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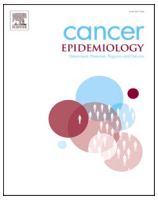

Stage-specific risk of colon and rectal cancer in patients presenting with rectal bleeding or change in bowel habit in primary care: A population-based cohort study

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ABSTRACT

Introduction: Rectal bleeding and change in bowel habit are red-flag symptoms for colon and rectal cancer but how they relate to advanced stage disease is not adequately understood.

Methods: We analysed primary care electronic health records data on patients aged 30–99 years. Using logistic regression, we first examined the risk of colon and rectal cancer within 12 months in patients presenting with change in bowel habit and rectal bleeding, and then the risk of advanced stage at diagnosis within cancer cases. We combined the results to estimate risk of advanced stage colon and rectal cancers at diagnosis.

Results: For both symptoms and sexes, risk of cancer (overall and by stage) increased with increasing age. We illustrate the findings for persons at the highest age-specific observed risk (typically aged around 80). In men, change in bowel habit (CIBH) and rectal bleeding were associated with different risk of advanced stage colon and rectal cancers (e.g., for colon, CIBH = 2.7% (95% CI 2.2–3.1) and rectal bleeding = 1.7% (95% CI 1.4–2.0)), but without evidence of risk difference between the two symptoms for non-advanced disease. The opposite pattern was apparent in women, with both symptoms associated with similar risk of advanced disease, but different risk of non-advanced colon and rectal cancers (e.g., for colon, CIBH = 1.0% (95% CI 0.8–1.3) and rectal bleeding = 1.3% (95% CI 1.1–1.6)).

Discussion: Change in bowel habit and rectal bleeding have different age-specific associations with advanced stage disease, which vary by sex. A substantial proportion of cases is diagnosed at non-advanced stage, supporting the need for prompt diagnostic assessment of patients who present with those symptoms, taking into account the age-specific nature of risks.

1. Introduction

Although early diagnosis of symptomatic patients has been widely endorsed as a strategy for improving cancer outcomes, symptomatic presentations may reflect advanced-stage cancer [1,2]. Since 2006, several studies have used information from electronic health records to estimate the risk of underlying cancer in patients with new onset symptoms; such evidence has supported the publication of the 2015 NICE clinical guideline 'Suspected Cancer in Primary Care' [3]. With few notable exceptions, this evidence relates to overall cancer risk, without considering disease stage at diagnosis [4,5].

Prior case-only analysis has demonstrated substantial variation between presenting symptoms in the proportion of patients with cancer diagnosed at advanced stage [6]. Given the generally low predictive value of presenting symptoms for cancer, assessing stage-specific risk of cancer requires extending this prior enquiry to the broader population of patients presenting with symptoms, whether or not cancer was subsequently diagnosed. In this study we attempt such an analysis focusing on two relatively common 'alarm' or 'red-flag' symptoms of colon and rectal cancer, rectal bleeding and change in bowel habit (CIBH) [3].

We examined age-sex-specific associations between these two symptomatic presentations and three outcomes. The absolute risk of colon and rectal cancer; the risk of advanced stage diagnosis of either cancer, conditional on cancer being diagnosed; and finally, the absolute

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risk of advanced stage colon and rectal cancer associated with either presenting symptom.

2. Methods

2.1. Data and study population

We analysed data on (1) patients presenting with CIBH or rectal bleeding, to estimate their associations with colon and rectal cancer; and (2) patients with colon or rectal cancer, to estimate associations between the two studied symptoms and stage at diagnosis.

The two symptom cohorts comprised patients aged 30–99 years in Clinical Practice Research Datalink (CPRD) Gold [7] presenting in primary care with rectal bleeding or CIBH between 1st January 2007 and 31st December 2017, linked to the national cancer registry in England for information on cancer diagnoses [8] (see Fig. 1a for inclusion and

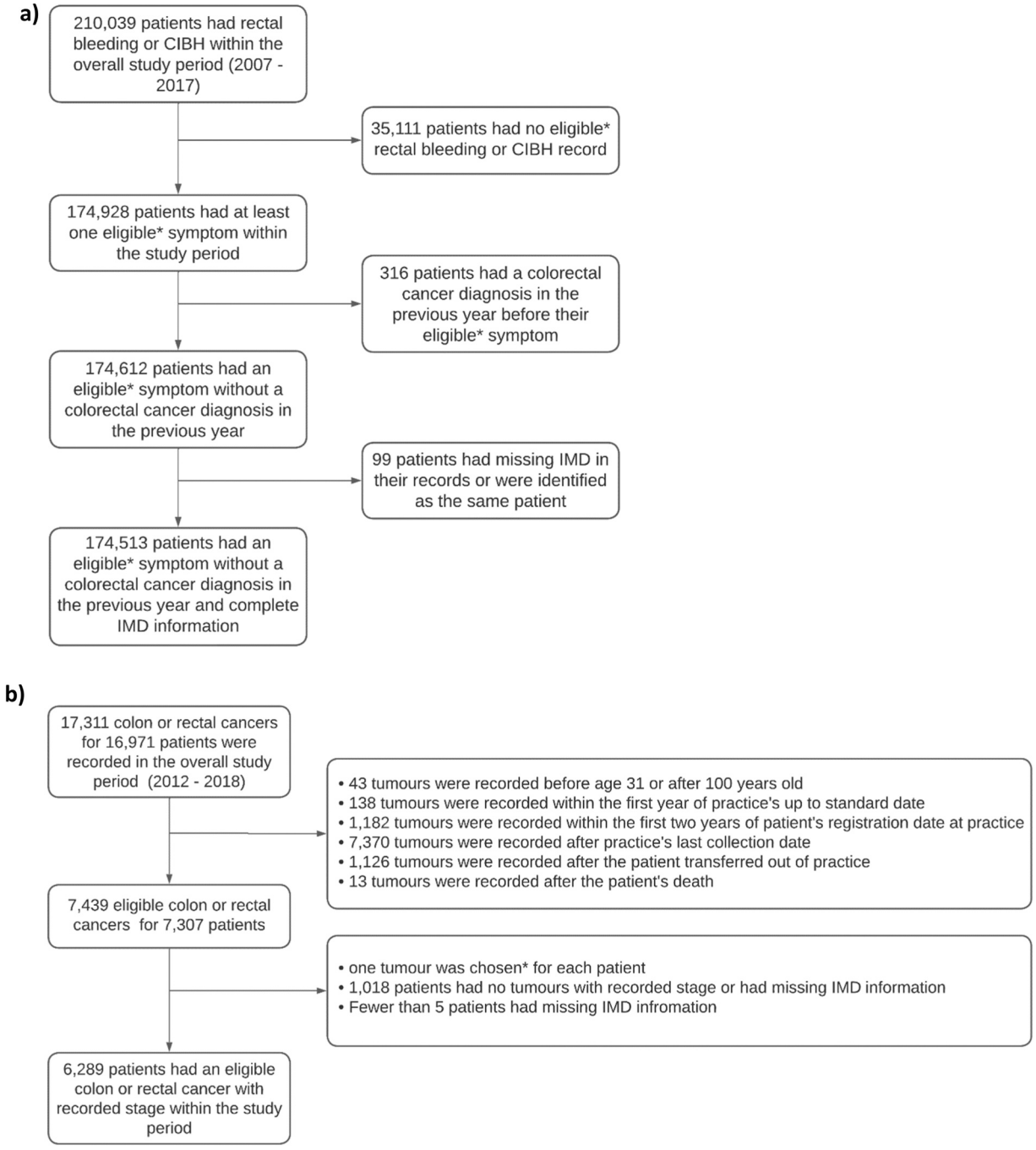

Fig. 1. (a) Symptom cohorts. *Symptom consultations were only eligible if the patient was aged 30–99 years old (due to database limitations) and met standard CPRD quality criteria; namely, the consultation happened after the patient had been registered at the practice for at least one year, the practice was viewed as up-to-standard by CPRD, and the consultation was recorded before the patient's transfer out date or death and before the practice's last data collection date. The patient must not have had a colorectal cancer diagnosis in the year prior to the symptom consultation. Patients could have had several consultations with the studied symptoms during the study period, and where applicable a specific index symptom was chosen at random for use in analysis for each patient. (b) Cancer cases. Cases were aged 31–99 and had at least a year of follow-up within the standard CPRD quality criteria (described in (a)) at the time of their cancer diagnosis. *If patients had two or more cancer diagnoses, then the cancer with either of the two studied symptoms was selected and where this left more than one cancer, one was chosen at random.

exclusion criteria).

The outcome was the earliest of colon (ICD-10: C18-C19) or rectal cancer (C20) diagnosis within 12 months following the index symptom. Where two or more colon or rectal cancers were recorded on the same date, then the cancer with the highest stage was chosen or randomly if not applicable.

Colon and rectal cancer patients were nested either within cohorts of patients presenting with one of 22 selected symptoms of possible cancer (Appendix 1), or within a random sample of 1 M individuals registered with CPRD during 2012–2018. After applying inclusion and exclusion criteria (see below), the two subgroups comprised 4537 and 1752 cases, respectively, with highly similar patient and tumour characteristics (Table A.1).

Cases were diagnosed between 2012 and 2018. The choice of the start of the study period for the cancer stage cohort was guided by 2012 being the first year in which more than 80% of colorectal cancer registrations had complete stage information. Cancer cases had a minimum age of 31 to be able to have a 1-year look back period up to 30 years old, consistent with the symptom cohort. Inclusion and exclusion criteria are described in Fig. 1b.

We defined three groups within cancer cases: those who consulted for CIBH in the year before diagnosis; those who consulted for rectal bleeding; and those who did not consult for either symptom. Few patients (0.6%) consulted for both CIBH and rectal bleeding, and this group was not examined separately in the analysis.

The outcome for the analysis of the cancer patients was stage at diagnosis, dichotomised into advanced (TNM stages III & IV) and non-advanced (stages I & II). Cancers with unknown stage (after earlier exclusions, comprising 14% of the eligible for analysis sample, Fig. 1b) were excluded from analysis; the proportion with missing stage was greater in patients over-70 (17%) versus those aged 25–69 (9%) (Fig. A1).

2.2. Analysis

A three-step approach was used: we first modelled the risk of colon and rectal cancer of any stage; then modelled the proportion of colon and rectal cancer diagnosed at advanced stage; and subsequently combined the two analyses to estimate risk of cancer diagnosed at an advanced (or non-advanced) stage. This approach was intended to maximise the sample of cancer cases with complete stage information; within our symptom cohort, 45% of cancers diagnosed had missing stage information. We maximised the sample of cancer cases with complete stage information by identifying all colon and rectal cancers in years of high-stage completeness (beyond 2012) regardless of whether the patients presented with rectal bleeding and/or CIBH in the year prior to their diagnosis. Adding patients without either symptom increased the sample size enabling the modelling of the effect of age on the proportion of colon and rectal cancer diagnosed at advanced stage, under the assumption that the age-effect does not vary by symptom.

2.2.1. Risk of colon and rectal cancer

Among patients presenting with CIBH and rectal bleeding, we examined the risk of colon and rectal cancer diagnosis in the subsequent 12 months. The analysis used sex-stratified logistic regression models with robust standard errors to estimate risk of colon and rectal cancer separately, including age (parameterised using a natural cubic spline with knots at 40, 60, 70 and 80 years), and the index symptom (rectal bleeding or change in bowel habit) as covariates. Models were used to predict the age-sex-specific probabilities of being diagnosed with colon or rectal cancer (separately) for patients presenting with each symptom.

2.2.2. Proportion of colon and rectal cancer diagnosed at advanced stage

Among cases, we described the proportion of colon and rectal cancers diagnosed at advanced stage, for either index symptom. The analysis used sex-stratified logistic regression models with robust standard errors for colon and rectal cancers separately, limiting to cancers with known stage, and including age (parameterised using a natural cubic spline with one knot at age 60), presence of rectal bleeding and presence of change in bowel habit as covariates. These models were used to predict the age-sex-specific proportion of cancer diagnosed at advanced and non-advanced and stage after presentation with each index symptom. The results were compared to the proportion of all colon and rectal cancers diagnosed at advanced stage in England (2018–2019) provided by the National Disease Registration Service (NDRS).

2.2.3. Risk of cancer diagnosed at advanced stage

The risk of advanced and non-advanced cancer in patients presenting with rectal bleeding or change in bowel habit in primary care was estimated by multiplying the estimated cancer risk by the estimated proportions of cancers diagnosed at advanced and non-advanced stage. Bootstrapping, with 10,000 repetitions, was used to produce confidence intervals.

2.2.4. Supplementary analysis

The analysis of the proportion of cancer cases diagnosed at advanced stage was additionally estimated when

(1) Screen detected cancers were excluded, based on their diagnosis route.
(2) Advanced stage was defined to be TNM stage IV and non-advanced stage to be stages I-III.

Data management was conducted in MySQL Workbench version 6.1 and statistical analysis in R version 4.1.2. Analysis made use of the following R packages: tidyverse version 2.0.0 [9] and marginaleffects version 0.7.0 [10].

3. Results

3.1. Risk of cancer after symptomatic presentation

There were 122,225 rectal bleeding presenters, of whom 1285 (1.1%) were diagnosed with colon and 1293 (1.1%) with rectal cancer in the 12 months post-presentation (Fig. 1a, Table 1); 52,288 CIBH presenters, of whom 751 (1.4%) were diagnosed with colon and 615 (1.2%) with rectal cancer. For both rectal bleeding and CIBH, cancer risk was

Table 1
Characteristics of patients who presented with rectal bleeding or change in bowel habit to primary care and percentage developing colon or rectal cancer by variable category.

	N	Colon cancer within 12 months	Rectal cancer within 12 months
Gender			
Men	84,147	1141 (1.36%)	1229 (1.46%)
Women	90,366	895 (0.99%)	679 (0.75%)
Age			
< 50	55,201	90 (0.16%)	133 (0.24%)
50–59	34,558	266 (0.77%)	307 (0.89%)
60–69	34,653	488 (1.41%)	484 (1.40%)
70–79	29,092	675 (2.32%)	608 (2.09%)
80 +	21,009	517 (2.46%)	376 (1.79%)
IMD (2015)			
1 – Least	44,860	549 (1.22%)	497 (1.11%)
2	39,292	475 (1.21%)	433 (1.10%)
3	36,859	405 (1.10%)	413 (1.12%)
4	29,661	357 (1.20%)	334 (1.13%)
5 – Most	23,841	250 (1.05%)	231 (0.97%)
Index Symptom			
Rectal bleeding	122,225	1285 (1.05%)	1293 (1.06%)
Change in bowel habit	52,288	751 (1.44%)	615 (1.18%)
Total	174,513	2036 (1.17%)	1908 (1.09%)

higher in men and older individuals (Fig. 2, Table A.2). Across ages, cancer risk was slightly higher following CIBH than rectal bleeding in men, but the opposite was true in women (Fig. 2, Table 2). For both symptoms, the highest risk of either colon or rectal cancer was observed at approximately 80 years of age: in patients aged 80 presenting with rectal bleeding, colon cancer risk was 3.6% (95% CI 3.1–4.1) in men (2.5% (95% CI 2.1–2.9) in women), and rectal cancer risk was 3.3% (95% CI 2.8–3.8) in men (1.5% (95% CI 1.2–1.9) in women); and in those presenting with CIBH, colon cancer risk was 4.3% (95% CI 3.7–5.0) in men (2.1% (95% CI 1.8–2.4) in women), and rectal cancer risk was 3.5% (95% CI 3.0–4.0) in men (0.96% (95% CI 0.8–1.2) in women).

Table 2
Odds ratios of symptoms from cancer incidence logistic regression model (also adjusted for age, data not shown).

Symptom	Colon Cancer		Rectal Cancer	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Men				
Rectal Bleeding	Reference	–	Reference	–
Change in Bowel Habit	1.21 (1.07, 1.37)	< 0.01	1.07 (0.95, 1.20)	0.29
Women				
Rectal Bleeding	Reference		Reference	
Change in Bowel Habit	0.85 (0.74, 0.98)	0.02	0.62 (0.53, 0.74)	< 0.01

3.2. Stage at diagnosis among cancer cases

Among 4539 patients with colon and 1750 with rectal cancer, 2484 (54.7%) and 969 (55.4%) were diagnosed at advanced stage, respectively (Fig. 1b, Fig. 3). In the year pre-diagnosis, among colon cancer patients, 10.9% had presented with rectal bleeding and 6.8% with change in bowel habit. Among rectal cancer patients, 33.3% had presented with rectal bleeding and 14.9% with change in bowel habit. Except for colon cancer in women where no such association was apparent, younger age was associated with higher risk of advanced stage at diagnosis of colon cancer in men and of rectal cancer in both men and women (Fig. 4, Table A.3). Age-stage associations were consistent with those observed in population-based data for colon and rectal cancer in men, and for rectal cancer in women (Figure A.2). For both cancers and across ages, advanced stage was less frequent with rectal bleeding than change in bowel habit, particularly in women with rectal cancer (Fig. 4, Table 3, Table A.3). For example, in patients with rectal cancer aged 60, 56% (95% CI: 50–62) of men and 45% (95% CI: 38–53) of women who consulted for rectal bleeding pre-diagnosis had advanced stage, vs 66% (95% CI: 58–73) of men and 62% (95% CI: 50–73) of women who consulted for change in bowel habit.

3.3. Risk of advanced stage at diagnosis among symptom presenters

The risk of advanced stage diagnosis increased with age in both men and women (Fig. 5, Table A.4). In men, across ages, the risk of advanced stage cancer was higher after CIBH compared to rectal bleeding presentation, without apparent risk differences by presenting symptom in

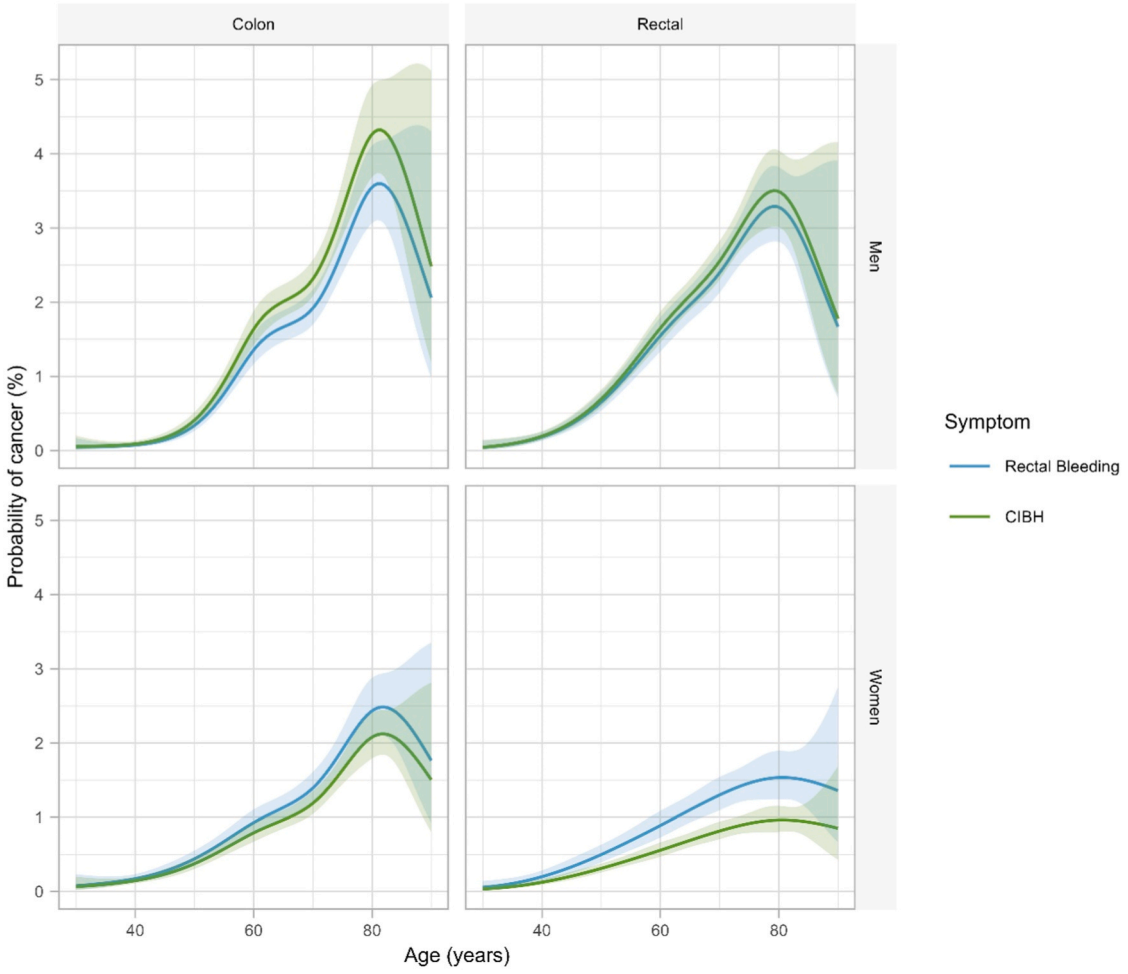

Fig. 2. Risk of colon and rectal cancers, in men and women, twelve months after rectal bleeding or change in bowel habit presentation in primary care.

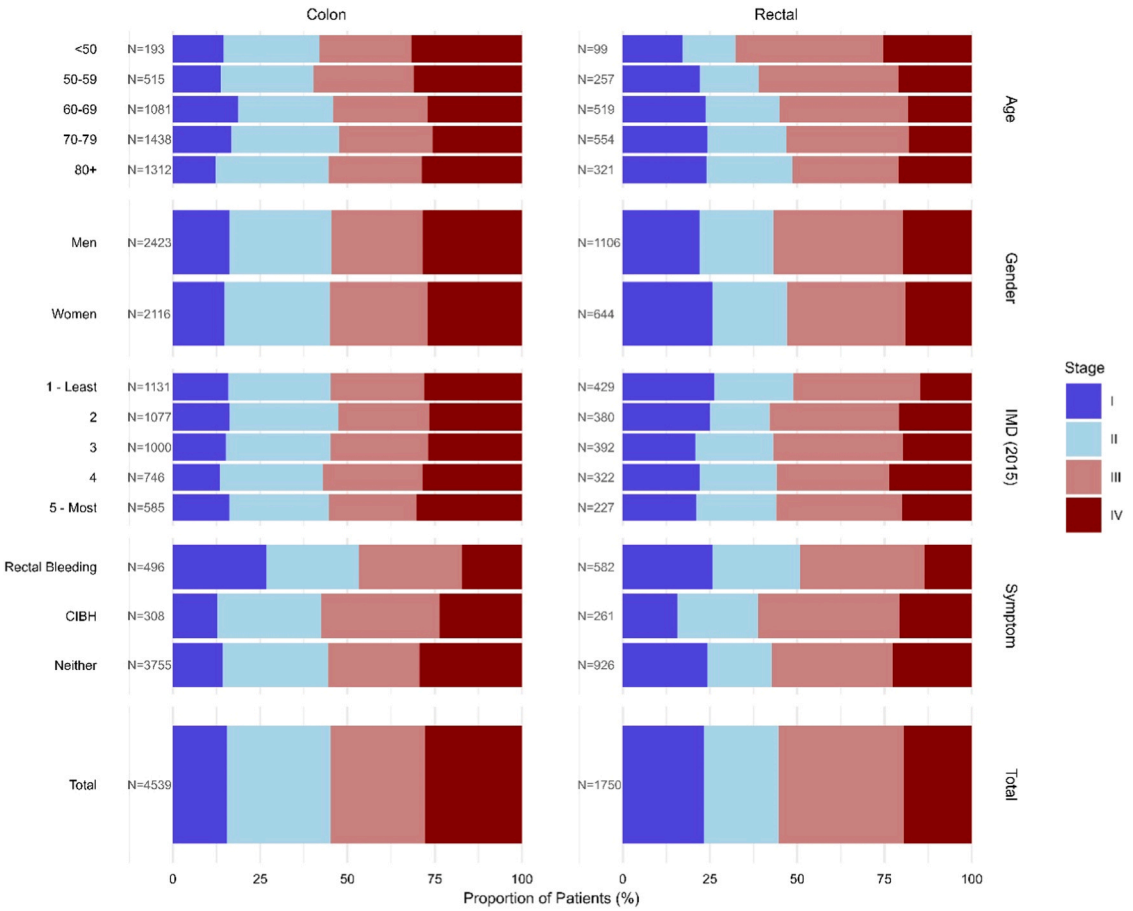

Fig. 3. Stage at diagnosis category by patient characteristic among patients with colon or rectal cancer.

women. The highest risk of advanced stage cancer was in men presenting with CIBH, being 2.7% (95% CI: 2.2–3.1) for advanced stage colon cancer at age 82 and 2.1% (95% CI: 1.7–2.5) for advanced stage rectal cancer at age 79.

The risk of non-advanced stage colon and rectal cancers was generally higher for patients presenting with rectal bleeding, particularly risk of non-advanced rectal cancer in women (Fig. 6, Table A.4).

3.4. Supplementary analysis

695 (11.1%) of all cancers were detected via screening and were excluded. This resulted in 4063 patients with colon cancer (2318, 57.1% at advanced stage) and 1531 with rectal cancer (863, 53.9% at advanced stage). In the year pre-diagnosis, among colon cancer patients, 12.0% had presented with rectal bleeding, 7.5% with change in bowel habit. Among rectal cancer patients, 37.3% had presented with rectal bleeding and 16.6% with change in bowel habit. After excluding screen-detected cancers, the proportion of cancers diagnosed at advanced stage slightly increased compared to the main analysis, especially for screening age individuals (50–70 years old) (Figure A.3). Defining advanced stage as IV vs I-III reduced the proportion of cancers diagnosed at advanced stage compared to the main analysis (Stage III-IV vs I-II) (Figure A.4). There was also a change in the association between age and stage in women with rectal cancer, where risk of advanced stage increased with age (vs decreased risk of stages III-IV with increasing age, in main analysis).

4. Discussion

4.1. Summary

We report age and sex-specific absolute risks of advanced and non-advanced colon and rectal cancer in the year following primary care consultations with rectal bleeding or CIBH. The associations between age and cancer risk varied by sex, symptom and cancer site. The risk of colon and rectal cancer, across stage categories, increased with age, and among patients diagnosed with cancer, the proportion with advanced stage decreased with age. Yet, the increase in incidence was larger than the decrease in proportion with advanced stage, and so older patients presenting with rectal bleeding or CIBH were at higher risk of advanced stage cancer than younger patients.

Risk of advanced stage colon and rectal cancer in men was higher following CIBH than it was following rectal bleeding, while there was minimal evidence of difference in risk of non-advanced disease. Women presenting with rectal bleeding and CIBH had similar risk of advanced stage disease, but those presenting with rectal bleeding had higher risk of non-advanced colon and rectal cancers than those presenting with CIBH.

4.2. Comparisons with literature

Our study concords with prior evidence on associations between CIBH and rectal bleeding presentations and colon and rectal cancer risk, and substantially enriches the sparse evidence characterising associations between symptoms and stage at diagnosis.

Most current literature on the predictive value for cancer of CIBH or rectal bleeding does not consider associations with specific stage

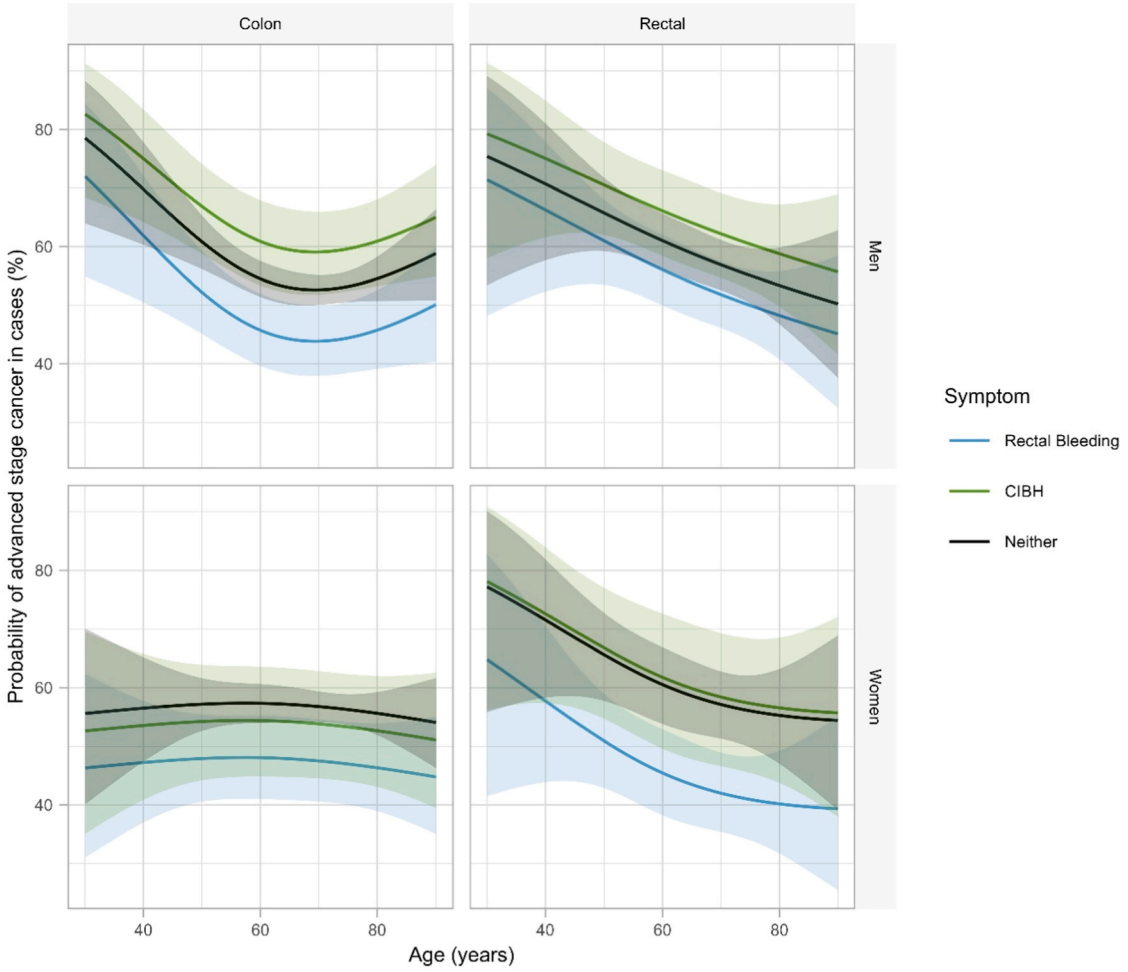

Fig. 4. Risk of having advanced stage cancer in men and women with colon and rectal cancers a year after presenting with rectal bleeding or change in bowel habit or neither.

Table 3
Odds ratios of advanced stage at diagnosis of cancer from logistic regression model (also adjusted for age, data not shown). Reference group were patients without either rectal bleeding or change in bowel habit.

Symptom	Colon Cancer		Rectal Cancer	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Men				
Rectal Bleeding	0.70 (0.55, 0.90)	< 0.01	0.81 (0.63, 1.06)	0.13
Change in Bowel Habit	1.30 (0.96, 1.76)	0.09	1.25 (0.90, 1.74)	0.20
Women				
Rectal Bleeding	0.69 (0.52, 0.92)	0.01	0.54 (0.39, 0.76)	< 0.01
Change in Bowel Habit	0.89 (0.61, 1.29)	0.53	1.05 (0.64, 1.76)	0.84

categories nor the absolute risk of stage-specific cancer. Consistent with previous studies, we have found that cancer risk is greater in men than in women and increases substantially with increasing age, but we provide considerable additional evidence on profiling the age- and sex-specific nature of risk [11–14].

Evidence relating to associations between symptoms and stage at diagnosis is sparse, and thus far limited to characterisation of associations of different presenting symptoms (including CIBH and rectal bleeding) with non-advanced disease [4,15,16]. However, prior evidence did not profile associations between presenting symptoms and advanced stage diagnosis of colon or rectal cancer, which is important for understanding the partitioning of overall predictive values into relevant components of risk.

A prior case-only analysis reported that among patients diagnosed with cancer, the proportion of patients with stage IV disease was 16% and 29% among those presenting with rectal bleeding and CIBH, respectively [6]; this concords with the gradient of risk observed in our study, which has additionally quantified risk among patients presenting with these symptoms. Further, the results of the SYMPLIFY study show that slightly more than half (78/143) of patients diagnosed with any cancer following referral down the lower gastrointestinal pathway had advanced stage disease, in keeping with the results of our study [17].

4.3. Strengths and limitations

The study's strength is its large size and use of patient cohort that is broadly representative of patients attending primary care in the UK. The weaknesses largely arise from use of electronic health record and registry datasets, primarily relating to missing data and accuracy of data recording. Missing stage at diagnosis, especially before 2012, motivated the use of a three-step analysis that should be more robust against missing stage information. But the exclusion of the relatively small proportion of patients from after 2012 who had missing stage may lead to an underestimation of risk of advanced stage cancer in groups with the most missing stage information, particularly older ages (Fig. A1) [18,19]. A proportion of patients may have presented with the study symptoms without this being recorded. Prior research indicates that

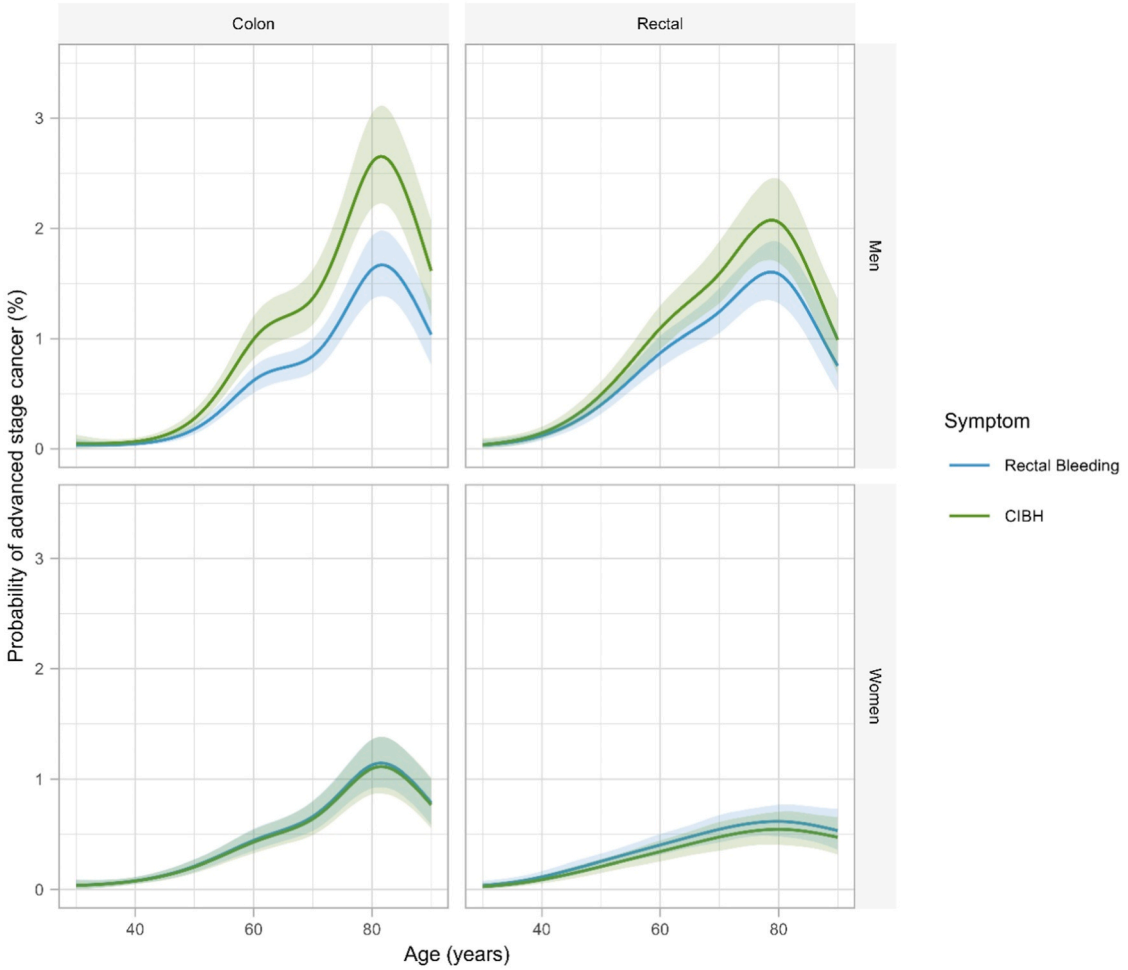

Fig. 5. Risk of advanced stage colon and rectal cancers, in men and women, a year after rectal bleeding or change in bowel habit. Noting little difference in advanced stage diagnosis risk by either symptom in women, though a preponderance of advanced stage risk in patients who presented with CIBH in men.

code entry for patients with known alarm symptoms (such as those studied here) tends to have high completeness [20]. The inclusion of patients drawn from other symptom cohorts in the analysis of the stage distribution of colon and rectal cancer (potentially leading to over-representation of patients with other less common symptoms of colorectal cancer) may have led to results being unrepresentative, but in practice the stage profile appeared similar to that of England as a whole (Figure A.2).

The findings need to be interpreted in the context of the study era and country (health system) setting. If, hypothetically, the same cohort of patients had experienced longer intervals to presentation or diagnosis, the stage-symptom association would have been expected to shift towards more advanced. The findings may therefore not be fully generalisable to other country populations and study periods.

As this was a descriptive, not aetiological, analysis, we present the age and stage-specific cancer risk estimates of each of the studied symptoms separately without further consideration of the exact link between the symptom and the cancer. Further research assessing reasons for the observed symptom-cancer associations would be of value.

4.4. *Interpretation and implications*

Our findings have implications for policy and research.

Despite both symptoms being more strongly associated with advanced stage at diagnosis in some patients, large proportions are diagnosed at non-advanced stage. These findings provide support for early diagnosis interventions aiming to raise awareness and support help-seeking for patients with CIBH and rectal bleeding, countering concerns that they might be simply expediting the detection of advanced stage disease. The findings also provide support for clinical guidelines supporting the referral of those patients for urgent assessment of cancer risk. However, the cost-effectiveness of these policies will vary by stage at diagnosis, given substantially different management options required for patients diagnosed at different disease stage; our study provides the empirical evidence to guide such health economics assessment.

While we have only considered two presenting symptoms relating to two specific cancer sites, the methods used can be generalised to the enquiry of other symptoms. A requirement for such analysis is high completeness of stage at diagnosis information.

The findings regarding the sex-specificity of associations between the two symptoms and stage at diagnosis are notable. Prior work has indicated that the stage distribution of colon and rectal cancer (among patients with any presenting symptom) varies little between the sexes [19]. We find that this overall null association varies when examining specific sub-cohorts of patients presenting with specific symptoms. Whether these differences relate to biological differences between the two sexes, or different appreciation and help-seeking of the two symptoms by men and women should be examined by future research. Men with either rectal bleeding or CIBH have greater risk of diagnosis at an advanced stage compared to women with the same symptoms for both studied cancers. This may indicate an opportunity for targeting men in public health education interventions aimed at increasing awareness and facilitating help-seeking for these symptoms. Similarly, among men, the findings also indicate a greater need for raising awareness of the

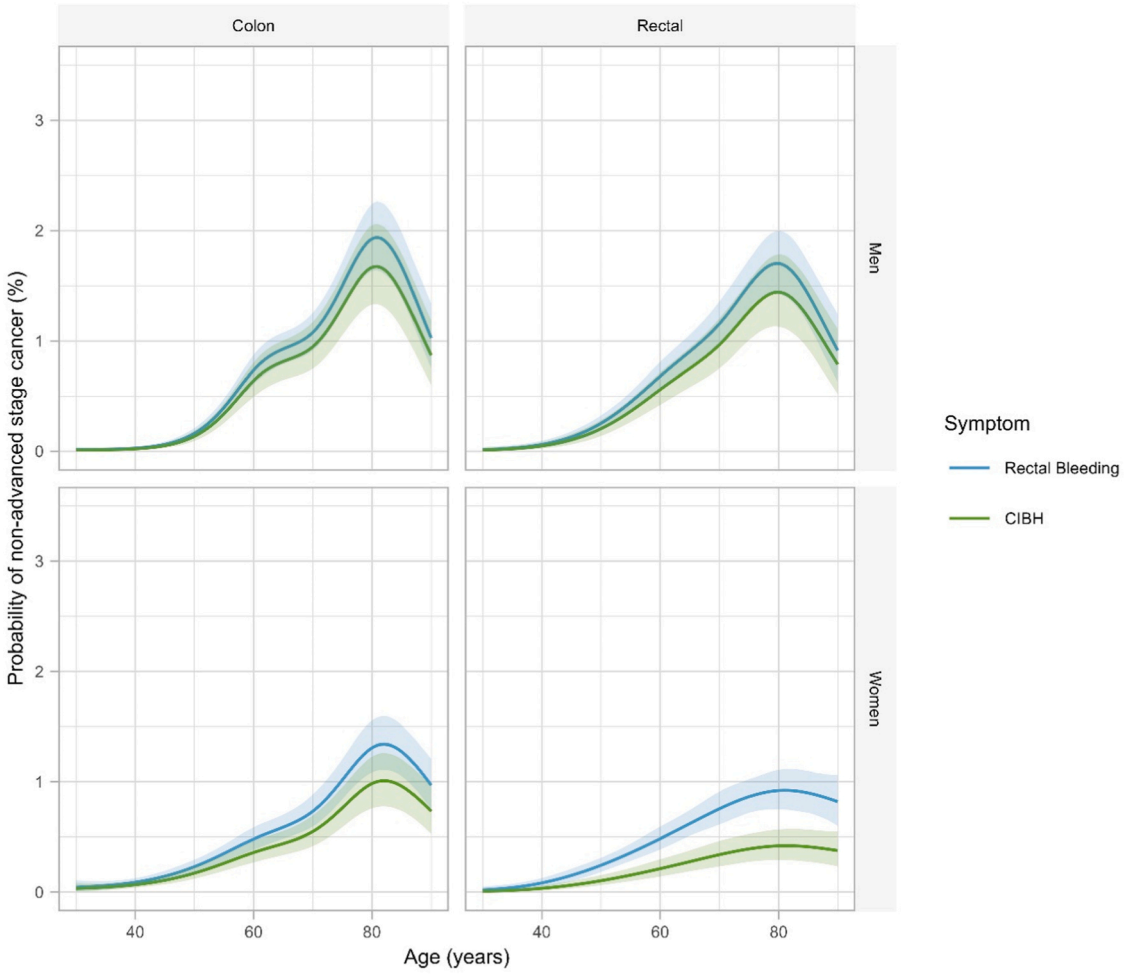

Fig. 6. Risk of non-advanced stage colon and rectal cancers, in men and women, a year after rectal bleeding or change in bowel habit. Noting that rectal bleeding is generally associated with higher risk of non-advanced disease across sex-cancer site strata, particularly in women with rectal cancer.

importance of change in bowel habit over rectal bleeding.

5. Conclusion

Red flag symptoms for colorectal cancer are highly predictive of presence of cancer, especially in older patients, but have limited association with stage at diagnosis. The findings support ongoing efforts to maintain public awareness of these symptoms and guideline recommendations urging their prompt investigation.

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CRediT authorship contribution statement

N. Zakkak: Data curation, Formal analysis, Visualization, Writing - original draft. **G. Lyratzopoulos:** Supervision, Resources, Writing – review & editing. **M. Barclay:** Conceptualization, Methodology, Writing – review & editing.

Declaration of Competing Interest

MB receives personal fees from GRAIL Inc, for Independent Data Monitoring Committee (IDMC) membership unrelated to this study.

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Appendix

Appendix 1: List of the symptom-defined cohorts used in deriving cancer cases (symptomatic sub-cohorts): Abdominal pain, abdominal bloating, breast lump, change in bowel habit, dyspepsia, dysphagia, dyspnoea, fatigue, haematuria, haemoptysis, jaundice, night sweats, post-menopausal bleeding, rectal bleeding, weight loss, abdominal mass or intestinal obstruction, constipation, cough, diarrhoea, pelvic pain, stomach disorders and urinary tract infections.

Table A.1
Comparison of sample composition by cohort origin (random sample vs. any of the 22 symptom cohorts).

		Cancer cases nested within random sample	Cancer cases nested within symptom cohorts	p-value
Age	Median (IQR)	72.1 (16.5)	72.6 (16.4)	0.880*
Gender	Men	981 (56.0%)	2548 (56.2%)	0.927+
	Women	771 (44.0%)	1989 (43.8%)	
IMD (2015)	1 - Least	417 (23.8%)	1143 (25.2%)	0.300+
	2	398 (22.7%)	1059 (23.3%)	
	3	417 (23.8%)	975 (21.5%)	
	4	288 (16.4%)	780 (17.2%)	
	5 - Most	232 (13.2%)	580 (12.8%)	
Cancer site	Colon	1259 (71.9%)	3280 (72.3%)	0.755+
	Rectal	493 (28.1%)	1257 (27.7%)	
Advanced stage		966 (55.1%)	2487 (54.8%)	0.841+
Emergency presentation		350 (20.0%)	930 (20.5%)	0.671+
Total		1752	4537	

*Wilcoxon-rank sum test
+Chi-squared test

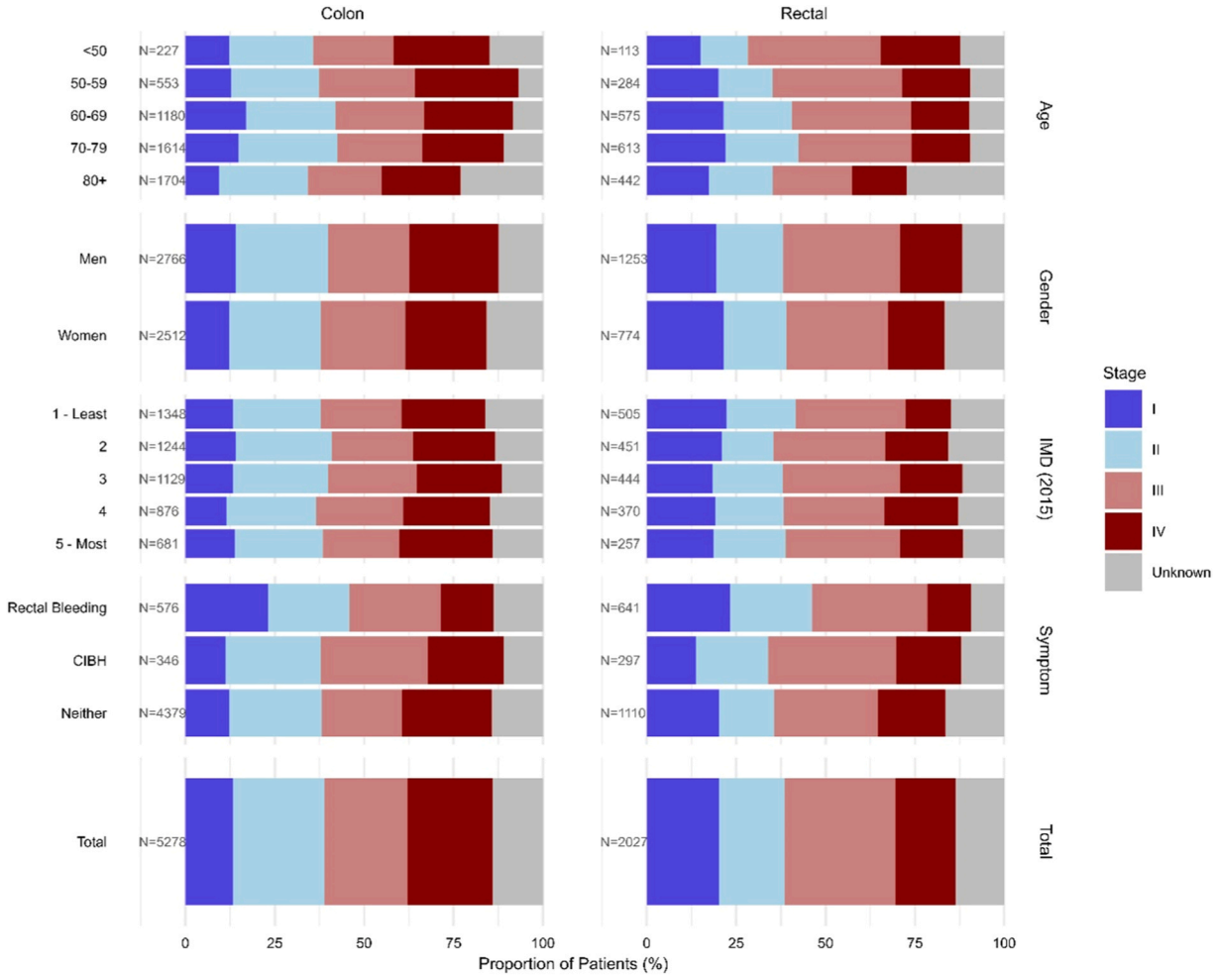

Fig. A1. Stage at diagnosis category by patient characteristic among patients with colon or rectal cancer, including cancers with missing stage.

Table A.2
Risk of colon and rectal cancers, in men and women, twelve months after rectal bleeding or change in bowel habit presentation in primary care at ages 40, 60 and 80 years old.

	Cancer site	Symptom	Probability of cancer % (95% CI)		
			Age 40	Age 60	Age 80
Men					
	Colon	Rectal Bleeding	0.08 (0.05, 0.11)	1.38 (1.19, 1.61)	3.57 (3.08, 4.13)
		CIBH	0.09 (0.06, 0.14)	1.67 (1.45, 1.92)	4.29 (3.71, 4.95)
	Rectal	Rectal Bleeding	0.19 (0.14, 0.26)	1.58 (1.36, 1.82)	3.27 (2.80, 3.81)
		CIBH	0.20 (0.15, 0.27)	1.68 (1.48, 1.90)	3.48 (3.00, 4.03)
Women					
	Colon	Rectal Bleeding	0.18 (0.13, 0.24)	0.94 (0.79, 1.12)	2.45 (2.07, 2.90)
		CIBH	0.15 (0.11, 0.20)	0.80 (0.68, 0.94)	2.09 (1.81, 2.42)
	Rectal	Rectal Bleeding	0.21 (0.15, 0.29)	0.90 (0.74, 1.10)	1.53 (1.24, 1.90)
		CIBH	0.13 (0.10, 0.18)	0.56 (0.48, 0.67)	0.96 (0.80, 1.15)

Table A3
Risk of having advanced stage cancer in men and women with colon and rectal cancers twelve months after presenting with rectal bleeding or change in bowel habit or neither in primary care at ages 40, 60 and 80 years old.

	Cancer site	Symptom	Probability of advanced stage cancer in cases % (95% CI)		
			Age 40	Age 60	Age 80
Men					
	Colon	Rectal Bleeding	61.6 (50.4, 71.7)	45.6 (39.5, 51.8)	45.9 (39.2, 52.7)
		CIBH	74.8 (64.1, 83.1)	60.8 (53.3, 67.8)	61.0 (53.3, 68.2)
		Neither	69.5 (60.2, 77.4)	54.4 (51.3, 57.4)	54.7 (50.7, 58.5)
	Rectal	Rectal Bleeding	66.1 (52.4, 77.6)	55.9 (49.8, 61.8)	48.2 (40.5, 55.9)
		CIBH	74.9 (61.7, 84.7)	66.0 (58.3, 72.9)	58.7 (49.6, 67.2)
		Neither	70.6 (57.8, 80.8)	60.9 (56.1, 65.5)	53.3 (46.5, 59.9)
Women					
	Colon	Rectal Bleeding	47.2 (37.1, 57.6)	48.1 (41.0, 55.2)	46.3 (38.8, 53.9)
		CIBH	53.5 (41.0, 65.7)	54.4 (44.8, 63.6)	52.6 (43.0, 62.0)
		Neither	56.5 (47.6, 65.0)	57.3 (54.0, 60.6)	55.6 (51.7, 59.3)
	Rectal	Rectal Bleeding	57.5 (43.9, 70.1)	45.3 (38.1, 52.7)	40.1 (31.5, 49.4)
		CIBH	72.4 (57.3, 83.7)	61.6 (49.5, 72.5)	56.5 (43.6, 68.6)
		Neither	71.3 (58.3, 81.6)	60.4 (53.7, 66.7)	55.2 (46.8, 63.3)

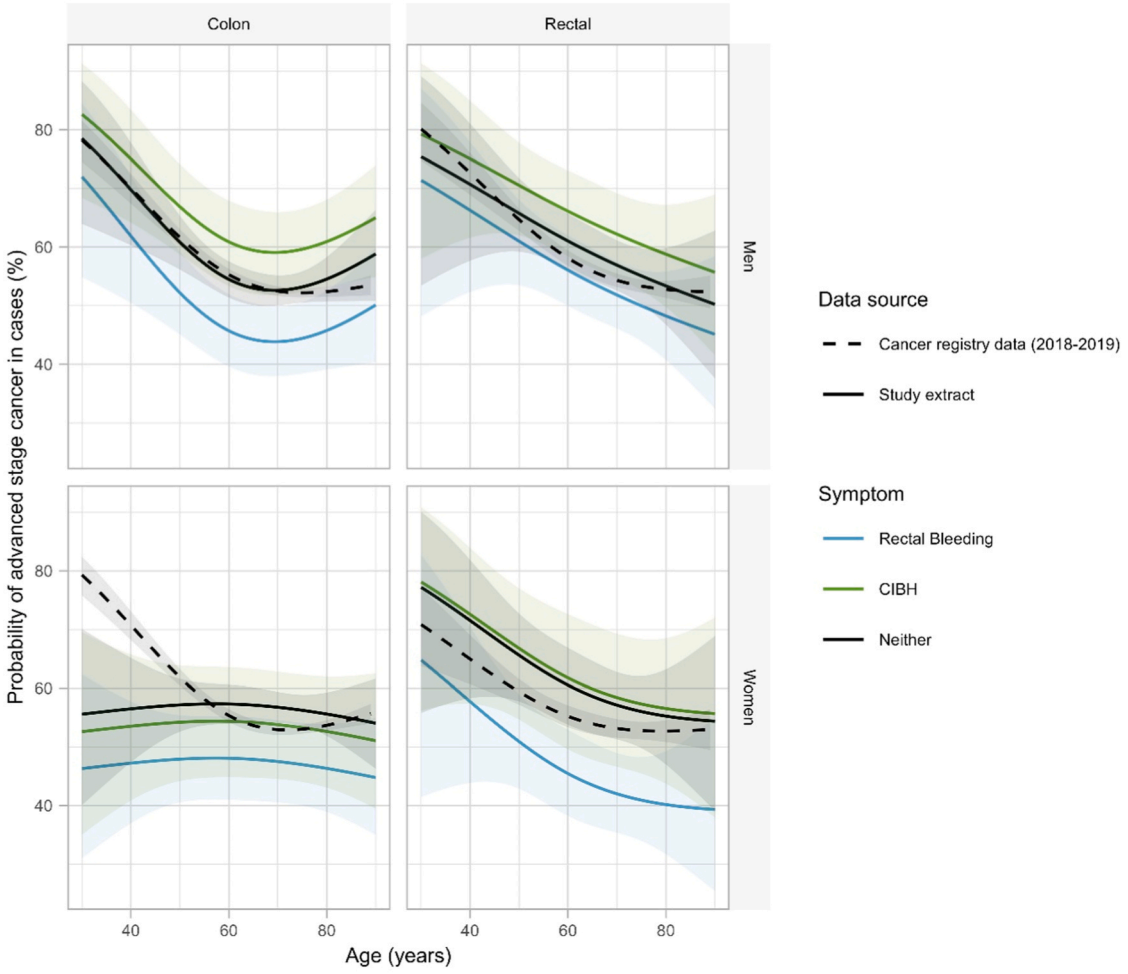

Figure A.2. Risk of having advanced stage cancer in men and women with colon or rectal cancers a year after presenting with rectal bleeding or change in bowel habit or neither (study extract defined in Methods Section 2.1) and in all men and women with colon or rectal cancer recorded in the cancer registry in years 2018 and 2019.

Table A.4
Risk of non-advanced and advanced stage colon and rectal cancers, in men and women, a year after rectal bleeding or change in bowel habit in primary care at ages 40, 60 and 80 years old.

Sex	Cancer site	Symptom	Probability of (non-)advanced stage cancer % (95% CI)		
			Age 40	Age 60	Age 80
Advanced Stage					
Men	Colon	CIBH	0.07 (0.04, 0.10)	1.01 (0.83, 1.22)	2.62 (2.20, 3.07)
		Rectal Bleeding	0.05 (0.03, 0.07)	0.63 (0.52, 0.76)	1.64 (1.36, 1.95)
	Rectal	CIBH	0.15 (0.10, 0.21)	1.11 (0.92, 1.32)	2.05 (1.68, 2.44)
		Rectal Bleeding	0.12 (0.08, 0.17)	0.88 (0.74, 1.04)	1.58 (1.31, 1.87)
Women	Colon	CIBH	0.08 (0.05, 0.12)	0.44 (0.33, 0.55)	1.10 (0.87, 1.37)
		Rectal Bleeding	0.08 (0.05, 0.12)	0.45 (0.36, 0.56)	1.13 (0.92, 1.37)
	Rectal	CIBH	0.09 (0.06, 0.14)	0.35 (0.26, 0.45)	0.55 (0.40, 0.71)
		Rectal Bleeding	0.12 (0.07, 0.17)	0.41 (0.32, 0.51)	0.62 (0.48, 0.77)
Non-advanced stage					
Men	Colon	CIBH	0.02 (0.01, 0.04)	0.66 (0.51, 0.82)	1.67 (1.33, 2.05)
		Rectal Bleeding	0.03 (0.02, 0.04)	0.75 (0.62, 0.90)	1.93 (1.64, 2.25)
	Rectal	CIBH	0.05 (0.03, 0.08)	0.57 (0.43, 0.73)	1.44 (1.13, 1.78)
		Rectal Bleeding	0.06 (0.03, 0.10)	0.69 (0.57, 0.83)	1.70 (1.42, 2.00)
Women	Colon	CIBH	0.07 (0.04, 0.10)	0.37 (0.27, 0.47)	0.99 (0.76, 1.24)
		Rectal Bleeding	0.09 (0.06, 0.13)	0.49 (0.39, 0.60)	1.32 (1.09, 1.57)
	Rectal	CIBH	0.04 (0.02, 0.06)	0.22 (0.15, 0.30)	0.42 (0.29, 0.57)
		Rectal Bleeding	0.09 (0.05, 0.13)	0.49 (0.39, 0.60)	0.92 (0.75, 1.11)

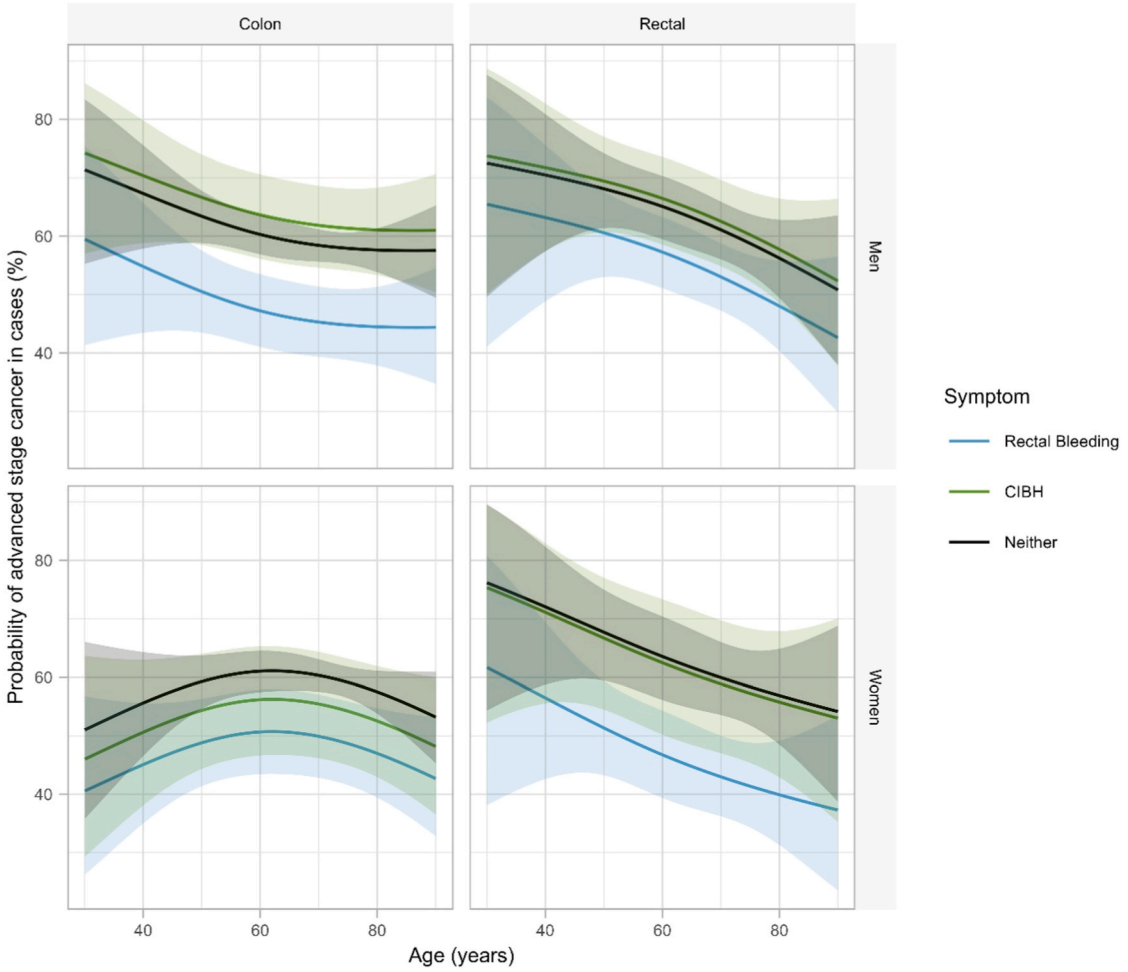

Figure A.3. After excluding cancer detected via screening, risk of having advanced stage (TNM III-IV) cancer in men and women with colon and rectal cancers a year after presenting with rectal bleeding or change in bowel habit or neither.

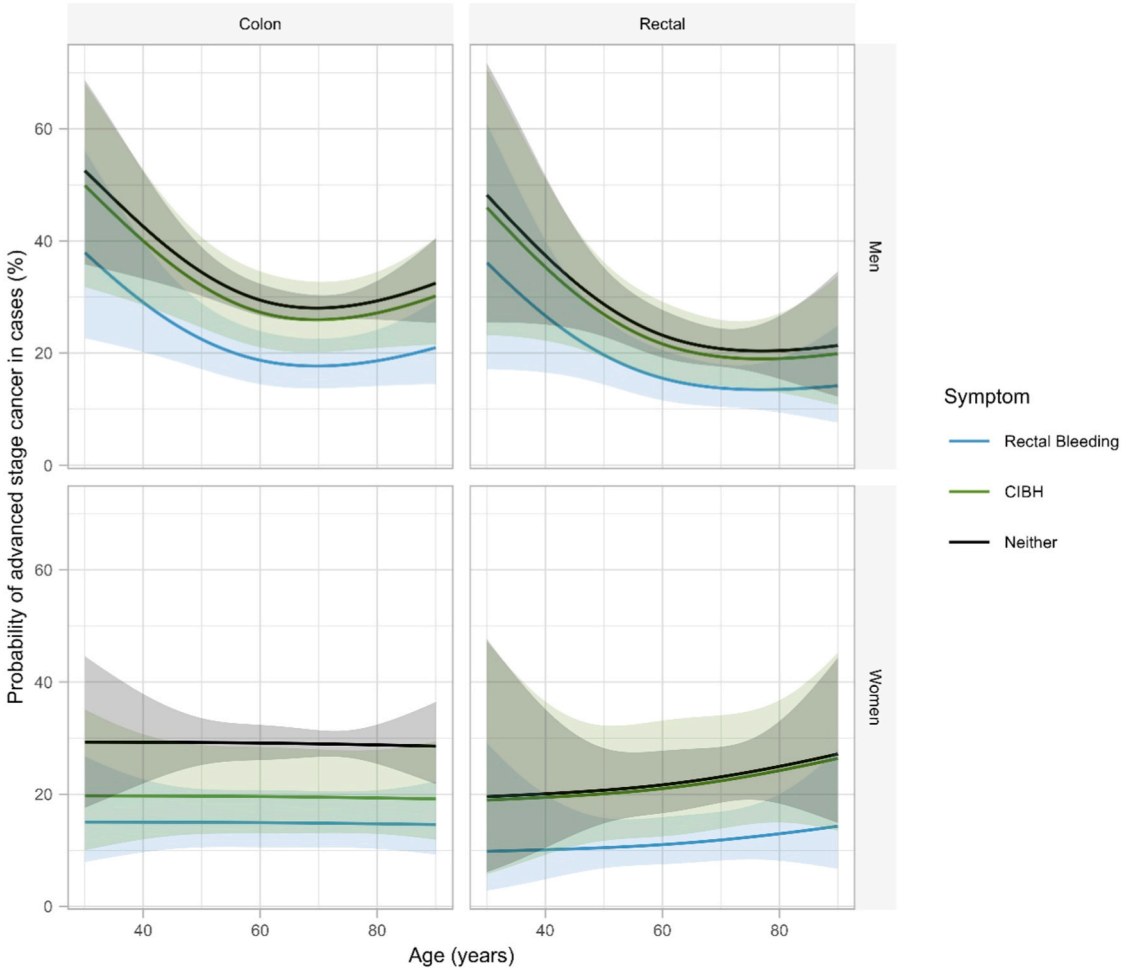

Figure A.4. Risk of having stage IV cancer in men and women with colon and rectal cancers a year after presenting with rectal bleeding or change in bowel habit or neither.

References

[1] D. Crosby, N. Lyons, E. Greenwood, S. Harrison, S. Hiom, J. Moffat, T. Quallo, E. Samuel, I. Walker, A roadmap for the early detection and diagnosis of cancer, Lancet Oncol. 21 (2020) 1397–1399, https://doi.org/10.1016/S1470-2045(20)30593-3.

[2] World Health Organization, Guide to cancer: early diagnosis, (2017). ⟨http://apps.who.int/iris/bitstream/handle/10665/254500/9789241511940-eng.pdf?sequence=1⟩ (accessed March 21, 2023).

[3] W. Hamilton, S. Hajioff, J. Graham, M. Schmidt-Hansen, Suspected cancer (part 2 - Adults): visual overview of updated NICE guidance, BMJ 350 (2015) 15–19, https://doi.org/10.1136/bmj.h2418.

[4] M. Ewing, P. Naredi, C. Zhang, J. Månsson, Identification of patients with non-metastatic colorectal cancer in primary care: a case-control study, Br. J. Gen. Pract. 66 (2016) e880–e886, https://doi.org/10.3399/bjgp16×687985.

[5] M. Ewing, P. Naredi, C. Zhang, L. Lindsköld, J. Månsson, Clinical features of patients with non-metastatic lung cancer in primary care: a case-control study, bjgpopen18×101397, BJGP Open. 2 (2018), https://doi.org/10.3399/bjgpopen18×101397.

[6] M.M. Koo, R. Swann, S. McPhail, G.A. Abel, L. Elliss-Brookes, G.P. Rubin, G. Lyratzopoulos, Presenting symptoms of cancer and stage at diagnosis: evidence from a cross-sectional, population-based study, Lancet Oncol. 21 (2020) 73–79, https://doi.org/10.1016/S1470-2045(19)30595-9.

[7] E. Herrett, A.M. Gallagher, K. Bhaskaran, H. Forbes, R. Mathur, T. van Staa, L. Smeeth, Data resource profile: clinical practice research datalink (CPRD), Int. J. Epidemiol. 44 (2015) 827–836, https://doi.org/10.1093/ije/dyv098.

[8] K.E. Henson, L. Elliss-Brookes, V.H. Coupland, E. Payne, S. Vernon, B. Rous, J. Rashbass, Data resource profile: national cancer registration dataset in England, 16–16H, Int. J. Epidemiol. 49 (2020), https://doi.org/10.1093/ije/dyz076.

[9] H. Wickham, M. Averick, J. Bryan, W. Chang, L.D. McGowan, R. François, G. Grolemund, A. Hayes, L. Henry, J. Hester, M. Kuhn, T.L. Pedersen, E. Miller, S. M. Bache, K. Müller, J. Ooms, D. Robinson, D.P. Seidel, V. Spinu, K. Takahashi, D. Vaughan, C. Wilke, K. Woo, H. Yutani, Welcome to the {tidyverse}, J. Open Source Softw. 4 (2019) 1686, https://doi.org/10.21105/joss.01686.

[10] V. Arel-Bundock, marginaleffects: Predictions, Comparisons, Slopes, Marginal Means, and Hypothesis Tests, (2023). ⟨https://vincentarelbundock.github.io/marginaleffects/⟩.

[11] R. Jones, R. Latinovic, J. Charlton, M.C. Gulliford, Alarm symptoms in early diagnosis of cancer in primary care: cohort study using General Practice Research Database, Br. Med. J. 334 (2007) 1040–1044, https://doi.org/10.1136/bmj.39171.637106.AE.

[12] A. Herbert, M. Rafiq, T.M. Pham, C. Renzi, G.A. Abel, S. Price, W. Hamilton, I. Petersen, G. Lyratzopoulos, Predictive values for different cancers and inflammatory bowel disease of 6 common abdominal symptoms among more than 1.9 million primary care patients in the UK: a cohort study, PLoS Med. 18 (2021) 1–20, https://doi.org/10.1371/journal.pmed.1003708.

[13] W. Hamilton, R. Lancashire, D. Sharp, T.J. Peters, K.K. Cheng, T. Marshall, The risk of colorectal cancer with symptoms at different ages and between the sexes: a case-control study, BMC Med 7 (2009) 1–9, https://doi.org/10.1186/1741-7015-7-17.

[14] M. Astin, T. Griffin, R.D. Neal, P. Rose, W. Hamilton, The diagnostic value of symptoms for colorectal cancer in primary care: a systematic review, Br. J. Gen. Pract. 61 (2011) e231–e243, https://doi.org/10.3399/bjgp11×572427.

[15] E. Nemlander, M. Ewing, E. Abedi, J. Hasselström, A. Sjövall, A.C. Carlsson, A. Rosenblad, A machine learning tool for identifying non-metastatic colorectal cancer in primary care, Eur. J. Cancer 182 (2023) 100–106, https://doi.org/10.1016/j.ejca.2023.01.011.

[16] E. Nemlander, A. Rosenblad, E. Abedi, J. Hasselström, A. Sjövall, A.C. Carlsson, M. Ewing, Validation of a diagnostic prediction tool for colorectal cancer: a case–control replication study, Fam. Pr. (2023), https://doi.org/10.1093/fampra/cmac147.

[17] B.D. Nicholson, J. Oke, P.S. Virdee, D.A. Harris, C. O'Doherty, J.E. Park, Z. Hamady, V. Sehgal, A. Millar, L. Medley, S. Tonner, M. Vargova, L. Engonidou, K. Riahi, Y. Luan, S. Hiom, H. Kumar, H. Nandani, K.N. Kurtzman, L.-M. Yu, C. Freestone, S. Pearson, F.R. Hobbs, R. Perera, M.R. Middleton, Multi-cancer early detection test in symptomatic patients referred for cancer investigation in England

and Wales (SYMPLIFY): a large-scale, observational cohort study, Lancet Oncol. 24 (2023) 733–743, https://doi.org/10.1016/S1470-2045(23)00277-2.

[18] G. Lyratzopoulos, G.A. Abel, C.H. Brown, B.A. Rous, S.A. Vernon, M. Roland, D. C. Greenberg, Socio-demographic inequalities in stage of cancer diagnosis: evidence from patients with female breast,lung, colon, rectal, prostate, renal, bladder, melanoma, ovarian and endometrial cancer, Ann. Oncol. 24 (2013) 843–850, https://doi.org/10.1093/annonc/mds526.

[19] M.E. Barclay, G.A. Abel, D.C. Greenberg, B. Rous, G. Lyratzopoulos, Socio-demographic variation in stage at diagnosis of breast, bladder, colon, endometrial, lung, melanoma, prostate, rectal, renal and ovarian cancer in England and its population impact, Br. J. Cancer 124 (2021) 1320–1329, https://doi.org/10.1038/s41416-021-01279-z.

[20] S.J. Price, S.A. Stapley, E. Shephard, K. Barraclough, W.T. Hamilton, Is omission of free text records a possible source of data loss and bias in clinical practice research datalink studies? A case-control study, BMJ Open 6 (2016), https://doi.org/10.1136/bmjopen-2016-011664.