

# Limited time Interval between Symptomatic Presentation in Primary Care and Colorectal Cancer Diagnosis

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## Research Article

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# Abstract

**Background:** Timely recognition of colorectal cancer related symptoms is essential to reduce time to diagnosis. This study aims to investigate the primary healthcare use preceding a colorectal cancer diagnosis.

**Methods:** A population-based case-control study was conducted using data from a cohort of linked data from the Netherlands Cancer Registry (NCR) and the PHARMO General Practitioner (GP) Database (NCR-PHARMO GP cohort). Primary healthcare use among colorectal cancer cases before diagnosis was compared with matched cancer-free controls. Information on primary health care use was derived from the GP Database of the PHARMO Database Network and included all GP consultations and prescribed medication. Mean monthly number of GP consultations and new drugs users was assessed in the year before index date (diagnosis date for cases). Results were stratified by colorectal cancer site: proximal colon cancer, distal colon cancer and rectal cancer.

**Results:** While mean monthly number of GP consultation were stable through the year among cancer-free controls, a statistical significant increase was seen among colorectal cancer cases in the last 4-8 months before diagnosis. Proximal colon cancer cases showed the longest time interval of increased mean monthly number of GP consultations. This increase was largely driven by a consultation for malignant neoplasm colon/rectum. The number of new drug users was stable around 120 per 1,000 persons per month until 8 months before index date for proximal colon cancer cases, 4 months before index date for distal colon cancer cases and 3 months for rectal cancer cases. This increase was mainly driven by the prescription of laxatives drugs.

**Conclusion:** A relatively short time interval of increased GP consultations and new drug users was seen before colorectal cancer diagnosis. The longest period of increased GP consultations and new drugs users was seen among patients diagnosed with proximal colon cancer. This can be explained by the difficulty to diagnose proximal colon cancer given the more subtle signs compared to distal colon cancer and rectal cancer. Therefore, faster diagnosis for this specific tumour subtype is only possible when clear clinical signs and symptoms are present.

## Background

The incidence of colorectal cancer continues to increase in Europe, with approximately 500,000 patients newly diagnosed with colorectal cancer each year(1). Colorectal cancer is the second most common cause of cancer-related death in Europe, accounting for over 240,000 deaths each year.

In most European countries screening programmes have been implemented to improve outcomes and reverse the increasing incidence trend of colorectal cancer.(2) In the Netherlands, a national screening program was implemented in January 2014 with a participation rate of almost 75% in 2018 among people aged 55 to 75 years(3). Despite population-based screening, patients remain to be diagnosed

outside the context of screening either as interval cancer, due to non-participation or because they fall outside of the screening age range.

In the Netherlands, the general practitioner (GP) is the gatekeeper to specialist care, so it is likely that the GP is the first point of contact for people who experience health problems which may relate to cancer. Persistent rectal bleeding, blood in the stools, abdominal pain and bloating, loss of appetite and unexplained weight loss may all be signs of colorectal cancer and should at some point be a reason for further assessment and a referral for endoscopy(4). Previous studies showed that the median time between first consultation with cancer-related complaints to referral varies greatly for colorectal cancer patients with duration of months and even years for 10-25% of the colorectal cancer patients(5, 6). The healthcare seeking behaviour of colorectal cancer patients prior to diagnosis may provide new knowledge on the 'diagnostic window', i.e. the time from first symptom presentation to actual diagnosis. Delay in the diagnosis may have several important consequences, such as higher mortality and a more advanced disease stage. It is therefore important to explore whether earlier and more expedient diagnosis is possible.

This study aims to investigate the number of GP consultations among colorectal cancer patients and the medication they have been prescribed in the year before diagnosis.

## Methods

### Data sources

For this population-based case-control study, we used data from the Netherlands Cancer Registry (NCR) linked to the PHARMO GP Database (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 including information on diagnoses and symptoms (coded according to the International Classification of Primary Care (ICPC) or entered as free text) and healthcare product/drug prescriptions (coded according to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) Classification System)(7).

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.

Further detailed information on the linkage and formation of the NCR-PHARMO GP cohort can be found elsewhere(8) (9).

### Study population

All patients who were diagnosed with primary colorectal cancer (International Classification of Diseases, Tenth Revisions, Clinical Modification (ICD 10-CM) code C18-C20) between January 1<sup>st</sup> 2007 and December 31<sup>st</sup> 2014 were selected. Patients with a previous diagnosis of cancer (except basal cell skin carcinoma) were excluded. The same pertained to patients with less than 12 months of history available in the GP Database (defined as the time between the date of entering the PHARMO Database Network to the date of colorectal cancer diagnosis).

Each colorectal cancer case was matched to four cancer-free controls based on gender, birth year GP practice and start follow-up in the PHARMO Database Network. Matched controls received the same index date as the diagnosis date in their matched case with colorectal cancer and could not be matched more than once. The same exclusion criteria for the cases were applied to the matched controls.

## Primary healthcare use

Information on primary healthcare use was derived from the GP Database of the PHARMO Database Network, which includes primary care data retrieved directly from the source, i.e. the electronic medical records of the healthcare providers.

According to the Medical Treatment Contract Act (*“Wet op de geneeskundige behandelingsovereenkomst”* (WGBO)), care providers (including general practitioners) are obliged to create and maintain a complete patient file for each patient. In the 1980s, the first automated system for general practices was introduced, replacing the handwritten files which were often difficult to read and incomplete. Since 2013, almost all general practices in the Netherlands work with an automated system to record the medical data of patients in the Electronic Patient File (EPD). In this EPD, GP consultations are grouped in episodes, i.e. a series of consultations related to a single reason for encounter (a symptom or a diagnosis). Besides information on the reason for encounter, prescriptions, laboratory results, referral letters and the summary of specialist letters are also registered in the system.

For this study, all GP consultations (face-to-face consultations, GP home visits and phone consultations) were extracted in the year prior index date for all colorectal cancer cases and their matched cancer-free controls. All information on diagnoses and symptoms registered by the GP (coded or entered as free text) was used for analyses. Furthermore, all prescribed medication based accompanied with an ATC codes in the year prior index date was extracted.

## Statistical analyses

Descriptive statistics were used to present baseline and tumour characteristics. The mean monthly number of GP consultations were calculated by dividing the monthly number of GP consultations by the number of colorectal cancer cases (or cancer-free controls) in each month. The Wilcoxon rank-sum test

was used for comparing the mean monthly number of GP consultations between colorectal cancer cases and cancer-free controls. A p-value of <0.05 was considered as a statistically significant difference.

Furthermore, in each month before the index date - going back 12 months - the number of colorectal cancer (or cancer-free controls) receiving a newly prescribed drug was assessed. Newly prescribed drugs were assessed based on the fourth level of the ATC code (i.e. A02BC) and defined as not receiving the drug in the year prior to that period. In each month, the incidence rate of new drug users was calculated by dividing the number of new drugs users by follow-up among colorectal cancer (or cancer-free controls) and presented per 1,000 persons per month. A Poisson regression analysis was used to examine whether the incidence rates per month significantly varied between colorectal cancer cases and cancer-free controls. A p-value of <0.05 was considered as a statistically significant difference.

A *post-hoc analysis* was performed to assess the type of newly prescribed medication and reason for GP consultation that triggered the increase in the last 6 months before index date among colorectal cancer cases. The type of newly prescribed drugs was assessed on the fourth level of the ATC code and presented if the absolute difference in receiving a specific drug between colorectal cancer cases and cancer-free controls was more than 5%. The reason for a GP consultation was determined by assessing the ICPC code associated with each consultation and by reviewing the free text of diagnosis and symptoms not accompanied by an ICPC code. Diagnoses and symptoms without an ICPC code (i.e. entered as free text) were reviewed and supplemented with an ICPC code where applicable. The reason for a GP consultation were separately listed based on ICPC codes if the absolute difference in the occurrence of a specific diagnosis or symptom between colorectal cancer cases and cancer-free controls was more than 2%.

As clinical features of colorectal cancer may vary significantly depending on the anatomical site, results were stratified by anatomical colorectal cancer site: proximal colon cancer, distal colon cancer and rectal cancer. Patients with colon cancer with an unspecified site or rectosigmoid cancer were not taken into account.

All data was analysed using SAS programs organized within SAS Enterprise Guide version 7.1 (SAS Institute Inc., Cary, NC, USA) and conducted under Windows using SAS version 9.4.

## Results

A total of 6,087 colorectal cancer cases could be matched to four cancer-free controls (N = 24,348) (Table 1). The mean ( $\pm$  SD) age of colorectal cancer cases and cancer-free controls was 68.7 ( $\pm$  10.0) years and 56% was male. Of the colorectal cancer cases, 19% were diagnosed with stage I colorectal cancer, 27% with stage II, 31% with stage III and 20% with stage IV. For 3% the tumour stage at colorectal cancer diagnosis was unknown. The primary tumour was located in the distal colon in 33% of cases, 31% had a tumour located in the proximal colon and 32% in the rectum.

Table 1  
Baseline characteristics of colorectal cancer cases and their matched cancer-free controls

<b>Characteristics</b>	<b>Colorectal cancer cases</b>	<b>Cancer-free control population</b>
	<b>N = 6,087</b>	<b>N = 24,348</b>
<b>Gender, n (%)</b>		
Male	3,434 (56)	13,736 (56)
Female	2,653 (44)	10,612 (44)
<b>Age at index date</b>		
< 44	79 (1)	316 (1)
45–54	493 (8)	1,972 (8)
55–64	1,405 (23)	5,620 (23)
65–74	2,208 (36)	8,832 (36)
75–84	1,652 (27)	6,608 (27)
≥ 85	250 (4)	1,000 (4)
Mean ± SD	68.7 ± 10.0	68.7 ± 10.0
<b>Year of diagnosis</b>		
2007–2009	1,495 (25)	5,980 (25)
2010–2012	2,451 (40)	9,804 (40)
2013–2014	2,141 (35)	8,564 (35)
<b>Duration of history available (years)</b>		
Mean (± SD)	4.7 ± 2.3	4.7 ± 2.3
<b>Tumour site</b>		
Colon	4,042 (66)	NA
Proximal	1,910 (31)	NA
Distal	2,022 (33)	NA
Unspecified	110 (2)	NA
Rectum	1,926 (32)	NA

SD = standard deviation; NA = Not applicable

<b>Characteristics</b>	<b>Colorectal cancer cases</b>	<b>Cancer-free control population</b>
Rectosigmoid	119 (2)	NA
<b>Tumour stage</b>		
I	1,171 (19)	NA
II	1,631 (27)	NA
III	1,884 (31)	NA
IV	1,242 (20)	NA
Unknown	159 (3)	NA
SD = standard deviation; NA = Not applicable		

For all different tumour sites, the mean monthly number of GP consultations increased in the last months before diagnosis, but the timing of the increased mean monthly number of GP consultations differed (Fig. 1). For proximal colon cancer, a statistically significant difference ( $p$ -value < 0.05) in GP consultation rates was observed from 8 months before diagnosis. This was 5 months for patients with distal colon cancer and 4 months in those with rectal cancer. The mean monthly GP consultation in the month before colorectal cancer diagnosis was highest among patients diagnosed with proximal colon cancer (1.8) compared with distal colon cancer (1.7) and rectal cancer (1.6).

The number of new drug users was stable around 120 per 1,000 persons per month. A statistically significant difference ( $p$ -value < 0.05) in new drugs users between colorectal cancer cases and cancer-free controls was seen from 8 months before index date for proximal colon cancer cases, 4 months before index date for distal colon cancer cases and 3 months for rectal cancer cases (Fig. 1). The highest number of new drug users was seen among rectal cancer where it increased and peaked at 604 new drug users per 1,000 persons in the month immediately before index date. The number of new drugs users among cancer-free controls remained stable throughout the year before index date.

In a post-hoc analysis assessing the type of newly prescribed drugs and reason for GP consultation that triggered the increase in the last months before diagnosed, it was seen that the increase in new drug users was mainly driven by the prescription of laxatives drugs to help resolve constipation or empty the bowel before procedures or surgery involving the lower bowel, which were most often prescribed among patients diagnosed with rectal cancer (Table 2). Other drugs that were often newly prescribed included proton pump inhibitors, which were more often prescribed to patients diagnosed with proximal colon cancer (15% vs. 9% among patients diagnosed with distal colon cancer and 7% among patients diagnosed with rectal cancer). Drugs to treat iron deficiency anaemia were also a common newly prescribed drug especially among patients diagnosed with proximal colon cancer (14% vs. 4% among patients diagnosed with distal colon cancer and 2% among patients diagnosed with rectal cancer).

Table 2

Type of newly prescribed treatment and reason for GP consultation among colorectal cancer and matched cancer-free controls in the six months before index date, stratified by tumour site

	Proximal		Distal		Rectum	
	Cases	Cancer-free controls	Cases	Cancer-free controls	Cases	Cancer-free controls
	N = 1,910 n (%)	N = 7,640 n (%)	N = 2,022 n (%)	N = 8,088 n (%)	N = 1,926 n (%)	N = 7,704 n (%)
<b>Common newly prescribed medication</b>						
<b>A06AD</b>						
<i>Osmotically acting laxatives</i>	729 (38)	175 (2)	928 (46)	194 (2)	914 (48)	173 (2)
<b>A06AB</b>						
<i>Contact laxatives</i>	260 (14)	32 (< 0.5)	426 (21)	47 (1)	444 (23)	36 (1)
<b>A02BC</b>						
<i>Proton pump inhibitors</i>	288 (15)	373 (5)	182 (9)	377 (5)	143 (7)	337 (4)
<b>B03AA</b>						
<i>Iron bivalent, oral preparations</i>	273 (14)	32 (< 0.5)	71 (4)	42 (1)	31 (2)	25 (< 0.5)
<b>A06AG</b>						
<i>Enemas</i>	40 (2)	22 (< 0.5)	117 (6)	35 (< 0.5)	50 (3)	23 (< 0.5)
<b>M01AB</b>						
<i>Acetic acid derivatives and related substances</i>	116 (6)	303 (4)	106 (5)	300 (4)	76 (4)	323 (4)
<b>Common reason for GP consultation</b>						
<b>D75</b>						
<i>Malignant neoplasm colon/rectum</i>	664 (35)	1 (< 0.5)	780 (39)	2 (< 0.5)	860 (45)	0 (0)
<b>D16</b>						

	Proximal		Distal		Rectum	
<i>Rectal bleeding</i>	10 (1)	13 (< 0.5)	94 (5)	11 (< 0.5)	78 (4)	12 (< 0.5)
<b>B80</b>						
<i>Iron deficiency anaemia</i>	99 (5)	9 (< 0.5)	27 (1)	10 (< 0.5)	15 (1)	2 (< 0.5)
<b>B82</b>						
<i>Anaemia other/unspecified</i>	64 (3)	11 (< 0.5)	12 (1)	10 (< 0.5)	9 (1)	12 (< 0.5)
<b>D06</b>						
<i>Abdominal pain localized other</i>	44 (2)	21 (< 0.5)	41 (2)	37 (1)	9 (1)	14 (< 0.5)

The increase in monthly GP consultations in the 4–9 months before index date was largely driven by a consultation for malignant neoplasm colon/rectum. Consultations for rectal bleeding was more prominent among distal colon cancer and rectal cancer compared to proximal colon cancer (5% and 4% versus 1%, respectively). Patients diagnosed with proximal colon cancer more often had a GP recording for iron deficiency anaemia or other anaemia compared to patients diagnosed with distal colon cancer or rectal cancer.

## Discussion

An increase in the mean monthly number of GP consultations and newly prescribed drugs was seen in the year before colorectal cancer diagnosis compared to a cancer-free control population with a steep increase in the last months before diagnosis. This increase was seen for all anatomic sites of colorectal cancer, but the timing of the increase differed. Patients diagnosed with proximal colon cancer had the longest period with increased GP consultations rates and newly prescribed drugs compared to cancer-free controls.

The increase in GP consultations rate in the months before colorectal cancer diagnosis was mainly driven by a contact coded as malignant neoplasm of colon/rectum. This might indicate that there is a small difference in the date of diagnosis recorded by the GP and the NCR. A previous study assessing the quality of cancer registration in Dutch primary care showed that in 80.6% of the cases the year of diagnosis in the primary care electronic health records is registered in accordance with the NCR(10). For the cases with a different recorded year of diagnosis, the deviation was found to be less than two years. It could also be that the GP already recorded a diagnosis of colorectal cancer based on certain definite symptoms or results from the faecal immunochemical tests without a confirmation from a specialist. Other reasons for the increase in consultations rates were rectal bleeding, iron deficiency anaemia or other, and abdominal pain. These are known alarm symptoms for colorectal cancer and especially rectal

bleeding and anaemia warrant further investigation, irrespective of whether other symptoms are present(4).

Tumours arising from the proximal colon tend to present with more subtle signs such as anaemia compared to tumours arising from the distal colon(11). This was also seen in our study in which proximal colon cancer cases presented more often with anaemia compared to distal colon cancer and rectal cancer cases. The more subtle signs of proximal colon cancer also explain the slightly longer increased intervals of GP consultations and newly prescribed drugs among proximal colon cancer as these cancers are more difficult to diagnose compared to distal colon cancer and rectal cancer. Although we know that there are differences between anatomic site of colorectal cancer in terms of developmental origin and molecular and genetic characteristics, there was only one previous study found that assessed differences in GP consultation rates and prescriptions between different tumour locations(16). Similar as in our study, this study also showed that patients diagnosed with proximal colon cancer had the longest intervals with increased rates of GP consultations. Rectal cancer patients had long intervals with higher prescription rates than references. This was not seen in our study, but we determined newly prescribed drugs in contrast to a previous study that only took prescriptions for haemorrhoids into account. These differences indicates that each anatomic site of colorectal cancer should be considered separately and have a different presentation in primary care.

Other previous research also showed an increased GP consultation rate before colorectal cancer diagnosis(12–16), but only a few studies also looked at the reasons for and the contents of the consultations with the GPs. In a previous study in which also data from Dutch general practices were used but a different region, the largest difference was observed for contacts related to the digestive system (coded as ICPC-D): 46.0% of patients with colorectal cancer showed two or more contacts for these reasons in the year before diagnosis, compared with 12.2% of controls. This specific ICPC chapter also includes the code related to malignant neoplasm of the colon/rectum and might also be in this study the main reason for the increase as index date was defined as a referral to colonoscopy indicating that the GP might already suspect colorectal cancer(15).

Laxatives drugs were often newly prescribed in the six months before diagnosis, most likely as preparation of a colonoscopy to clear the upper bowel. Similar to the prescription of enema to empty the lower part of the bowel, but less often prescribed compared to laxatives. An increase in prescribed drugs before colorectal cancer diagnosis was also seen in other previous studies with a peak in the last month before colorectal cancer diagnosis. In line with our study, drugs used for constipation showed the highest increase in use(17, 18). Proton pump inhibitors were also common newly prescribed, especially among patients diagnosed with proximal colon cancer. Tumours in the proximal colon may result in symptoms that are similar to diseases in the upper gastrointestinal tract, such as the stomach. It is unlikely that proton pump inhibitors are prescribed to treat colorectal cancer if they expect the pain to be cancer related.

A strength of this study is the use of a database with GP recorded information extracted directly from the source instead of survey data which may lead to inaccurate information on primary care use. Thereby, information on the actual diagnosis of colorectal cancer was obtained from the NCR. As shown in a previous study, 40% of cancer cases can be missed when using only GP recorded information, and almost half can be false positive(10). Relying solely on GP recorded information will result in misclassification of colorectal cancer cases and cancer-free controls and will bias the results. Furthermore, diagnoses coded with an ICPC code or entered as free-text are available for research purposes (taken the privacy regulations into account) and used in this study. A GP is obliged to record all relevant health information of the patients but is not obliged to code all diagnoses and symptoms accordingly. As a result, taking into account coded diagnoses and symptoms only may result in missed signs of colorectal cancer. Furthermore, colorectal cancer cases were matched – among other things – with cancer-free controls on GP practice resulting in evenly distributed inaccuracies in recording and prescribing among colorectal cancer cases and cancer-free controls.

## Conclusions

In conclusion, this large population-based study showed a steep increase in the number of GP consultations and newly prescribed drug especially in the last 4-8 months before colorectal cancer diagnosis. This increased healthcare use can be seen as a proxy variable for symptom presentation. Improvements in the diagnostic window in the primary care setting may not always be possible as GPs acts swiftly on alarm symptoms indicated by the limited time interval between symptomatic presentation in primary care and actual diagnosis. The longest period of increased primary healthcare use was seen among patients diagnosed with proximal colon cancer, which may indicate a potential for a faster diagnostic pathway among this specific tumour subtype. However, the period of increased primary healthcare use among this group is still acceptable given the difficulty to diagnose proximal colon cancer compared to distal colon cancer and rectal cancer. Shortening the diagnostic pathway may therefore only be possible among those patients presenting with clear signs and symptoms.

## Abbreviations

ATC	Anatomical Therapeutic Chemical
CM	Clinical Modification
EPD	Electronic Patient File
GP	General practitioner
NCR	Netherlands Cancer Registry
ICD	International Classification of Diseases
ICPC	International Classification of Primary Care
IKNL	Comprehensive Cancer Centre the Netherlands
SD	Standard deviation
STIZON	Stichting Informatievoorziening voor Zorg en Onderzoek
WGBO	Wet op de geneeskundige behandelingsovereenkomst
WHO	World Health Organization

## Declarations

### Ethical approval:

This study is conducted using de-identified data from existing databases without any direct enrolment of subjects. Ethical approval or informed consent is not necessary according to the Dutch law regarding human medical scientific research (Wet Medisch-wetenschappelijk Onderzoek met mensen (WMO)), which is enforced by the Central Committee of Research involving Human Subjects (Centrale Commissie Mensgebonden Onderzoek (CCMO)).

### Consent for publication:

Not applicable

### Availability of data and materials:

The datasets generated and analysed during the current study are not publicly available due to privacy reasons but are available from the corresponding author on reasonable request.

### Competing interest:

Josephina G. Kuiper, Myrthe P.P. van Herk-Sukel, Valery E.P.P. Lemmens, Ernst J. Kuipers and Ron M.C. Herings declare that they have no competing interest.

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## Authors' contributions:

JGK, MPPH, VEPPL, EJK and RMCH designed the study and interpreted the study results. JGK analysed the data and wrote the manuscript with input from all authors.

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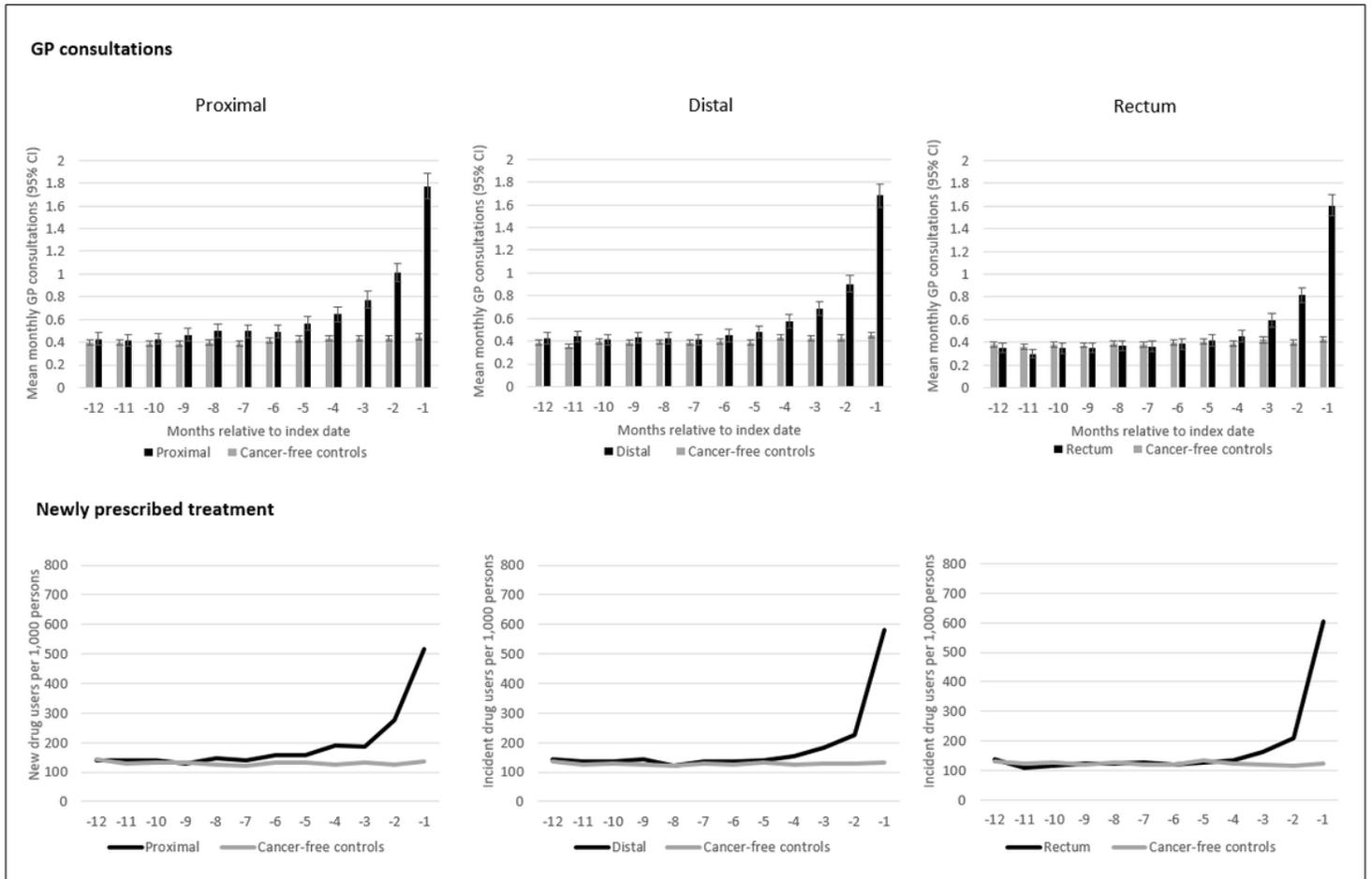
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## Figures



**Figure 1**

Mean monthly GP consultations and new drugs users in the year before index date, stratified by tumour site