	Confounding by indication Prevalent users Time-window bias
Lai (2013)	Nested case-control	3,989	OR: 2.54 (2.31 to 2.79)	Confounding by indication Latency bias Prevalent users Time-window bias
Hwang (2017)	Cohort	451,284	Low dose PPI HR: 0.96 (0.88 to 1.06) High dose PPI HR: 0.98 (0.78 to 1.24)	Confounding by indication Latency bias
Lei (2020)	Cohort	90,764	HR: 2.03 (1.56 to 2.63)	Confounding by indication Immortal time bias
Babic (2020)	Cohort	175,859*	HR: 0.89 (0.71 to 1.12)	Confounding by indication Prevalent users Self-reported exposure
Kuiper (2020)	Case-control	9,890	OR: 1.08 (0.97 to 1.21)	Confounding by indication Latency bias Prevalent users Time-window bias
Lee (2020)	Nested case-control	178,717	OR: 1.05 (0.99 to 1.12)	Confounding by indication Differential exclusion by case/control status

Abbreviations: OR: odds ratio; HR: hazard ratio, PPI: proton pump inhibitors.
*Combined from three separate cohorts.

Supplementary Method 1. Inverse Probability of Censoring Weights

We used inverse probability of censoring weighting to assess the potential impact of differential censoring from drug switching (i.e. PPI users adding-on or switching to H2RAs, and vice versa)[2] [3] and to investigate death as a competing risk between PPI and H2RA users.[4] This analysis was completed in three steps.

Step 1: For both exposure groups, the follow-up period was sudivided into one-year intervals. Within each interval, inverse probability of censoring weights (IPCWs) were fit, separately for the PPI and H2RA cohorts, using multivariable logistic regression within 5-year bands of calendar year to predict the probability of remaining uncensored (i.e. not switching or adding on from PPI to H2RA and vice versa). The models were conditional on the following variables, all measured in the previous interval: age, sex, alcohol related disorders (alcohol dependency, alcoholic cirrhosis of the liver, alcoholic hepatitis, hepatic failure), smoking status (current, former, never, unknown), body mass index, type 2 diabetes, hypertension, coronary artery disease, chronic obstructive pulmonary disease, cancer (other than nonmelanoma skin cancer), Crohn's disease, ulcerative colitis, other inflammatory bowel disease, gastrointestinal polyps, cholecystectomy, solid organ transplant, indications for acid suppressant drug use (approved indications: Barrett's esophagus, *Helicobacter pylori* infection, gastro-oesophageal reflux disease, peptic ulcer disease, dyspepsia; off-label indications: gastritis/duodenitis and stomach pain) and use of the following medications: hormone replacement therapy, aspirin, other non-steroidal anti-inflammatory drugs, statins and bisphosphonates, and use of synthetic prostaglandin analogues and measures of health-seeking behaviour, including mammographic screening, prostate exams, colorectal cancer screening, and influenza vaccination.

Step 2: We repeated step 1 by fitting a multivariable logistic regression model for remaining alive at a given interval (i.e. not having death as a competing event), using the same covariates as above.

Step 3: Using the fitted logistic models generated in Steps 1 and 2, we took the product of the weights (i.e. inverse of the probability of being uncensored from drug switching and from not dying) across all intervals for a given patient. IPCWs were stabilized using intercept only models as the numerator, and truncated at the 0.5^{th} and 99.5^{th} percentile. These stabilized weights were combined with standardized mortlaity ratio wegiths for each patient to generate a final weight. Marginal hazard ratios of colorectal cancer associated with the use of PPIs compared with H2RAs were estimated using the final weights.

Supplementary Method 2. High-dimensional Propensity-scores

To investigate the impact of residual confounding, we reweighted our cohort using high-dimensional propensity scores (HD-PS). The HD-PS is a seven-step algorithm which empirically selects covariates from different data dimensions based on their prevalence and potential for confounding.[5] As the HD-PS is a summary score, it is an efficient way to control for a wide range of confounders. The HD-PS may also account for some unmeasured confounders, as the empirically selected covariates may include proxies for unknown or unmeasured confounders.[6]

Using the HD-PS algorithm, we empirically selected 200 covariates from five data dimensions: prescriptions, procedures, diagnoses, disease history and administrative files. Using multivariable logistic regression, conditional on the empirically selected and predefined covariates (including calendar year of cohort entry), we estimated the predicted probability of received a PPI versus an H2RA. Using these propensity score values we reweighted the cohort using standardized mortality ratio weighting, where exposed to PPIs were given a weight of 1, and patients exposed to H2RAs were given a weight of the odds of treatment probability (PS/[1-PS]).[7] For this analysis, we then combined the SMR weights with IPCWs, and marginal hazard ratios for colorectal cancer for users of PPIs compared to users of H2RAs were estimated using Cox proportional hazards models.

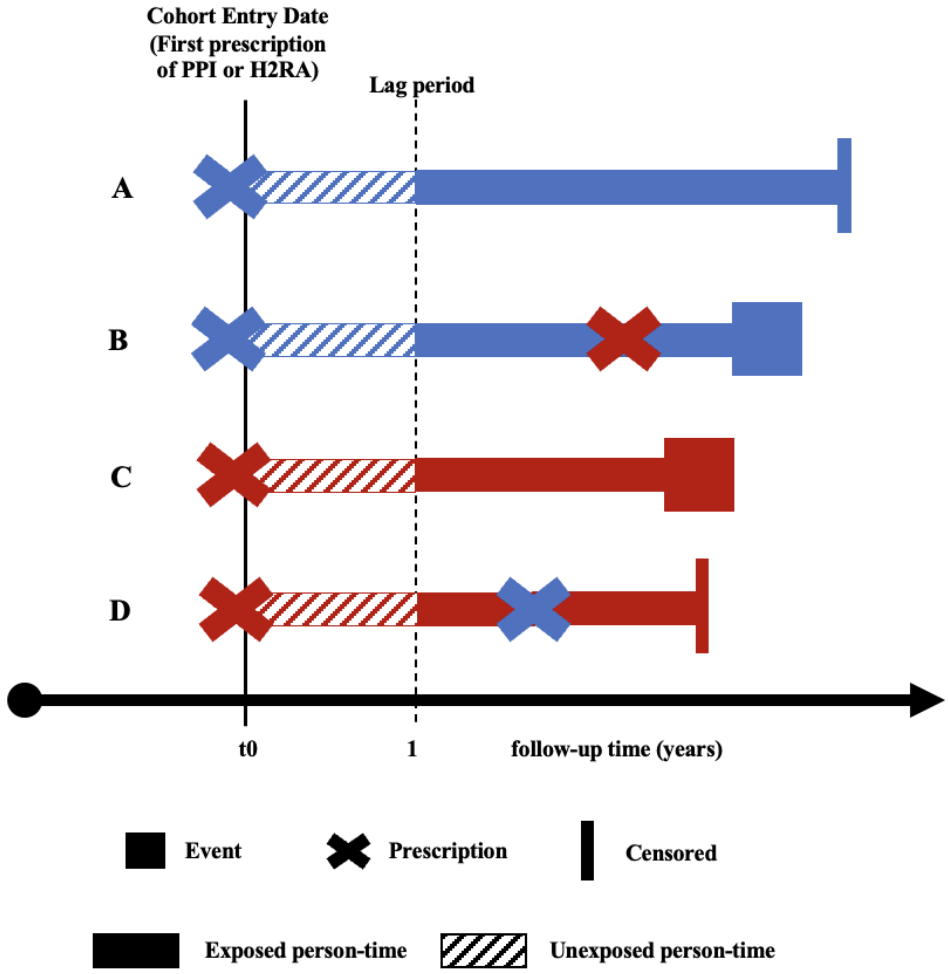
Supplementary Method 3. Inverse Probability of Screening Weights

To investigate the potential for detection bias from differential screening uptake between exposure groups, we used inverse probability of screening weights (IPSWs) to reweight our cohort.[8] For this analysis, the cohort was divided into 2-year intervals of follow-up. Within each interval, we estimated the predicted probability (P_{screen}) of colorectal screening (i.e., fecal occult blood testing or colon neoplasm screening) using multivariable logistic regression, conditional on the following covariates, all measured in the previous interval:

age, year of cohort entry, sex, alcohol-related disorders, smoking status (current, former, never), BMI, type 2 diabetes, hypertension, coronary artery disease, chronic obstructive pulmonary disease, cancer (other than nonmelanoma skin cancer), Crohn's disease, ulcerative colitis, other inflammatory bowel disease, gastrointestinal polyps, cholecystectomy, and solid organ transplant. We also considered the indication for acid suppressant drug use (approved indications: peptic ulcer disease, gastroesophageal reflux disease, dyspepsia, *Helicobacter pylori* infection, and Barrett's oesophagus; off-label indications: gastritis/duodenitis and stomach pain). We also included the following drugs previously associated with colorectal cancer incidence, measured at any time before cohort entry: hormone replacement therapy, aspirin, other non-steroidal anti-inflammatory drugs, statins, bisphosphonates, and use of synthetic prostaglandin analogues, which are older drugs used to manage gastric conditions.[1] We also included measures of health-seeking behaviours, such as mammographic screening, prostate-specific antigen testing, influenza vaccination and the number of physician visits in the previous interval. Finally, we included the country, to account for differences in screening programs by region, and use of anticoagulants, which may be associated with closer patient monitoring.

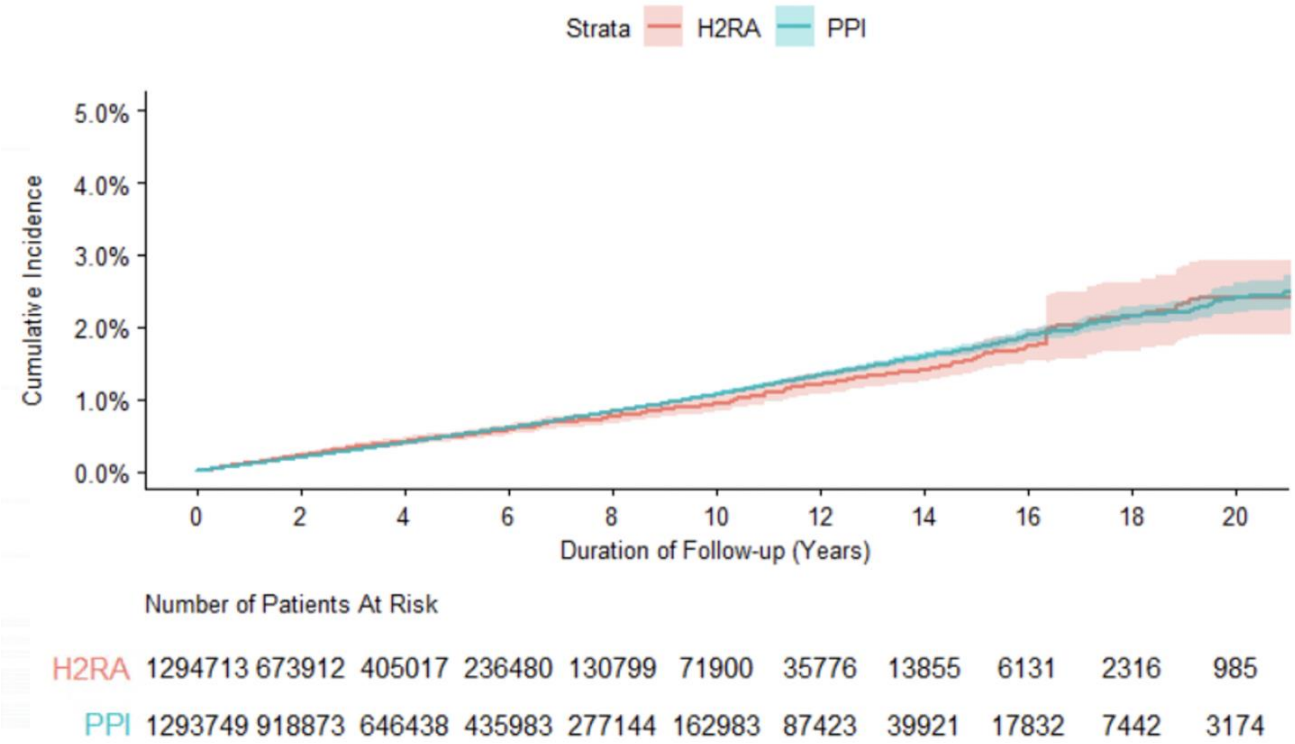
Any screening events that were considered diagnostic were not included. The weights were stabilized using the overall proportion of screening within the population (20%). Thus, patients who were screened were given a weight of $0.2/P_{screen}$, and patients who were not screened were given a weight of $0.8/(1- P_{screen})$.[8] Screening weights calculated at each interval were combined with standardized mortality ratio weights, and the overall weight was used to reweight the study cohort. Thus, marginal hazard ratios for colorectal cancer, adjusted for screening and treatment, were calculated using Cox proportional hazards models.

Supplementary Figure 1. Exposure Definition



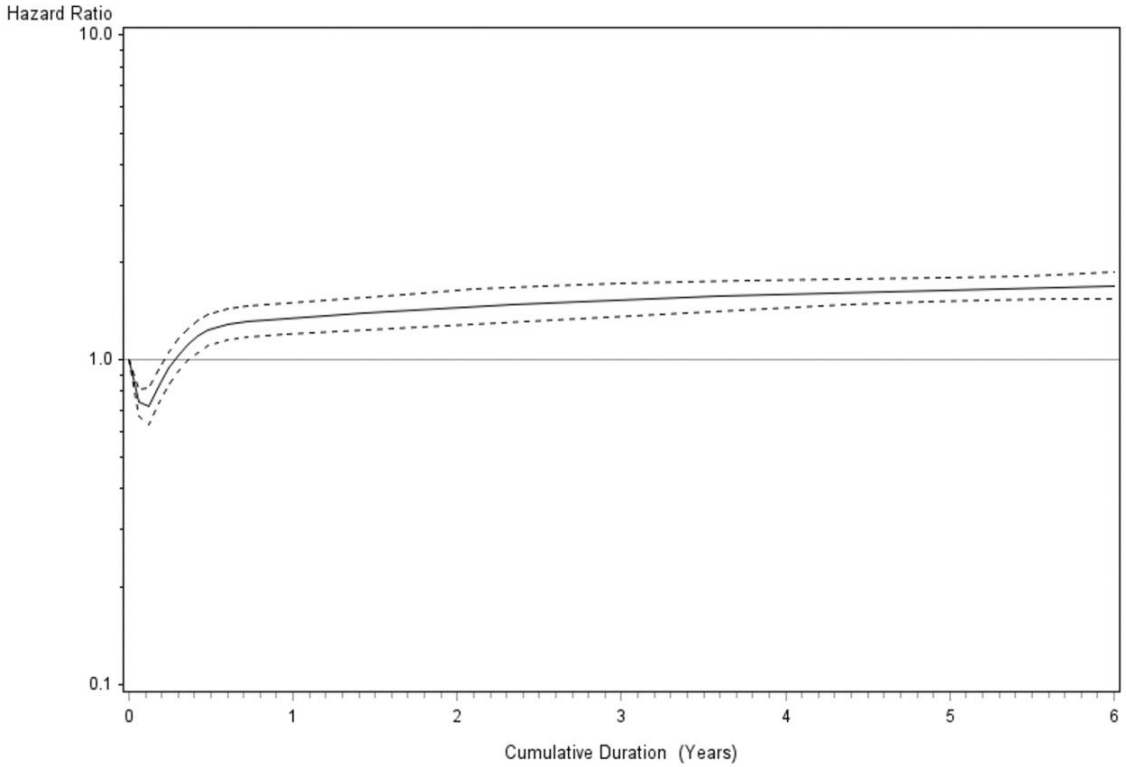
Supplementary figure 1 illustrates the exposure definition used to define incident PPI and H2RA users. Blue graphics represent PPIs, and red graphics represent H2RAs. Patients A and B enter the cohort as PPI users. Following the one-year lag period, illustrated by the dashed box, both patients contribute PPI exposed person-time to the analysis. When patient B switches to an H2RA (red X), they are considered exposed to PPIs for one additional year (lag period = one year). Thus, when patient B has an event, it is considered a PPI event. Patients C and D enter the cohort as H2RA users. Following the one year-lag period, they contribute person-time to the H2RA exposed group. Patient C has an event during follow-up, classified as an event for the comparator. Patient D switches to a PPI during follow-up (blue X) and thus contributes one additional year as an H2RA user before they are censored.

Supplementary Figure 2. Weighted Kaplan-Meier Curve of the Cumulative Incidence of Colorectal Cancer



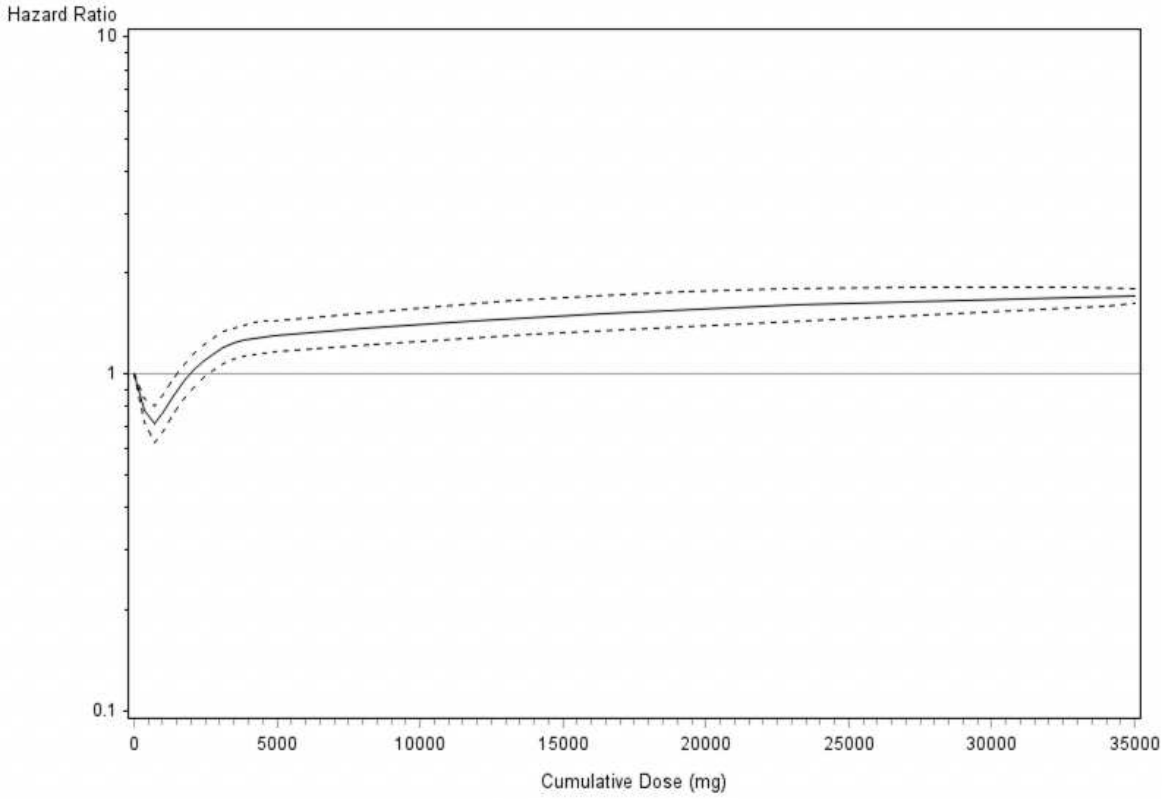
Follow-up starts one year after cohort entry
Curves are weighted using standardized mortality ratio weights

Supplementary Figure 3. Restricted Cubic Spline of Cumulative Duration of Proton Pump Inhibitor Use



Smooth restricted cubic spline curve of weighted hazard ratio of colorectal cancer disease (solid line) and 95% confidence limits (dashed lines) as function of cumulative duration of proton pump inhibitor use. Cumulative duration was truncated at six years of use because of few events.

Supplementary Figure 4. Restricted Cubic Spline of Cumulative Dose of Proton Pump Inhibitor Use



Smooth restricted cubic spline curve of weighted hazard ratio of colorectal cancer disease (solid line) and 95% confidence limits (dashed lines) as a function of cumulative omeprazole equivalents. Cumulative dose was truncated at 35,000 mg because of few events.

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