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Proton pump inhibitors are not associated with an increased risk of colorectal cancer

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Abstract

Background: The clinical relevance of proton pump inhibitors use as a risk factor for colorectal cancer in humans is still unclear.

Aims: To investigate the risk of colorectal cancer after the use of proton pump inhibitors within a linked Cancer Registry-General Practitioner Database cohort.

Methods: Colorectal cancer patients diagnosed between 2007 and 2014 with at least 6 years of primary care data available prior to diagnosis (index date) were identified and matched to four controls on gender, birth year, general practice and period of primary care data availability. Proton pump inhibitor use was determined in the 6 years prior to the index date and analysed with conditional logistic regression, adjusted for potential confounders.

Results: 1041 cases (53%) and 4161 controls (53%) ever used a proton pump inhibitor, yielding an odds ratio (OR) of 1.08 (95% confidence interval (CI) 0.97-1.21). Current use showed the highest OR (1.30 (95% CI 1.16-1.47)). Long-term use of proton pump inhibitors (≥4 years) was not associated with colorectal cancer (OR 0.92 (95% CI 0.76-1.11)). A variation in OR for tumour stage and tumour subsite was observed with the highest OR for stage I tumour (1.28 (95% CI 0.87-1.87)) and proximal colon (1.19 (95% CI 0.87-1.63)).

Conclusions: No increased risk in colorectal cancer was seen with the use of proton pump inhibitors. Current use was associated with an increased likelihood to be diagnosed with colorectal cancer, but this is likely the result of reverse causality. No increased risk was seen for long-term use of proton pump inhibitors.

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1 | INTRODUCTION

Proton pump inhibitors (PPIs) are widely used in the management of acid peptic disorders and as preventive medication to avoid gastrointestinal bleeding associated with non-steroidal anti-inflammatory drug (NSAID) use. Because of their efficacy, the use of PPIs increased largely in the Netherlands in the last two decades and especially among older patients.[1] Between 2001 and 2015, the prevalence of PPI use increased from 6% to 15%.

Colorectal cancer is one of the most common types of cancer in the Netherlands. The survival rate of colorectal cancer improved in the last decade, but the incidence of colorectal cancer increased by 25% in the past 25 years.[2] This increased incidence may be related to an increasingly sedentary lifestyle, an unhealthy diet and increasing rates of obesity and diabetes.[3,4] Besides these risk factors, a concern has risen regarding the possible link between PPI-induced hypergastrinemia and gastrointestinal cancer, including colorectal cancer. High gastrin levels are associated with the growth and proliferation of adenoma cells and might increase the risk of colorectal cancer.[5,6] The increased risk of colorectal cancer is mainly seen in experimental and animal model studies,[7,8] but whether an association between PPI use and risk of colorectal cancer exists in humans is less clear.

One study performed in the United States found a possible association between use of PPIs and colorectal cancer.[9] However, this study suffered from a small sample size. Two other studies performed in Taiwan also found an association between the use of PPI and the risk of colorectal cancer, but this pertained to recent use or short duration of PPI use. This seemed less likely to have causally contributed to colorectal cancer due to the long latency period of this disease.[10,11] Other studies on the use of PPI and risk of colorectal cancer found no or a marginal association.[11-14] The results of previous studies examining the association between the use of PPI and risk of colorectal cancer were based on small numbers of exposed patients, did not account for duration of use or the use of other medication such as NSAIDs, which is an indication for the prescription of PPIs and inversely associated with colorectal cancer.[15] Also only one study differentiated between the left and right hemicolon.[16]

In the current study, a comprehensive large cohort with detailed data was used to investigate the risk of colorectal cancer with the use of PPIs taking into account timing and duration of PPI use and concomitant use of NSAIDs. In addition, a further analysis was performed determining whether the association varied across various subgroups with long-term use of PPIs.

2 | MATERIALS AND METHODS

2.1 | Setting

Data for this population-based case-control study were obtained from the Netherlands Cancer Registry (NCR) linked on a patient-level to the General Practitioner (GP) Database of the PHARMO Database Network (the NCR–PHARMO GP cohort). This cohort covers a catchment area of approximately 4 million inhabitants (approximately 20%-25% of the Dutch population). The GP Database comprises data from electronic patient records registered by GPs. The records include information on diagnoses and symptoms, laboratory test results, referrals to specialists and healthcare product/drug prescriptions. The prescription records include information on type of product, prescription date, strength, dosage regimen, quantity and route of administration. Drug prescriptions are coded according to the WHO Anatomical Therapeutic Chemical (ATC) Classification System.[17]

The NCR is a population-based registry which is maintained by the Comprehensive Cancer Centre the Netherlands (IKNL) and comprises information on newly diagnosed cancer patients in the Netherlands. The NCR is notified for new patients with cancer by pathology departments, general hospitals and radiotherapy institutes. On a daily basis, trained data managers register data from hospital records within all Dutch hospitals using the NCR's registration and coding manual.

Further detailed information on the linkage and formation of NCR-PHARMO GP cohort can be found elsewhere.[18-20]

2.2 | Case population

From the NCR-PHARMO GP cohort, all subjects who were diagnosed between 2007 and 2014 with primary colorectal cancer (ICD 10-CM code C18-C20) were identified. The date of diagnosis was defined as the index date. In order to determine long-term use of PPI, patients without 6 years of exposure information available (defined as the time between date of registration at a GP practice and date of colorectal cancer diagnosis) were excluded. To reduce the potential for including patients with heritable colorectal cancer syndromes, patients younger than 40 years of age at diagnosis were excluded as well.

2.3 | Control population

Each colorectal cancer case was randomly matched to four controls based on gender, birth year, GP practice and period of available primary care data. Matched controls received the same index date as their matched colorectal cancer case. Controls were not allowed to have a diagnosis of cancer before index date (excluding basal cell carcinoma) and could not be matched more than once.

2.4 | Exposure definition

Data on PPI exposure was derived from the PHARMO GP Database, which contains detailed information on prescribed medication by GPs. The prescription records include detailed information on type of product, prescription date, strength, dosage regimen, quantity and route of administration. Drug prescriptions are coded according

to the WHO Anatomical Therapeutic Chemical (ATC) Classification System. Drugs starting with the fifth-digit ATC code A02BC were classified as PPIs. In addition, PPI combination drugs were included as well (ATC code A02BD04 and M01AE52).

Duration of PPI use was calculated by constructing treatment episodes of PPIs based on quantity prescribed and prescribing information. Ever use of PPIs was defined as using a PPI in the 6 years before index date. Current use of PPIs was defined as using a PPI in the 90 days before index date. Recent use of PPIs was defined as using a PPI in the 91-365 days before index date, but not in the 90 days before index date. Past use of PPIs was defined as using a PPI more than 365 days before index date. Use of NSAIDs was determined in the same manner in order to assess concomitant use with PPIs.

2.5 | Confounding factors

The following covariates were evaluated as potential confounders: use of aspirins, nonsteroidal inflammatory drugs, histamine 2 receptor antagonists, statins and antidiabetics in the 6 years before index date. Age, sex and calendar time were inherently adjusted using the matching procedure.

Other risk factors, such as cigarette smoking history, body mass index, family history of cancer and helicobacter pylori status are important but unfortunately less uniformly reported by general practitioners.

2.6 | Statistical analyses

Conditional logistic regression was used to estimate the odds ratio (OR) and two-sided 95% confidence interval (CI) for colorectal cancer associated with the use of PPI, adjusted for preselected confounders. Analyses were conducted stratified by timing of use (current, recent, past), duration of use and concomitant use of NSAIDs. Furthermore, the association between colorectal cancer and long-term use of PPIs (>4 years) was examined stratified by age, gender, tumour stage and tumour subsite.

All data were analysed using SAS programs organised within SAS Enterprise Guide version 7.1 (SAS Institute Inc) and conducted under Windows using SAS version 9.4.

3 | RESULTS

A total of 6087 colorectal cancer cases could be matched to at least four cancer-free controls. Of those, 1987 colorectal cancer cases and 7912 cancer-free controls had at least 6 years of history available and were included in the analyses. The population of colorectal cancer cases with at least 6 years of history available did not differ from those with less than 6 years of history available in terms of age, gender and tumour characteristics(data not shown). The mean (±SD) age of colorectal cancer cases and cancer-free controls was 69.1 (±9.7) years and 58% was male (Table 1). About one-third (31%) of the colorectal cancer cases were diagnosed with stage III colorectal cancer. A tumour in the distal colon occurred in 34% of the colorectal cancer cases, 32% had a tumour in the proximal colon and 31% in the rectum.

TABLE 1 Characteristics of colorectal cancer cases and matched cancer-free controls

	Colorectal cancer cases	Cancer-free controls
	N = 1978	N = 7912
Age, mean (±SD)	69.1 ± 9.7	69.1 ± 9.7
Gender, male	1147 (58)	4588 (58)
Tumour stage		
I	406 (21)	NA
II	482 (24)	NA
III	619 (31)	NA
IV	436 (22)	NA
Unknown	35 (2)	NA
Tumour subtype		
Colon, proximal	638 (32)	NA
Colon distal	664 (34)	NA
Colon, unspecified	39 (2)	NA
Rectum	615 (31)	NA
Rectosigmoid	22 (1)	NA

Abbreviation: SD, standard deviation.

Overall, 1041 colorectal cancer cases (53%) and 4161 cancer-free controls (53%) ever used a PPI in the 6 years before index date (Table 2). No significant increased risk was seen for ever use PPIs (adjusted OR 1.08 (95% CI 0.97-1.21)). There were slightly more current PPI users among colorectal cancer cases (52%) compared to cancer-free controls (44%), resulting in an adjusted OR of 1.30 (95% CI 1.16-1.47). When looking at recent and past use of PPIs, no association was found with colorectal cancer (adjusted OR 0.94 (95% CI 0.78-1.14) and adjusted OR 0.84 (95% CI 0.74-0.96), respectively). There were 178 colorectal cancer cases (17%) and 824 cancer-free controls (20%) who had used PPIs for 4 years or longer. No increased risk in colorectal cancer was seen among those using PPIs for 4 years or longer (OR 0.92 (95% CI 0.76-1.11)). A significant increased risk was seen between current use of PPI in combination with NSAID (OR 1.40 (95% CI 1.15-1.71)) (Table 3). Adjusting for potential confounders only marginally change this association (OR 1.57 (95% CI 1.27-1.93)). However, this association was attenuated for recent and past use of PPI in combination with NSAID.

The use of PPI for longer than 4 years and the risk of colorectal cancer was further explored by stratifying the risk by several subgroups (Figure 1). Risk variations for long-term use were seen when stratifying by tumour stage; the OR for stage IV colorectal cancer was close to unity (OR 0.74 (95% CI 0.47-1.17) while the OR for stage I colorectal cancer was 1.28 (95% CI 0.87-1.87)) (Figure 1).Also, the association differed when stratifying by colorectal subsite, including

TABLE 2 Use of proton pump inhibitors and the risk of colorectal cancer, by timing and duration of use

	Colorectal cancer cases N = 1978	Cancer-free controls N = 7912	OR matched (95% CI)	OR adjusted (95% CI)[a]
Never users	937 (47)	3751 (47)	1.00 (reference)	1.00 (reference)
Ever users	1041 (53)	4161 (53)	1.00 (0.91-1.11)	1.08 (0.97-1.21)
Current	537 (52)[b]	1830 (44)	1.24 (1.11-1.39)	1.30 (1.16-1.47)
Recent	140 (13)[b]	615 (15)	0.90 (0.75-1.09)	0.94 (0.78-1.14)
Past	364 (35)[b]	1716 (41)	0.81 (0.72-0.92)	0.84 (0.74-0.96)
Duration (y)				
>0-<2	762 (73)[b]	2853 (68)	1.07 (0.96-1.19)	1.16 (1.03-1.31)
≥2-<4	101 (10)[b]	484 (12)	0.84 (0.67-1.05)	0.89 (0.71-1.13)
≥4	178 (17)[b]	824 (20)	0.86 (0.72-1.03)	0.92 (0.76-1.11)

[a]Adjusted for use of antidiabetics, aspirins, H2 receptor antagonist, NSAIDs, statins.

[b]Percentage relative to the number of ever users of PPI.

TABLE 3 Use of proton pump inhibitors and NSAID alone or combined and the risk of colorectal cancer

	Colorectal cancer cases N = 1978	Cancer-free controls N = 7912	OR matched (95% CI)	OR adjusted (95% CI)[a]
Current use				
Neither PPI nor NSAID	1356 (69)	5724 (72)	1.00 (reference)	1.00 (reference)
PPI but no NSAID	394 (20)	1400 (18)	1.19 (1.05-1.35)	1.24 (1.08-1.41)
PPI and NSAID	143 (7)	430 (5)	1.40 (1.15-1.71)	1.57 (1.27-1.93)
NSAID but no PPI	85 (4)	358 (5)	1.00 (0.79-1.28)	1.12 (0.87-1.43)
Recent use				
Neither PPI nor NSAID	1699 (86)	6682 (85)	1.00 (reference)	1.00 (reference)
PPI but no NSAID	71 (4)	295 (4)	0.95 (0.73-1.23)	0.97 (0.75-1.27)
PPI and NSAID	69 (4)	320 (4)	0.85 (0.65-1.11)	0.90 (0.69-1.18)
NSAID but no PPI	139 (7)	615 (8)	0.89 (0.73-1.08)	0.95 (0.78-1.16)
Past use				
Neither PPI nor NSAID	1190 (60)	4346 (55)	1.00 (reference)	1.00 (reference)
PPI but no NSAID	108 (6)	538 (7)	0.73 (0.59-0.91)	0.74 (0.60-0.92)
PPI and NSAID	256 (13)	1178 (15)	0.79 (0.68-0.92)	0.82 (0.69-0.97)
NSAID but no PPI	424 (21)	1850 (23)	0.84 (0.74-0.95)	0.86 (0.74-1.00)

[a]Adjusted for use of antidiabetics, aspirins, H2 receptor antagonist, statins

an increased risk for proximal colon cancer (OR 1.19 (95% CI 0.87-1.63)). Rectosigmoid cancer was not taken into account in this stratification due to the low number of cases diagnosed with rectosigmoid cancer.

4 | DISCUSSION

In this large population-based case-control study, no increased risk of colorectal cancer was seen with ever use of PPIs. There was also no association seen when stratifying by duration of PPI use. When considering timing of use, current use of PPI, alone or in combination with NSAID, showed the highest risk for colorectal cancer. However, these findings are most likely the result of reverse causality as the use of PPIs and also NSAIDs shortly before diagnosis is probably prescribed for symptoms resulting from undetected colorectal cancer. This is more likely as recent or past use of PPI was found not to be associated with colorectal cancer.

Previous studies mainly focused on the association of PPI use and upper gastrointestinal tract neoplasia rather than on lower gastrointestinal tract neoplasia, including colorectal cancer. A few previous studies examined the risk of colorectal cancer with the use of PPI of which the majority found no association. There are a few studies who found contradicting results. In a study among 4432 incident colorectal cancer cases and 44 292 controls, an increased colorectal cancer risk was seen with use of PPI.[11] Another study in Taiwan also found an increased risk of colorectal cancer with the use of PPI.[10] However, in these studies an association was only seen for recent or short duration of use prior to the diagnosis of cancer, which can probably not contribute to an increased risk

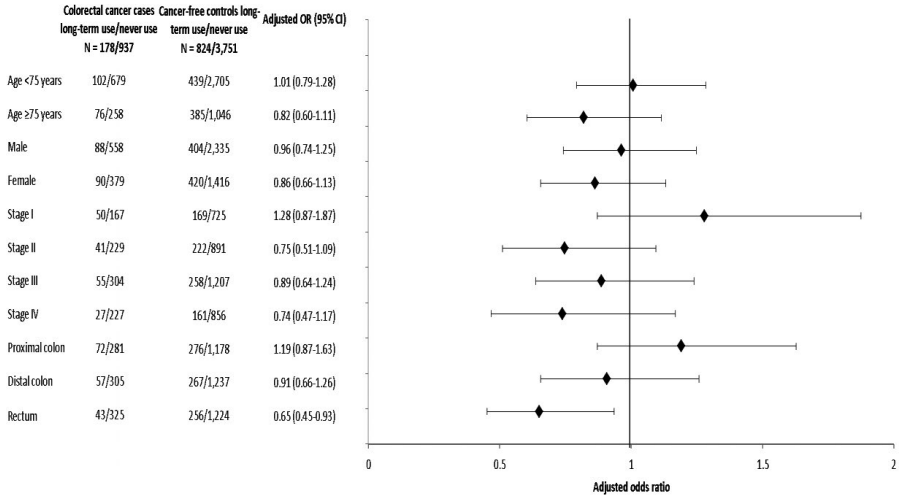

FIGURE 1 Stratified analysis for long-term use of proton pump inhibitors (≥4 y)

of colorectal cancer taken into account the long latency period of the disease.

As the majority of the PPI users require long-term therapy, it is especially of interest to study the association between long-term use of PPIs and colorectal cancer. One recently published meta-analysis demonstrated an increased risk of colorectal cancer with long-term PPI use.[21] However, the pooled OR was based on five studies with marked heterogeneity which may have led to a biased pooled OR. The transition from anadenomatous or serrated polyp to cancer may take 10 years or longer. The period in which long-term use of PPI was assessed in our study and previous studies may therefore be too short to examine new incident cases of colorectal cancer. The majority of the patients may already have had pre-neoplastic colorectal lesions and PPI use may only influence tumour biology. In our study, risk variations were observed by tumour subsite, with the highest risk found for proximal cancer with long-term use of PPI. Differences exist between the proximal and distal colon in terms of developmental origin and molecular and genetic characteristics.[22] These differences could lead to tumour subsite differences in the impact of PPI use. Further studies are required to elucidate the mechanisms of PPI use and their effect on the occurrence of different subsites of colorectal cancer.

Strengths of the study include the large number of individuals exposed to treatment with PPIs. To our knowledge, this is the largest study to date on this topic. Furthermore, colorectal cancer cases were identified from the Netherlands Cancer Registry, in which data has shown to be of high quality due to thorough training of the registrars.[23] The completeness is estimated to be at least 95%. Moreover, the use of the GP Database of the PHARMO Database Network ensured complete and high-quality assessment of prescription drug use. In the Netherlands, every inhabitant is registered with a GP which allows comprehensive follow-up of patients in the primary care setting.[24]

This study also had some limitations. We lacked information on smoking status and body mass index, which are established risk factors for colorectal cancer.[25,26] Also, we used prescription data as a surrogate for actual use. This could lead to misclassification of some persons as users who were actually nonusers. However, it is not expected that this occur in long-term users as it is unlikely that there are patients who repeatedly fill prescriptions but not use them.

In summary, no overall increased risk of colorectal cancer was seen with the use of PPIs. Current use of PPIs was significantly associated with colorectal cancer, but this is probably the result of reverse causality. Also no increased risk was observed for long-term use of PPIs, but risk variations were seen by tumour stage and subsite. Further research needs to be conducted studying prolonged use of PPIs given the long latency period of cancer. Thereby, colorectal cancer located at different anatomical subsites should be investigated separately.

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AUTHORSHIP

Guarantor of article: Josephina G. Kuiper.

Author contributions: Josephina G. Kuiper designed the research study, collected the data, analysed the data, contributed to the interpretation of the study results and wrote the paper. Myrthe PP van Herk-Sukel, Valery EPP Lemmens, Ernst J. Kuipers and Ron MC Herings designed the research study, contributed to the

interpretation of the study results, and critically reviewed and revised the article. All authors approved the final version of the article, including the authorship list.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The datasets generated during and/or analysed during the current study are not publicly available due to privacy reasons.

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