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Pre-diagnostic clinical features and blood tests in patients with colorectal cancer: a retrospective linked data study

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## Abstract:

**Background:** The majority of colorectal cancer cases are diagnosed following symptomatic presentation in the United Kingdom.

**Aim:** To identify windows of opportunity for timely investigations or referrals in patients presenting with colon and rectal cancer-relevant symptoms or abnormal blood tests.

**Design and setting:** Retrospective cohort study using linked primary care and cancer registry data of colorectal cancer patients diagnosed in England between 2012-2015.

**Methods:** Monthly consultation rates for relevant clinical features (change in bowel habit, rectal bleeding, abdominal pain, mass, constitutional symptoms, and other bowel symptoms) and abnormal blood test results (low haemoglobin, high platelets and inflammatory markers) up to 24 months pre-diagnosis were calculated. Poisson regression adjusted for age, sex and relevant comorbidities was used to estimate the most likely month when consultation rates increased above baseline.

**Results:** 5033 colon and 2516 rectal cancer patients were included. Consultations for all examined clinical features and abnormal blood tests increased in the year pre-diagnosis. Rectal bleeding was the earliest clinical feature to increase from baseline rate: 10 months (95%CI 8.3-11.7) pre-diagnosis for colon cancer; 8 months (95%CI 6.1-9.9) for rectal cancer. Low haemoglobin, high platelets and inflammatory markers increased from as early as 9 months pre-diagnosis.

**Conclusion:** Our study found evidence for early increase in rates of consultation for relevant clinical features and abnormal blood tests in patients with colorectal cancer, suggesting that earlier instigation of cancer-specific investigations or referrals may be warranted in some symptomatic patients.

## Keywords

primary health care; colon cancer; rectal cancer; early diagnosis

## BJGP: How this fits in

*Summarise, in no more than four short sentences, what was previously known or believed on the topic and what your research adds, particularly focusing on the relevance to clinicians.*

Understanding pre-diagnostic patterns of relevant clinical features and abnormal blood test results in patients with colon and rectal cancer could elucidate windows of opportunity during which more timely investigations and referrals could be performed, and earlier diagnosis of cancer could be achieved. We found that consultation rates increased in the year leading up to diagnosis for relevant clinical features such as low haemoglobin, rectal bleeding and change in bowel habits, as well as non-specific blood tests, from as early as 9-10 months before diagnosis. Our findings suggest that potential opportunities for more timely use of cancer investigations or referral exist, and could improve diagnostic pathways, expediting diagnosis and treatment for some patients with colorectal cancer.

## Introduction

Colorectal cancer (CRC) is the fourth most common cancer and the second most common cause of cancer-related deaths in the United Kingdom (UK) (1). Despite the existence of bowel cancer screening programmes, the majority (about 53%) of CRC cases are diagnosed following symptomatic presentation in primary care (2). Timely diagnosis following symptomatic presentation matters because earlier detection allows earlier treatment and improved outcomes, with better survival when cancer is diagnosed at an earlier stage (3).

In the UK, most patients with undiagnosed CRC first present to general practitioners (GPs) (2). Patients with alarm symptoms of colorectal cancer, including rectal bleeding, change in bowel habit, rectal or abdominal mass and unexplained anaemia, can be fast-tracked for assessment by a specialist within 14 days under the two-week-wait system (hereafter known as fast-track referral), based on the National Institute for Health Care and Excellence (NICE) guidelines (4,5). However, not all patients experience alarm symptoms in the year leading up to CRC diagnosis. Many patients with CRC report non-specific gastrointestinal and constitutional symptoms such as abdominal pain, weight loss or fatigue in the years before diagnosis (6,7). They also have higher consultation rates for musculoskeletal, neurological, respiratory and endocrine dysfunction than matched controls (8). The low positive predictive values (PPV) of these less specific symptoms pose a challenge for timely diagnosis. The faecal immunochemical test (FIT), which is now available in UK general practice (9), may be a useful test to triage lower risk patients with possible colorectal cancer for further investigations or referral.

Existing evidence demonstrates that clinical activities such as consultation rates increase before cancer diagnosis, suggesting that opportunities may exist to initiate investigations sooner, and therefore expedite diagnosis, in some cancer patients (10–12). In population-based cohort studies in Denmark, CRC patients had higher overall consultation rates than matched controls as early as 9 months before diagnosis (13). Prescriptions for any medication (8) and specifically for haemorrhoid medications, and performance of haemoglobin tests (13), were also higher in CRC patients than matched controls in the year leading up to diagnosis.

In addition to clinical activities, cohort studies in UK primary care have identified non-specific blood-based biomarkers associated with increased risk of cancer in general, including high platelet counts (14) and markers of inflammation (15). We do not currently know if and with what frequency these generic abnormal blood tests occur in the pre-diagnostic period in CRC patients. Examining pre-diagnostic patterns of these abnormal test results may be helpful for informing clinicians of the possible time during which these generic tests first become abnormal, which may represent the first signals of possible CRC, therefore prompting clinicians to arrange for suitable and timely follow-up or investigations as appropriate.

Against this background, we aim to provide a comprehensive and up-to-date description of the pattern of relevant symptoms and abnormal blood tests in patients with CRC in the months leading up to diagnosis, and to identify when first signals of possible CRC might occur, so that timely investigations can be initiated.

## Methods

We used linked primary care data from the Clinical Practice Research Datalink (CPRD) GOLD and National Cancer Registration Analysis Service (NCRAS) which included all patients with a first record of CRC recorded in CPRD between 01/04/2012 and 31/12/2015. The cohort was supplemented with all patients with CRC recorded in the Cancer Registry using International Classification of Disease (ICD-

10) codes C18 (colon cancer) and C19-20 (rectal cancer) (CRC diagnosis codes are reported in Supplementary Table 1). When diagnosis or date differs between CPRD and the Cancer Registry, Cancer Registry data were retained.

Colorectal cancer symptom and gastro-intestinal comorbidity code lists were derived from previously published studies (7,16–18). Lists were cross-checked by two English GPs (FW and YZ) and categorised into clinically relevant groups for analysis. We included relevant symptom categories, including alarm symptoms drawn from the NICE 2015 cancer referral guidelines (5). After discussing with clinical co-authors, we included rectal bleeding, change in bowel habit (including constipation and diarrhoea), abdominal pain, constitutional symptoms (including fatigue, appetite loss and weight loss, combined due to the low frequency of individual symptoms), and other bowel symptoms (including bloating, flatulence, wind and obstruction) (code lists in Supplementary Table 2). The choice of constitutional symptoms and other bowel symptoms were chosen due to their likelihood of triggering clinical and cancer-excluding investigations (including FIT), based on the experience of the clinical co-authors.

We selected and grouped relevant comorbidities based on previous literature (19) and clinical consensus among the co-authors. Group 1 included inflammatory bowel disease (IBD) and diverticular disease which are associated with increased risk of CRC (20). Group 2 included irritable bowel disease (IBS), coeliac and gall bladder disease, which may mimic CRC presentations and present diagnostic challenges. Patients were counted as having an IBD, diverticular, coeliac or gall bladder disease if they ever had a recording for one of these diseases, and IBS if they had a diagnosis prior to two years before diagnosis (due to possible misdiagnosis of IBS in the 2 years immediately before CRC diagnosis (17)). Group 3 included patients with haemorrhoids in the 5 years leading up to diagnosis, as these patients are likely to have had rectal bleeding but not referred on a fast-track pathway due to them being given an alternative non-malignant diagnosis. Code lists for all comorbidities are presented in Supplementary Table 3.

Based on previously reported associations with cancer, we analysed blood test results for platelets, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and haemoglobin (15,16,21). We chose to focus on the key blood tests in the literature, and in which we can make more reliable inferences due to their larger sample sizes. Cut-offs for normal values were taken from NICE guidelines (5) or the literature (14,15). Patients were regarded as having raised inflammatory markers if either CRP or ESR were abnormal. Reference ranges for each marker are described in Table 1.

We first described the rates of recordings for each clinical feature and abnormal blood test up to two years before diagnosis, as previous studies found differences in clinical activity between CRC patients and controls as early as 18 months pre-diagnosis (13). We constructed a series of 24 multi-level Poisson regression models to identify the most likely month (28-day period) when cohort-level rates of clinical feature recordings increased above baseline. Each model included a continuous month term, to account for any background trend, and a second “inflection month” variable to capture deviation from the background trend. This second variable was equal to the number of months between the specified inflection point for that model and the month of interest for months between the inflection point and diagnosis, and equal to zero otherwise. The month with the model corresponding to the largest log likelihood was selected and considered the best-fitting model, with confidence intervals for this month provided via bootstrapping. Adjustments were made in all models for age, gender, relevant comorbidity groups, and month pre-diagnosis. We considered colon and rectal cancer separately in the analysis because they can present differently (7).

All analysis was carried out in STATA/IC 16.1 (22), graphs were drawn using R and the *ggplot* package (23).

## Results

7,547 patients consisting of 5,031 (67%) with colon and 2,516 (33%) rectal cancer respectively, were included in the study. The proportions of baseline demographic characteristics by cancer site are shown in Table 2.

In the year pre-diagnosis, the most frequently recorded symptom was abdominal pain (25.9%) in colon cancer patients and rectal bleeding (32.2%) in rectal cancer patients (Table 3). The most frequent abnormal blood test result in the year pre-diagnosis was low haemoglobin in colon cancer patients (28.2%) and high inflammatory markers in rectal cancer patients (18.4%).

In both colon and rectal cancer there was an increasing rate of recordings for rectal bleeding, change in bowel habit, abdominal pain, other bowel function, abdominal mass and constitutional symptoms in the year before diagnosis. Similarly, the rate of recorded abnormal blood tests we examined - low haemoglobin, high inflammatory markers and platelets increased towards diagnosis during the same period (Figure 1).

In patients with colon cancer, rectal bleeding was the earliest clinical feature to increase from baseline at 10 months before diagnosis (95% CI 8.3-11.7). This was followed by change in bowel habit (8 months; 95% CI 6.8-9.2), abdominal pain (8 months; 95% CI 5.0-11.0) and constitutional symptoms (8 months; 95% CI 4.6-11.4), then abdominal mass (6 months; 95% CI 3.4-8.6) and other bowel function (3 months; 95% CI -0.3-6.3). Among the blood tests, rates of low haemoglobin and high inflammatory markers both increased from 9 months pre-diagnosis (low haemoglobin 95% CI 7.4-10.6, high inflammatory markers 95% CI 7.1-8.9). The rate of high platelets increased from 8 months (95% CI 6.0-10.0) pre-diagnosis.

In patients with rectal cancer, the earliest inflection point estimate was for other bowel function, albeit this estimate had a large confidence interval (10 months; 95% CI 1.5-18.5). This was followed by rectal bleeding (8 months; 95% CI 6.1-9.9), change in bowel habit and abdominal pain (7 months; 95% CI 5.5-8.5, and 6 months; 95% CI 3.0-9.0 pre-diagnosis respectively). Among blood tests, low haemoglobin and high platelets increased from baseline as early as 9 months pre-diagnosis (low haemoglobin 95% CI 5.0-13.0, high platelets 95% CI 6.5-11.5). We did not observe statistical evidence for an increase above baseline for constitutional symptoms (estimated inflection point 6 months pre-diagnosis, 95% CI -2.3-14.3). The number of observations for abdominal mass was too low to calculate an inflection point in rectal cancer patients.

## Discussion

### Summary

We found increasing rates of consultation for gastrointestinal alarm symptoms and abnormal test results among patients diagnosed with CRC in the year before diagnosis. Rates of rectal bleeding increased as early as 10 months pre-diagnosis in colon cancer patients, and 8 months pre-diagnosis in rectal cancer patients. Low haemoglobin and changes in non-specific blood tests including high inflammatory markers and platelets were found to increase as early as 9 months pre-diagnosis in patients with colon and rectal cancer. Our findings indicate that there may be opportunities to initiate specific cancer investigations or referrals sooner, and therefore expedite diagnosis and treatment in some CRC patients.

### Strengths and Limitations

The strength of this study includes using a large representative sample (24), and prospectively recorded electronic health records, which are not subject to recall or survivorship biases. Furthermore, results for the blood tests are automatically coded within CPRD when received from the laboratories, and are less likely to be subject to manual coding issues.

Despite having only cancer cases, our Poisson modelling allowed estimation of inflection points without data from non-cancer controls, and bootstrapping allowed estimation of 95% confidence intervals which are more informative than point estimates alone. Although we were unable to determine the clinical indications for the performance of these blood tests and whether the patients with alarm symptoms met fast-track referral guidelines, our analysis method, which includes the adjustment for relevant co-morbidities, allowed us to account for background rates of abnormal blood tests due to chronic disease monitoring or other existing conditions. Therefore, we believe our inflection points reflect new changes in rates of abnormal tests which may require further investigation or monitoring.

Coded data do not contain information about symptom severity or duration (25), and might be subject to clinician recording bias. A previous study using CPRD found that one third of all abdominal pain records were present as free text in patients with pancreatic or bladder cancer (26). Although these factors may contribute to under-estimation of symptom prevalence, our study focused on changes in rates of recordings over time, and therefore the results are less affected by the effect of underestimation.

We found no statistically significant effect of deprivation (based on individual-level Index of Multiple Deprivation) on the rate of pre-diagnostic clinical features (results not shown). We did not examine the effect of ethnicity due to the very small number of non-White patients with ethnicity recorded in our sample. Although not biasing the results of this study, this may limit the generalisability of the findings to other populations with different ethnicity mix. Lastly, it is important to note that our results only represent population level signals of change in clinical activity, and do not relate to associations seen at an individual level, including the predictive values of the clinical features.

### **Comparison with existing literature**

Similar to previous studies looking at patterns of pre-diagnostic activities in cancer patients in Denmark (13,27), we found increasing rates of consultation for relevant symptoms and abnormal tests in CRC patients in the year before diagnosis. Previous studies examined the overall number of consultations during the pre-diagnostic period. Our study enhanced existing evidence by examining consultation rates for relevant clinical symptoms, signs, and blood test results of patients with colorectal cancer. Our findings therefore improve the characterisation of symptomatic presentations of CRC patients prior to diagnosis. This increased granularity can help identify windows of opportunity for timely referral of patients presenting with alarm symptoms or prompt use of further triaging tests in patients with lower risk symptoms.

### **Implications for research and/or practice**

Existing studies suggest that diagnostic intervals longer than 3 months may be associated with worse survival in some cancer patients, including those with CRC (28). Other primary care studies examining pre-diagnostic activity in urological cancer patients also used 3 months as a conservative cut-off to examine the timeliness of diagnosis (29,30). We therefore consider below the implications of a time to diagnosis longer than 3 months following an abnormal blood test.

In our study, consultation rates for almost all examined clinical features (including gastrointestinal and constitutional symptoms, but excluding other bowel function symptoms) started increasing significantly earlier than 3 months pre-diagnosis in colon cancer patients, suggesting that, in at least some patients, opportunities exist for an earlier initiation of cancer-specific investigations. For example, the rates of rectal bleeding and change in bowel habit increased from 10 and 8 months pre-diagnosis respectively. Although it is possible that the increased diagnostic intervals were due to variations in the duration and intensity of symptom presentation which could not be fully captured by our study, it is likely that at least some patients with these two alarm symptoms would have qualified for a fast-track referral but did not receive one, resulting in the long diagnostic interval. This concurs with a recent study showing that GPs in England did not make timely expedited referrals for 82% of patients presenting with rectal bleeding (31). Other evidence also found that lack of knowledge of NICE referral criteria and concerns of over-referring contributed to the delayed referral of abnormal CRC clinical features (32).

The early increase in rates of consultation for abdominal pain at 8 months pre-diagnosis in colon cancer patients may reflect the diagnostic challenges posed by the symptom's low PPV for cancer (ie. a less specific symptom for cancer) (33). Our findings suggest that some patients with colorectal cancer who present with less cancer-specific symptoms or non-alarm symptoms may benefit from further investigations available in primary care, such as FIT, as early as 8 months before diagnosis. There is therefore considerable opportunity to initiate cancer-specific investigations sooner to rule out cancer.

In patients with rectal cancer, consultation rates for change in bowel habit, rectal bleeding and abdominal pain also increased significantly earlier than 3 months pre-diagnosis, suggesting that opportunities also exist for better triage of patients for further referral for definitive cancer investigations. Although patient- or system-level factors may also contribute to delays in diagnosis, it is unlikely that these factors will cause substantial delays once a referral (especially a fast-track referral) has been made.

Early increases in rates of all three examined blood tests were found in patients with both colon and rectal cancers. It is likely that further investigations using FIT could be useful in a significant proportion of patients who had low haemoglobin, which was reported as early as 9 months pre-diagnosis, in order to better identify those who would need further cancer investigations. Although high inflammatory markers and platelets are non-specific for cancer, the abnormality should prompt earlier investigative actions in at least a proportion of patients, especially in combination with other risk factors and abnormal clinical features or blood tests. It is worth noting that the predictive values of high inflammatory markers and platelets alone are not currently high enough to warrant a specialist referral under both the 2005 (in place at the time of our data collection) and 2015 NICE guidelines (14,34–36). Therefore, a thorough systems enquiry and examination may be indicated when inflammatory markers and platelets are unexpectedly raised, and subsequent cancer-specific investigations performed if indicated. Further research into the impact of the lowering of referral threshold in the 2015 NICE guidelines on diagnostic intervals are in progress and will shed more light on the effect of these guidelines on cancer diagnosis (37).

Our findings provide evidence for the existence of early signals of CRC-related symptoms and blood test abnormalities, which should prompt appropriate further investigations or safety-netting depending on the clinical context. Increasing GP awareness of the less cancer-specific symptoms and further characterisation of thresholds of abnormal blood tests (eg. High platelets) (34) may improve timely follow-up of symptoms and abnormal blood tests. The increased availability of FIT since our study period may also contribute to accelerations of cancer-specific investigations and referrals. Furthermore, the implementation of Rapid Diagnostic Centres has the potential to expedite diagnosis

of both cancer and non-cancer conditions in patients presenting with non-specific symptoms, and offer additional opportunities for reassurance and safety-netting (38).

### **Conclusion**

We found evidence for increasing rates of consultation for CRC-relevant symptoms and abnormal test results in the two years period prior to diagnosis. Our findings showed that long diagnostic intervals of 8-9 months followed many CRC-relevant clinical features and abnormal blood tests. It is likely that a proportion of people who present with alarm symptoms such as rectal bleeding, change in bowel habit and anaemia will benefit from more timely referrals for further investigations, and that windows of opportunity exist for earlier use of tests such as FIT for triaging patients for referral in those presenting with less specific symptoms and signs. Our study demonstrated that there is scope to optimise timely referral for definitive diagnosis in symptomatic patients with colorectal cancer.

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Table 1: Blood markers included in this study and thresholds

Marker	Threshold (Source)
Haemoglobin	<110 g/L for men, <100 g/L for women (5)
Platelets	>400x10 <sup>9</sup> /L (5)
CRP	>7mg/L (15)
ESR	Previously defined age- and sex-specific thresholds (15).

Table 2: Population demographic characteristics, by diagnosis

	Cancer diagnosis					
	Colon		Rectal		Total	
	No.	%	No.	%	No.	%
<b>Total</b>	5033	100	2516	100	7549	100
<b>Sex</b>						
Male	2624	52.1	1561	62	4185	55.4
Female	2409	47.9	955	38	3364	44.6
<b>Age group</b>	No.	%	No.	%	No.	%
25-59	849	16.9	578	23	1427	18.9
60-69	1200	23.8	721	28.7	1921	25.4
70-79	1533	30.5	729	29	2662	25.7
80+	1451	28.8	488	19.4	1939	25.7
<b>Relevant comorbidities</b>						
Group 1: IBD* and diverticular disease	926	18.4	341	13.6	1,267	16.8
Group 2: IBS <sup>^</sup> , coeliac and gall bladder disease	316	6.3	102	4.2	418	5.5
Group 3: haemorrhoids	615	12.2	226	9	841	11.1

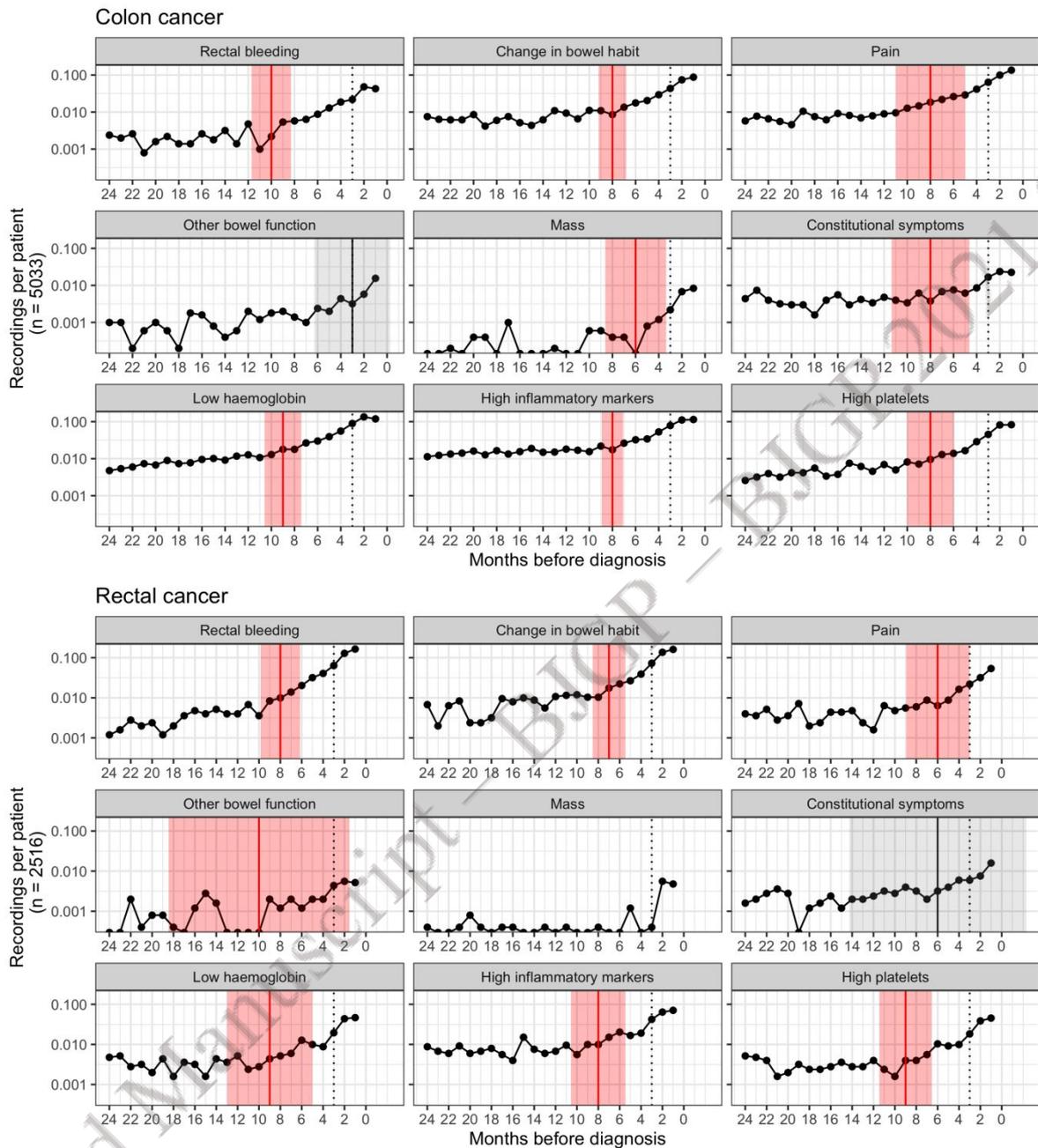
\*IBD: inflammatory bowel disease

<sup>^</sup>IBS: irritable bowel syndrome

Table 3: Prevalence of clinical feature recordings in each pre-diagnostic period

Clinical features for each pre-diagnostic period		Cancer diagnosis					
		Colon		Rectal		Total	
		No.	%	No.	%	No.	%
Abdominal pain	0-1 year	1305	25.9	271	10.8	1576	20.9
	1-2 years	262	5.2	72	2.9	334	4.4
Change in bowel habit	0-1 year	1091	21.7	787	31.3	1878	24.9
	1-2 years	236	4.7	117	4.7	353	4.7
Rectal bleeding	0-1 year	584	11.6	810	32.2	1394	18.5
	1-2 years	82	1.6	63	2.5	145	1.9
Constitutional symptoms	0-1 year	436	8.7	123	4.9	559	7.4
	1-2 years	170	3.4	47	1.9	217	2.9
Other bowel function	0-1 year	165	3.3	57	2.3	222	2.9
	1-2 years	41	0.8	17	0.7	58	0.8
Mass	0-1 year	83	1.6	21	0.8	104	1.4
	1-2 years	7	0.1	5	0.2	12	0.2
<b>Abnormal blood tests</b>							
Low haemoglobin	0-1 year	1417	28.2	231	9.2	1648	21.8
	1-2 years	213	4.2	55	2.2	268	3.6
High inflammatory markers	0-1 year	1392	27.7	463	18.4	1855	24.6
	1-2 years	367	7.3	127	5	494	6.5
High platelets	0-1 year	932	18.5	244	9.7	1176	15.6
	1-2 years	142	2.8	52	2.1	194	2.6

Figure 1: Rates of recordings of each clinical feature in the two years leading up to diagnosis, by cancer diagnosis



Full line indicates the most likely inflection point, shaded area represents 95% confidence interval (red when confidence interval excludes 0, grey otherwise). Dotted line represents 3 months before diagnosis. Inflection points are estimated in models adjusted for age, sex and comorbidities. Months represent 28 day periods.

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**Ethical approval**

A research protocol (17\_107R) was submitted to and approved by the CPRD Independent Scientific Advisory Committee before the study was conducted. This study is a secondary analysis of anonymised patient data.

**Competing interests**

All authors declare no competing interests.

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