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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

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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.

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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

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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

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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.

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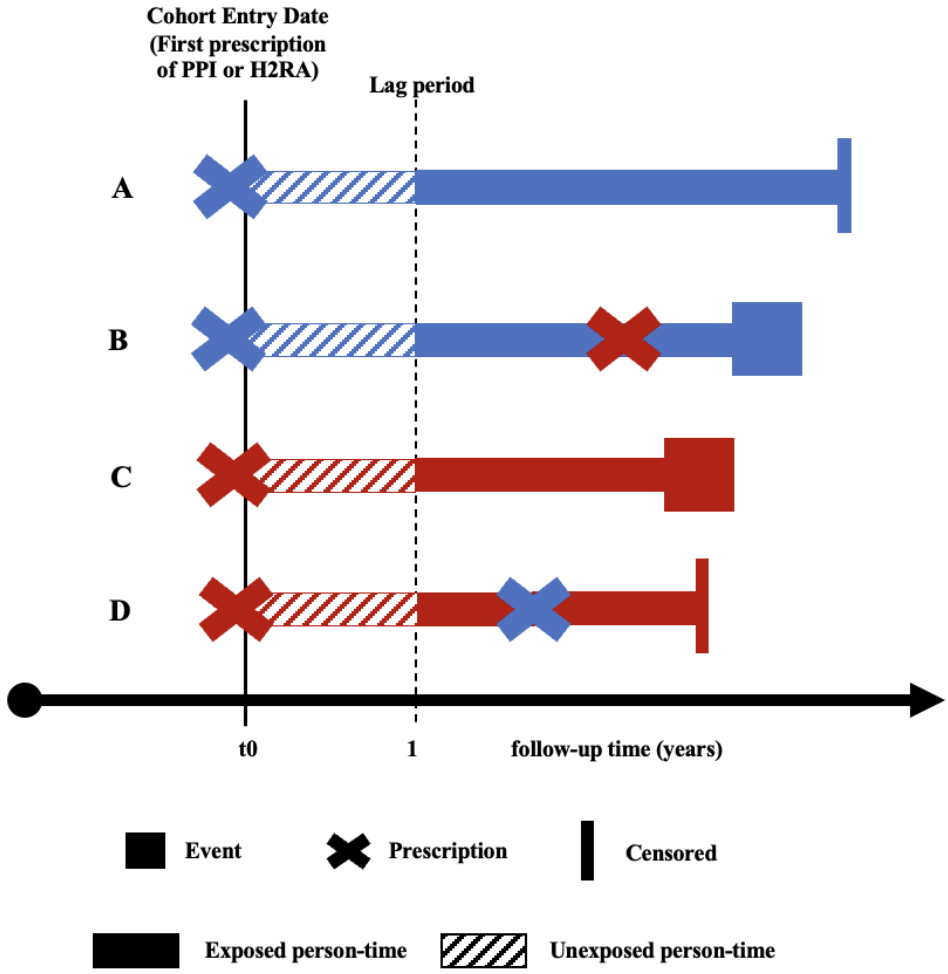
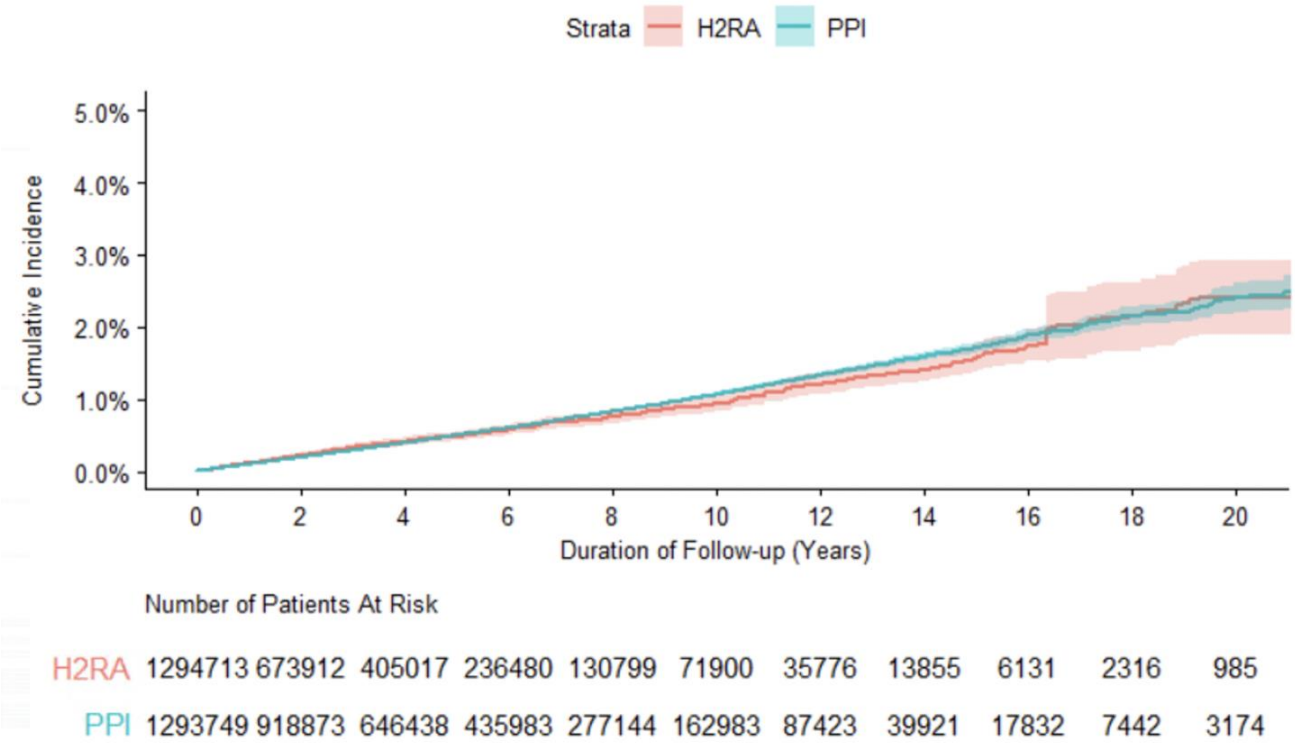
Supplementary Figure 1. Exposure Definition



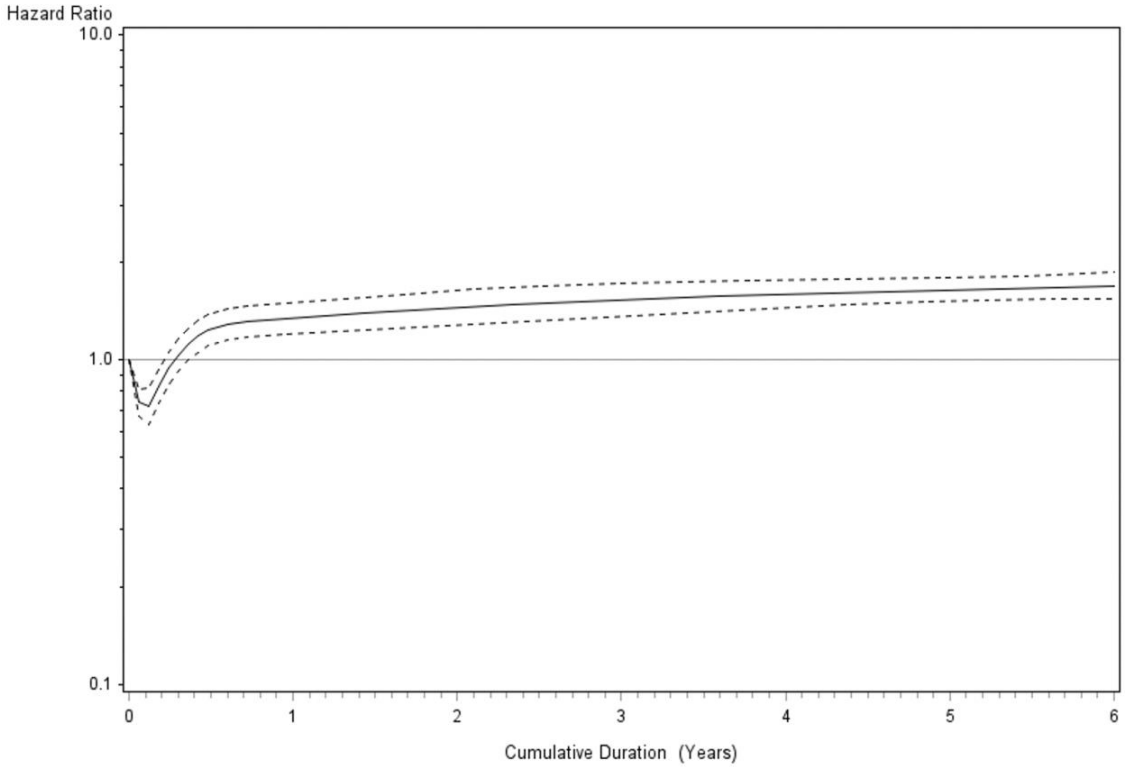
Supplementary figure 1 illustrates the exposure definition used to define incident PPI and H2RA users. Blue graphics represent PPIs, and red graphics represent H2RAs. Patients A and B enter the cohort as PPI users. Following the one-year lag period, illustrated by the dashed box, both patients contribute 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



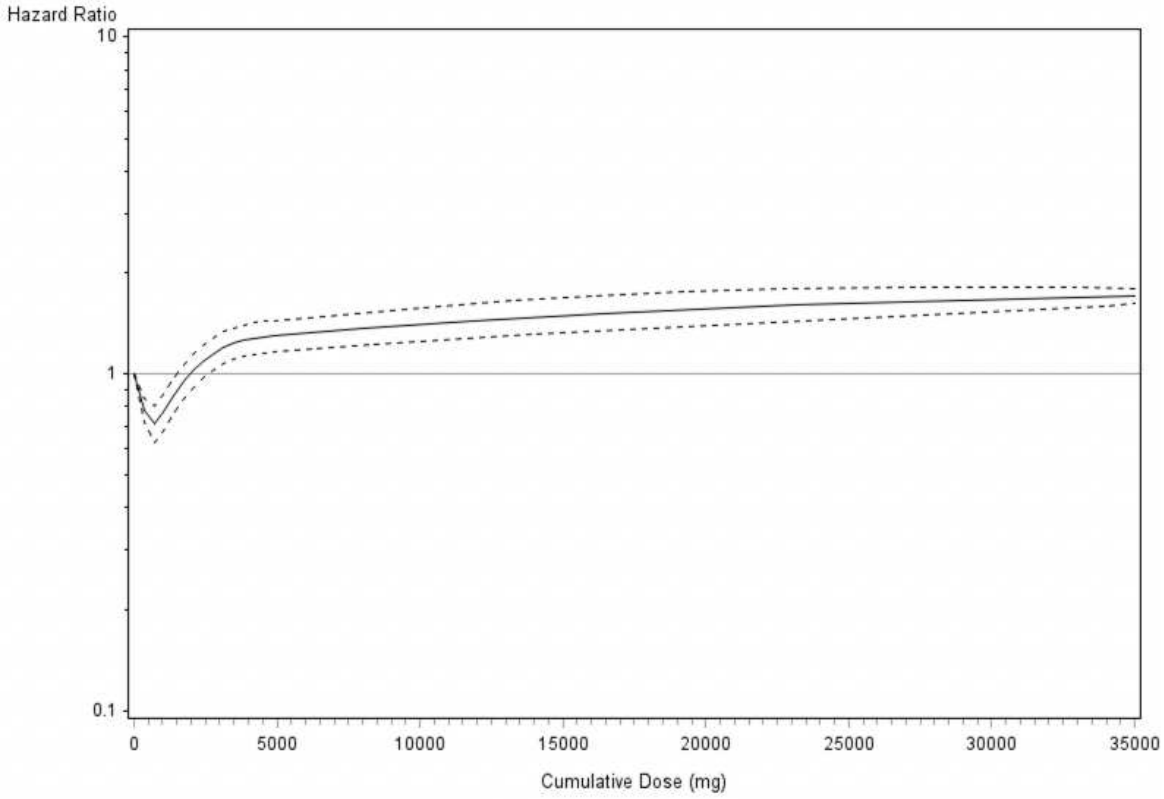
Follow-up starts one year after cohort entry
Curves are weighted using standardized mortality ratio weights

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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