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Colorectal cancer risk in relation to use of acid suppressive medications

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Abstract

Purpose—Acid suppressants are commonly prescribed medications. Laboratory studies suggest a mechanism by which they could increase colorectal cancer (CRC) risk. A few epidemiologic studies have investigated acid suppressant use and CRC risk; none has documented an overall association. We sought to investigate whether acid suppressants are associated with CRC risk.

Methods—We conducted a case-control study among members of an integrated healthcare delivery system in Washington State. Cases (N=641) were diagnosed with CRC between 2000-2003; controls (N=641) were randomly selected from enrollees and matched to cases on age, sex, and length of enrollment. We used conditional logistic regression to estimate the odds ratios (OR) and 95% confidence intervals (CI) for CRC associated with the use of any acid suppressive medication, proton pump inhibitors (PPIs) only, histamine receptor antagonists (H2 blockers) only, or both PPIs and H2 blockers in relation to the use of neither PPIs nor H2 blockers.

Results—Use of PPIs exclusively was modestly associated with increased risk of CRC, however this finding was consistent with chance and based on a small number of patients exposed (OR=1.7; 95% CI=0.8, 4.0). H2 blocker use alone was not related to CRC risk (OR=0.8; 95% CI = 0.6, 1.1).

Conclusions—PPI use may be modestly associated with CRC risk; further research should be conducted in populations with long-term PPI use.

Keywords

colorectal cancer; acid suppressive medications; proton pump inhibitors; histamine receptor antagonists

INTRODUCTION

Acid suppressive medications, which include proton pump inhibitors (PPIs) and histamine receptor antagonists (H2 blockers), are among the most commonly used medications to treat

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gastrointestinal disorders.[1, 2] These drugs may increase the levels of gastrin, a hormone that stimulates the secretion of gastric acid, 2-to-4-fold.[3, 4] A possible association between acid suppressant medications and colorectal cancer risk is supported by a growing body of evidence from *in vitro* studies that hypergastrinaemia promotes proliferation of normal and cancerous colon cancer cell.[5-7] Most animal studies,[8-13] but not all, [14, 15] have confirmed these findings. Several human studies also show an increase in proliferative activity with higher levels of gastrin;[16, 17] however it is unclear whether elevated gastrin in humans is a cause of colorectal cancer or a consequence of local secretion by the underlying tumor .[18] Most studies of the association between gastrin levels and colorectal cancer have been cross-sectional, though a nested case-control study reported a nearly 4-fold increased risk associated with hypergastrinemia (>90 pg/mL) as measured in sera collected an average of 15 years before colorectal cancer diagnosis.[19] Several recent large studies did not find an association overall between PPI use and colorectal cancer risk.[20-22] Given the high prevalence of acid suppressant use currently, we sought to further investigate this question.

MATERIALS AND METHODS

Study setting and population

We conducted a population-based case-control study in members of Group Health, an integrated healthcare delivery system that provides comprehensive healthcare to approximately 550,000 members in western Washington State. Using the western Washington Surveillance Epidemiology and End Results (SEER) cancer registry, we identified cases of first primary colorectal cancer, diagnosed between January 1, 2000 and December 31, 2003.[23] To reduce the potential for including patients with heritable colorectal cancer syndromes, we restricted analyses to patients 40 years of age and older at diagnosis or reference date.

We randomly sampled controls from the Group Health enrollment file. Controls were matched 1:1 to cases on age (month/year), gender, and duration of Group Health enrollment prior to the case's diagnosis date. Controls were assigned a reference date (month/year) corresponding to case diagnosis.

Patients were ineligible for the study if they were enrolled in Group Health for fewer than two years, had a prior diagnosis of colorectal cancer at any time, or were diagnosed with inflammatory bowl disease, given differences in the presumed mechanism of carcinogenesis and colorectal cancer risk in these diseases. Analyses were conducted on 641 eligible case-control pairs.

Data Collection

Data collection was restricted to the 10 years prior to diagnosis/reference date. Trained chart abstractors used a standardized data collection instrument. Medical records, including electronic pharmacy records, were abstracted for medication use and potential covariates including: weight; race; any prescription or over-the-counter use of non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin and Cox-2 inhibitors; diagnoses of diabetes; Helicobacter Pylori (H. Pylori) infection; peptic ulcer disease; and smoking status. Electronic pharmacy records were the primary source of information on prescriptions. Since 1976, the Group Health pharmacy database has included a record for all medications dispensed to Group Health enrollees. Each record includes a patient identifier, drug name, strength, date dispensed, quantity dispensed, instructions for use, and form. It is estimated that Group Health enrollees obtain 97% of their prescription medications at Group Health pharmacies.[24] Study methods were approved by Group Health's Institutional Review Board.

Medication use

We defined use of PPIs or H2 blockers as two or more prescription fills for any drug in that class within a 6-month period to give some assurance that the medication was actually being taken. We did not count PPI and H2 blocker use that occurred in the year before diagnosis or reference date to reduce the likelihood that the medication was being taken for symptoms resulting from undetected colorectal cancer. Among users, we calculated the cumulative duration of use for each drug class. For each prescription filled, we estimated the date when the pills should have run out (run-out date) based on quantity dispensed and instructions for use. A new run-out date was set with each successive dispensing. A sixty-day lag period between the run-out date of one dispensing and fill date of the successive dispensing was used to define continuous use. Periods of continuous use were summed for total duration of use.[25] Persons were classified as either: non-user, user of PPIs only, user of H2 blockers only, and user of both PPIs and H2-inhibitors. We also assessed the association between the risk of colorectal cancer and the use of any acid suppressive medication, i.e., either PPIs and/or H2 blockers.

Statistical Analyses

All analyses were conducted in Stata 9.2. (Stata Corporation, College Station, TX). We compared colorectal cancer cases and controls with respect to demographic and relevant health characteristics. Non-users of PPIs and H2 blockers served as the reference group for all analyses. Because cases and controls were matched on age, gender, and length of enrollment at Group Health, we used conditional logistic regression with robust standard errors to estimate odds ratios (OR) and two-sided 95% confidence intervals (CI). We computed unadjusted odds ratios as well as odds ratios that were adjusted for the following set of potential confounders that were identified *a priori*: smoking status, NSAID/aspirin use, peptic ulcer disease, and diabetes. We also investigated whether body mass index (BMI), H. pylori infection, race, or diagnosis of a previous cancer confounded the relationship between PPI use and colorectal cancer in univariate analyses. Since none changed the odds ratio by more than 10%, they were not included in the final model.

RESULTS

Characteristics of the 641 case-control pairs are given in table 1. On average, subjects were 70 years old, 51.6% were female, and the average duration of enrollment prior to diagnosis or reference was 19 years prior to their diagnosis or reference date. Cases had a higher prevalence of diabetes and smoking compared to controls. Fewer cases than controls had a history of NSAID/aspirin use. While cases were also more likely to be white, race was missing for a high proportion (15%) of control subjects. Among cases and controls, respectively, 24.8% and 26.5% used any acid suppressant, 7.8% and 7.3% used PPIs, and 22.3% and 25.1% used any H2 blockers. The median duration of PPI use was 9.1 months in cases compared to 5.5 in controls; and the median duration of H2 blocker use was 13 months in cases compared to 12 in controls (data not shown).

Table 2 shows that compared to persons who did not use acid suppressive medications, the use of PPIs exclusively was modestly associated with colorectal cancer risk (OR=1.7; 95% CI=0.8, 4.0); however, the prevalence of use in this population was low and this result was consistent with chance. H2 blocker use alone was not related to colorectal cancer risk (OR=0.8; 95% CI = 0.6, 1.1). We found no evidence that PPI use was associated with colorectal cancer risk when they were used in conjunction with H2 blockers (OR=0.9; 95% CI = 0.5, 1.4).

DISCUSSION

In this population-based case-control study, we observed that PPIs may be modestly associated with the risk of colorectal cancer, but found no evidence of a relation between H2 blockers and colorectal cancer risk. Strengths of this study include that exposure was ascertained from electronic records of prescriptions dispensed within a healthcare delivery system and thus not subject to recall bias, a potential limitation of self-report. Previous studies report that approximately 97% of patients in this setting fill most or all of their prescriptions at GH pharmacies,[24] underscoring the completeness of these records for research purposes. Additionally, PPIs did not become available over-the-counter until 2003, the final year of diagnosis for this study, so PPI use is likely captured in the pharmacy records. H2 blockers, however, were available over-the-counter in the mid-1990s and therefore may not have been completely captured in the electronic pharmacy records.

The main limitation in this study was power to examine the association between PPI use and colorectal cancer risk. Among cases and controls, respectively, 7.8% and 7.3% used PPIs. The median duration of PPI use was 9.1 months in cases compared to 5.5 in controls. The low prevalence and relatively short duration of use would have affected our ability to detect an association if one existed. This would be true particularly if increased risk were restricted to subgroups, such as persons who had used for many years, initiated use many years ago, or took a high dose. Due to limitations in sample size, we were unable to evaluate dose-response relationships.

Sample size constraints prevented us from examining possible interactions between acid suppressive medications and selected medications such as NSAIDs/aspirin. Several studies have shown that NSAIDs/aspirin reduce the risk of colorectal cancer;[26-28] our data also support this relationship, though our findings were not statistically significant (data not shown). Because inhibition of cyclo-oxygenase may attenuate the proliferative effects of gastrin on colorectal cancer cells,[29] NSAIDs could potentially mitigate an increased risk of colorectal cancer associated with PPI use. In a post-hoc exploration, our data suggested that the risk associated with PPI use was higher among non-users of NSAIDs/aspirin than users. However, our limited statistical power and high potential for misclassification of exposure of non-prescription medications (e.g. NSAIDs) preclude reporting and drawing conclusions from these analyses. Nevertheless, we believe potential modification of risk of colorectal cancer associated with PPIs by exposure to NSAIDs should be examined in larger population studies and through laboratory-based research.

Another important limitation of the study was that data collection was restricted to 10 years before the diagnosis/reference date. Given the potentially long induction period of colorectal cancer, it is possible that the etiologically relevant period of exposure is more than 10 years before diagnosis. However, because the median duration of enrollment before the index date was 18 years, we did have a full 10 years of exposure data on most subjects.

Three recent studies in European populations reported no association between PPI use and colorectal cancer.[20-22] Yang et al. identified incident colorectal cancer cases in the UK General Practice Research Database and adjusted for smoking status, BMI, and NSAID/aspirin use [22]. Similar to our study, data on BMI and smoking were not complete. No association between long-term PPI use (≥ 5 years) or H2 blocker use and colorectal cancer risk was observed, although there was a non-significant two-fold increase in risk associated with long-term high dose use. A Danish study did not, however, detect an association overall or with long term (≥ 5 years), high intensity use of PPIs.[21] The most recent study, conducted in the Netherlands, also did not detect an association between PPI use and colorectal cancer;

however, their median exposure assessment period prior to the index date was only three years.[20]

Given the modest association reported here as well as the suggestion of an increased risk with long-term, high dose risk in a previous study, it will be important to further investigate the relationship between PPI use and colorectal cancer risk in populations with long-term use.

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Key points

- Laboratory studies suggest acid suppressive medications could increase colorectal cancer risk via hypergastrinaemia.
- Our population-based case control study suggests a modest, but not statistically significant, association between proton pump inhibitor (PPI) use and colorectal cancer risk.
- It will be important to further investigate the relationship between PPI use and colorectal cancer risk in populations with long-term use.

Table 1

Characteristics of colorectal cancer cases and controls, Group Health, 2000-2003

	Cases (N=649)	Controls (N=656)
Sex		
Female	336 (51.8)	337 (51.4)
Male	313 (48.2)	319 (48.6)
Mean age, years (SD)	70 (12)	70 (12)
Mean enrollment at Group Health, years (SD)	19 (11)	19 (11)
Body Mass Index (BMI), kg/m^2 [1]	28.6 (7.0)	27.3 (5.9)
Missing	185	180
Race		
White	581 (89.5)	501 (76.4)
African American	27 (4.2)	23 (3.5)
Asian/Pacific Islander	40 (6.2)	31 (4.7)
Other/unknown	1 (0.2)	101 (15.4)
Diabetes mellitus[2,3]		
No	491 (75.7)	540 (82.3)
Yes	158 (24.3)	116 (17.7)
Previous cancer diagnosis[2]		
No	487 (75.0)	536 (81.7)
Yes	162 (25.0)	120 (18.3)
Ever smoker[4]		
No	271 (41.8)	333 (50.8)
Yes	378 (58.2)	323 (49.2)
Hormone therapy use[2] (among women only, N=673)		
No	208 (61.9)	172 (51.0)
Yes	128 (38.1)	165 (49.0)
NSAID/Aspirin use (dispensed from Group Health pharmacy or use noted in medical record)[2]		
No	255 (39.3)	238 (36.3)
Yes	394 (60.7)	418 (63.7)

SD = standard deviation

[1] Based on weight 12-36 months before reference date

[2] In the 10 years before reference date

[3] Diabetes defined as one or more of the following: 2+ dispensings for a medication used to treat diabetes; fasting glucose >125 mg/dL confirmed by a second out-of-range test within 1 year; random glucose >200 mg/dL confirmed by a second test within 1 year; hospital discharge of diabetes; or 2 outpatient diagnosis of diabetes (ICD-9=250, 250.0, 250.1, 250.2, 250.3, 250.4, 250.5, 250.6, 250.7, 250.8, 250.9)

[4] At least 12 months before reference date

Table 2

Association between use of antidepressant medications and colorectal cancer risk, Group Health, 2000-2003

	Cases (N=649)	Controls (N=656)	Minimally adjusted odds ratio (95% CI)[1]	Fully adjusted odds ratio (95% CI)[1,2]
	n (%)	n (%)		
No antidepressant use	521 (80.3)	497 (75.8)	Reference	Reference
Any antidepressant use	128 (19.7)	159 (24.2)	0.8 (0.6, 1.0)	0.7 (0.5, 0.9)
SSRI use exclusively	29 (4.5)	40 (6.1)	0.7 (0.4, 1.1)	0.7 (0.4, 1.1)
TCA use exclusively	47 (7.2)	55 (8.4)	0.8 (0.5, 1.2)	0.7 (0.5, 1.1)
Other antidepressant use exclusively	6 (0.9)	16 (2.4)	0.4 (0.1, 0.9)	0.3 (0.1, 0.9)

SSRI = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressants; CI = confidence interval

[1]Adjusted for matching factors: sex, age, and length of enrollment at Group Health prior to reference date

[2]Also adjusted for smoking status, NSAID/aspirin dispensed from Group Health pharmacy or use noted in medical record, and history of diabetes mellitus

Table 3

Association between use of antidepressant medications and colorectal cancer risk, according to duration and recency of use, Group Health, 2000-2003

	Cases (N=649)	Controls (N=656)	Minimally adjusted odds ratio (95% CI)[1]	Fully adjusted odds ratio (95% CI)[1,2]
	n (%)	n (%)		
Non-users	521 (80.3)	497 (75.8)	*Reference*	*Reference*
Any antidepressant use				
Duration of use <2 years, & current use or last use <2 years before reference	38 (5.9)	59 (9.0)	0.6 (0.4, 0.9)	0.5 (0.3, 0.8)
Duration of use <2 years, & last use ≥2 years before reference	29 (4.5)	45 (6.9)	0.6 (0.4, 1.0)	0.6 (0.4, 1.0)
Duration ≥2 years	61 (9.4)	55 (8.4)	1.1 (0.7, 1.6)	1.0 (0.7, 1.5)
SSRI use exclusively				
Duration of use <2 years	20 (3.1)	31 (4.7)	0.6 (0.3, 1.1)	0.6 (0.3, 1.1)
Duration of use ≥2 years	9 (1.4)	9 (1.4)	1.0 (0.4, 2.4)	1.0 (0.4, 2.8)
TCA use exclusively				
Duration of use <2 years	29 (4.5)	42 (6.4)	0.6 (0.4, 1.0)	0.6 (0.3, 1.0)
Duration of use ≥2 years	18 (2.8)	13 (2.0)	1.3 (0.6, 2.7)	1.3 (0.6, 2.7)

SSRI = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressants; CI = confidence interval

[1] Adjusted for matching factors: sex, age, and length of enrollment at Group Health prior to reference date

[2] Also adjusted for smoking status, NSAID/aspirin dispensed from Group Health pharmacy or use noted in medical record, and history of diabetes mellitus