Bowel Symptoms in Relation to Colorectal Cancer

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Key Points

- Bowel symptoms are common in the community, and their predictive value for colorectal cancer is low.
- Bowel symptoms provide little additional predictive value to that conferred by considering age alone.
- The predictive value of immunochemical faecal occult blood tests is also much higher than that of any symptom.
- In our study, 95% of cancers could have been detected by doing only 60% of the colonoscopies.

The value of bowel symptoms in the diagnosis of colorectal cancer has been debated for many years, but there remains conflicting information about which bowel symptoms, if any, are useful predictors of colorectal cancer. The earliest paper we have identified that evaluated symptoms for colorectal cancer was written in 1960 [1], and there have been numerous studies conducted since. The symptoms

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with which colorectal cancer are purported to present have been well documented and most commonly include rectal bleeding, alteration in bowel habit, abdominal pain and weight loss [2–4].

Bowel symptoms occur very commonly in the community and are often self-limiting, with estimates that over a third of the population have such symptoms at any time [5]. The incidence of rectal bleeding reported in a Dutch national survey was found to be 1.6 per 1000 (quoted in Olde Bekkink [6]). There is little information available about when or why people seek medical attention for these symptoms [7, 8].

Currently, many colorectal cancers are diagnosed following symptomatic presentation. However, the evaluation of bowel symptoms results in diagnosis of other gastrointestinal disease more frequently than colorectal cancer. Comparison of colonoscopy findings between symptomatic (done for diagnosis in patients 18–49 years) and non-symptomatic people (done for screening, patients aged 50–54 years) showed that many more neoplastic lesions were found in the screening group (28.5% compared to 14.1%) [9] and most likely reflects age related risk.

Nevertheless, despite increasing evidence that bowel symptoms are not harbingers of colorectal cancer in most instances, numerous investigations of bowel symptoms are done for this purpose. Further, it is widely acknowledged that colorectal cancer can—and should—be detected in the absence of symptoms through screening programs and that the presence of symptoms does not necessarily imply the presence of colorectal cancer. However, information provided by screening programs often includes lists of "common symptoms" of bowel cancer. These usually include a persistent change in bowel habit, rectal bleeding, abdominal pain and an abdominal lump [10], incomplete evacuation, weight loss, and fatigue [11]. Advice is still given that "recognising bowel cancer symptoms and acting quickly is important for early detection of the disease" [12].

To evaluate the importance of symptoms in the diagnosis of colorectal cancer, we undertook a systematic review of the literature in 2008. We identified and evaluated information from 62 eligible papers that provided relevant information about cancers [13]. Details of this systematic review are given at the end of this chapter, and results are shown in Table 2.1.

One of the findings from this systematic review was that the majority of the studies done had methodological flaws. This assessment has also been made by systematic reviews done subsequently (albeit with slightly varying inclusion criteria) [6, 14, 15]. We therefore undertook a large prospective primary clinical study which addressed many of the deficiencies of the previous studies, and was large enough to provide a definitive answer. In this study, the CRISP Study (Colonoscopy Research in Symptom Prediction), we evaluated the association between symptoms and colorectal cancer in 8204 patients undergoing colonoscopy for any reason [16]. We did not collect information about the indication for the colonoscopy; the patients were not a select group, but were referred for all the indications for which colonoscopies are done. A brief summary of the methods of this study is given at the end of this chapter, and our results are shown in Table 2.2.

Table 2.1 Overview of results from systematic review: symptoms associated with cancer

Symptom	DOR (95% CI)	AUC	Sensitivity (95% CI)	1-specificity (95% CI)	LR+ (95% CI)	LR− (95% CI)
Rectal bleeding[a]	2.6 (1.9–3.6) p < 0.001	0.66	0.46 (0.38–0.55)	0.25 (0.19–0.31)	1.9 (1.5–2.3)	0.7 (0.6–0.8)
Blood mixed with stool	*3.1 (2.0–4.8) p < 0.001*	*0.68*	*0.49 (0.30–0.69)*	*0.24 (0.13–0.40)*	*2.1 (1.5–2.8)*	*0.7 (0.5–0.9)*
Blood: dark red	*3.9 (1.7–9.2) P = 0.004*	*0.71*	*0.29 (0.09–0.65)*	*0.10 (0.03–0.28)*	*3.1 (1.6–6.0)*	*0.8 (0.6–1.1)*
Change in bowel habit	1.5 (0.8–2.8) p = 0.16	0.57	0.32 (0.21–0.46)	0.24 (0.15–0.35)	1.4 (0.9–2.1)	0.9 (0.7–1.1)
Abdominal pain	0.7 (0.5–1.1) p = 0.12	0.45	0.19 (0.13–0.28)	0.24 (0.17–0.33)	0.8 (0.6–1.1)	1.1 (1.0–1.2)
Constipation	1.1 (0.8–1.5) p = 0.48	0.52	0.12 (0.08–0.18)	0.11 (0.07–0.16)	1.1 (0.8–1.5)	1.0 (1.0–1.0)
Diarrhoea	0.9 (0.4–1.7) p = 0.65	0.47	0.15 (0.07–0.28)	0.17 (0.09–0.29)	0.9 (0.5–1.6)	1.0 (0.9–1.1)
Weight loss	2.9 (1.6–5.0) p = 0.001	0.67	0.20 (0.12–0.31)	0.08 (0.05–0.13)	2.5 (1.5–4.0)	0.9 (0.8–1.0)

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DOR = diagnostic odds ratio, No association between symptoms and cancer if DOR=1

AUC = area under the receiver operator curve (ROC). No association between symptom and cancer if AUC = 0.5

[a]Bleeding of any type

Note: rectal mucus, fatigue and anaemia were not evaluated in the systematic review

Table 2.2 The CRISP study: Symptoms, history and demographic variables—single and multivariable model

	People with symptom		Cancer Prevalence (/100)[a]	OR: individual symptom (95% CI)	OR: individual symptom in multivariate model[b] (95% CI)
	Number	Percent (%) (of all participants)			
Rectal bleeding (all)	3023	37.3	2.99	1.99 (1.45–2.73)	
No bleeding	5803	62.7		1.00 (referent)	
Present <12 months; occurring weekly	*689*	*8.40*	*6.18*	*4.27 (2.88–6.33)*	*5.69 (3.65–8.87)*
Present <12 months; occurring occasionally	*1226*	*14.9*	*2.51*	*1.67 (1.08–2.57)*	*2.06 (1.30–3.27)*
Present >12 months; occurring weekly	*356*	*4.3*	*1.79*	*1.18 (0.51–2.73)*	*>12 months: 1.50 (0.80–2.81)*
Present >12 months; occurring monthly/ occasionally	*689*	*8.40*	*1.08*	*0.71 (0.33–1.55)*	

(continued)

Table 2.2 (continued)

	People with symptom		Cancer Prevalence (/100)[a]	OR: individual symptom (95% CI)	OR: individual symptom in multivariate model[b] (95% CI)
	Number	Percent (%) (of all participants)			
Change in bowel habit (all)	3780	46.8	2.67	1.73 (1.25–2.38)	
No change in bowel habit	4303	53.2	1.56	1.00 (referent)	
Present <12 months	*2338*	*28.5*	*3.52*	*2.30 (1.64–3.21)*	
Present >12 months	*1365*	*16.6*	*1.30*	*0.83 (0.49–1.43)*	
Rectal mucus (all)	1318	16.2	2.76	1.46 (1.00–2.14)	
No rectal mucus	6809	83.8	1.91	1.00 (referent)	
Present <12 months; occurring weekly	*328*	*3.4*	*6.39*	*3.51 (2.16–5.72)*	*3.19 (1.82–5.59)*
Present <12 months; occurring occasionally	*393*	*4.8*	*2.38*	*1.25 (0.63–2.49)*	*1.30 (0.62–2.71)*
Present >12 months; occurring weekly	*201*	*2.5*	*0.51*	*0.26 (0.04–1.89)*	*>12 months: 1.25 (0.49–3.21)*
Present >12 months; occurring monthly/ occasionally	*265*	*3.2*	*1.57*	*0.82 (0.30–2.24)*	
Abdominal pain	3905	48.0	2.19		
No abdominal pain				1.00 (referent)	
Present <12 months; occurring weekly	*1522*	*18.6*	*3.82*	*2.02 (1.42–2.86)*	*2.16 (1.48–3.15)*
Present <12 months; occurring occasionally	*787*	*9.6*	*1.88*	*0.97 (0.55–1.73)*	*1.05 (0.57–1.93)*
Present >12 months; occurring weekly	*956*	*11.6*	*0.87*	*0.45 (0.21–0.93)*	*(>12 months): 1.12 (0.25–4.92)*
Present >12 months; occurring monthly/ occasionally	*560*	*6.8*	*0.37*	*0.19 (0.05–0.78)*	
Incomplete evacuation	3724	46.2	2.26	1.20 (0.87–1.64)	
No incomplete evacuation	4365	53.8	1.89	1.00 (referent)	
Present <12 months; occurring weekly	*1393*	*17.0*	*3.47*	*1.86 (1.29–2.70)*	
Present <12 months; occurring occasionally	*630*	*7.7*	*1.51*	*0.79 (0.55–1.73)*	
Present >12 months; occurring weekly	*860*	*10.5*	*1.20*	*0.63 (0.21–0.93)*	

Table 2.2 (continued)

	People with symptom		Cancer Prevalence (/100)[a]	OR: individual symptom (95% CI)	OR: individual symptom in multivariate model[b] (95% CI)
	Number	Percent (%) (of all participants)			
Present >12 months; occurring monthly/ occasionally	*443*	*5.4*	*0.72*	*0.37 (0.05–0.78)*	
Abdominal lump	288	3.6	2.20	1.08 (0.47–2.47)	
No abdominal lump	7822	96.4	2.03	1.00 (referent)	
Anal pain	1942	24.0	2.12	0.91 (0.63–1.33)	
No anal pain	6139	76.0	1.94	1.00 (referent)	
Urgency	3187	40.0	2.14	0.91 (0.65–1.26)	
No urgency	4784	60.0	1.94	1.00 (referent)	
Anal lump	1025	12.7	1.63	0.77 (0.46–1.29)	
No anal lump	7057	87.3	2.11	1.00 (referent)	
Weight loss (all)	957	11.7		1.78 (1.19–2.67)	
No weight loss	7136	88.2		1.00 (referent)	
≥6 kg	*288*	*3.51*	*5.88*	*3.27 (1.92–5.59)*	
4–6 kg	*234*	*25.6*	*3.20*	*1.73 (0.80–3.75)*	
≤4 kg	*391*	*2.85*	*1.58*	*0.84 (0.37–1.92)*	
Fatigue	3266	40.2	2.65	1.67 (1.21–2.29)	
No fatigue	4864	59.8	1.61	1.00 (referent)	
Anaemia	821	10.1	4.97	2.96 (2.05–4.29)	3.61 (2.42–5.40)
No anaemia	7287	89.9	1.73	1.00 (referent)	
History and demographic information					
Age					
<50 years	2220	27.1	0.46	1.00 (referent)	
50–59 years	2135	26.1	1.73	3.78 (1.87–7.64)	7.37 (3.57–15.18)
60–69 years	2032	24.9	2.64	5.82 (2.94–11.51)	15.96 (7.80–32.64)
>70 years	1792	21.9	3.85	8.60 (4.40–16.80)	27.28 (13.26–56.11)
Gender					
Male	3860	47.1	2.45	1.00 (referent)	1.42 (1.01–2.00)
Female	4344	54.0	1.71	0.70 (0.51–0.95)	
Previous colonoscopy in last 10 years					0.23 (0.15–0.33)
>10 years	296	3.7	1.75	0.50 (0.20–1.22)	
5–10 years	1380	17.4	0.60	0.17 (0.08–0.35)	

(continued)

Table 2.2 (continued)

	People with symptom		Cancer Prevalence (/100)[a]	OR: individual symptom (95% CI)	OR: individual symptom in multivariate model[b] (95% CI)
	Number	Percent (%) (of all participants)			
3–4 years	1428	18.0	1.10	0.31 (0.18–0.53)	
0–2 years	1446	18.2	1.33	0.37 (0.23–0.62)	
No previous colonoscopy	3385	42.7	3.49	1.00 (referent)	
Diverticular disease	804	9.8	0.93	0.42 (0.20–0.90)	0.38 (0.17–0.86)
No diverticular disease	7400	90.2	2.18	1.00 (referent)	
NSAID use	759	10.4	0.95	0.43 (0.20–0.93)	0.34 (0.16–0.74)
No NSAID use	6514	89.6	2.17	1.00 (referent)	
Aspirin use	1330	18.2	2.01	0.99 (0.64–1.53)	0.54 (0.34–0.86)
No aspirin use	5979	81.8	2.03	1.00 (referent)	

Note: Numbers for subgroups may not add up to numbers in group because results for "not known" category are not presented

[a]Cancer prevalence calculated as (number of cancers/total number − number of advanced adenomas) × 100

[b]Only variables found to be significant or included in the final model are shown

To answer the question about the association of symptoms and colorectal cancer conclusively, we present the findings of our systematic review and our primary clinical study, together with findings from other systematic reviews undertaken.

2.1 Number of Symptoms

Systematic review: The most commonly reported symptoms were rectal bleeding, abdominal pain, change in bowel habit, constipation, diarrhoea and weight loss.

Primary clinical study: Bowel symptoms are common. In our primary clinical study of patients undergoing colonoscopy for any reason, patients often reported having more than one symptom. Most commonly, patients reported having 3 symptoms, but some patients reported having all 11 of the symptoms asked about. Only 14% of patients reported having no bowel symptoms (Table 2.3).

The more symptoms a patient reported, the higher their risk of cancer. Compared to those with no symptoms, patients with 5–11 symptoms had 3.7 times (95% CI 1.8–7.8) the risk of colorectal cancer, those with 3–4 symptoms had 3 times (95% CI 1.4–6.4) the risk and those with 1–2 symptoms had 2.6 times (95% CI 1.2–5.6) the risk.

There were 8204 participants in our study, with colorectal cancer diagnosed in 159 (1.9%).

Table 2.3 Outcome and number of symptoms per patient

Number of symptoms per patient				Total (%)	
	Cancer	Advanced adenoma	Nil	n	%
0	8	93	1072	1173	14.3
1	19	78	1031	1128	13.7
2	21	76	1059	1156	14.1
3	25	71	1118	1214	14.8
4	23	59	1025	1107	13.5
5	26	38	886	950	11.6
6	21	32	624	677	8.3
7	8	13	420	441	5.4
8	6	5	242	253	3.1
9	0	2	73	75	0.9
10	2	0	21	23	0.3
11	0	1	6	7	0.1
Total	159	468	7577	8204	100

2.2 Rectal Bleeding

Systematic review: Rectal bleeding is associated with colorectal cancer.

From the 40 papers which provided information about the relationship between rectal bleeding of any type and colorectal cancer, we found that bleeding is expected to occur in about half the patients with cancer (sensitivity 0.46 (95% CI 0.38–0.55), but are also expected to occur in about a quarter of patients without cancer (1-specficity; 0.25 (95% CI 0.19–0.31). Therefore, the likelihood of cancer is approximately doubled in people with bleeding (Positive likelihood ratio (LR+) = 1.9 (95% CI 1.5–2.3). The corresponding likelihood of cancer in people presenting with no bleeding (Negative likelihood ratio (LR−) was 0.7 (95% CI 0.6–0.8).

These results are similar to those reported in other systematic reviews. Ford et al [14], who reported LR+ = 1.3 (95% CI 1.2–1.5) and LR− = 0.8 (95% CI 0.7–0.9), based on 14 studies.

Nevertheless, even though rectal bleeding is associated with colorectal cancer, for most people presenting with rectal bleeding, colorectal cancer will not be the cause. Based on our systematic review findings, even if cancer is present in as many as 5% of people asked about symptoms, only 9% of those with rectal bleeding will have cancer.

The methodology, quality and population characteristics of the studies also influenced how bleeding was associated with cancer. The accuracy of bleeding in diagnosing colorectal cancer was higher when colonoscopy, compared to all other diagnostic modalities, was used as the reference standard.

2.2.1 Type of Bleeding

Systematic review: Few papers provided information about bleeding type. Of these, only bleeding mixed with stool (3.1, 95% CI 2.0–4.8 times higher) and dark red blood (3.9, 95% CI 1.7–9.2 times higher) were significantly associated with colorectal cancer.

These findings are consistent with another systematic review which reported LR+ = 1.9 (95% CI 0.8–5.5) for blood mixed with stool and LR+ of 1.4 (95% CI 0.6–3.3) for dark red blood [6].

Primary clinical study: Our primary clinical study results were consistent with the findings from the systematic reviews. We found that colorectal cancer was about twice as common in those with rectal bleeding than in those with no bleeding (OR 1.99, 95% CI 1.45–2.73). Rectal bleeding was the most common symptom, with 48% of people in our study having this symptom. However, this has to be seen in context: 1.9% of all participants had colorectal cancer, and while 3% of those who reported rectal bleeding had colorectal cancer and the relative increase was approximately 50%, the absolute increase was for those with bleeding was 1.1%, although this may increase if the duration and frequency of bleeding is taken into account.

People with bleeding that was described as being mixed (with fresh, bright blood and old, dark blood—reported by 12% of people who reported bleeding) were more than 4 times more likely to have colorectal cancer (prevalence 5.9%; OR 4.1 95% CI 2.4–6.8) than those with no bleeding (cancer prevalence 1.5%). People with bleeding described as fresh were about twice more likely than to have cancer than those with no bleeding (prevalence 2.5%; OR 1.7; 95% CI 1.2–2.4). There was no evidence of association between colorectal cancer and estimated quantity of bleeding.

The length of time bleeding was present and the frequency with which it occurred were important factors in assessing the significance of bleeding. The more frequent the bleeding, and the less time it had been present were associated with higher risk of colorectal cancer. These factors are discussed later in the chapter.

2.3 Change in Bowel Habit

Systematic review: 32 papers provided information about the relationship between change in bowel habit and colorectal cancer, but we found no association between change in bowel habit and cancer. Change in bowel habit was expected to occur in 32% of patients with cancer.

Other systematic reviews evaluating change in bowel habit also found that this symptom had low diagnostic value, although Ford reported a LR+ of 1.3 (95% CI 1.0–1.6) [14, 15].

Primary clinical study: Contrary to the findings from the systematic reviews, we found that change in bowel habit was found to have a slight association with colorectal cancer—patients with this symptom were 1.7 times (95% CI 1.3–2.4) more likely to have cancer. Change in bowel habit was the second most common symptom in our study, with 47% of people having this symptom.

The highest risk for colorectal cancer was in males with a change in bowel habit present for less than 12 months, with three times the risk of those with no change in bowel habit. This is discussed later in the chapter.

The frequency with which the change in bowel habit occurred and the type of change in bowel habit did not influence the association with colorectal cancer.

2.4 Rectal Mucus

Systematic review: rectal mucus was not assessed in the systematic review as there were insufficient papers describing this symptom.

Primary clinical study: rectal mucus was weakly associated with colorectal cancer. There was no association with the quantity of the mucus, but the frequency and time present were important and are discussed later in the chapter.

2.5 Constipation, Diarrhoea, Abdominal Pain, Abdominal or Anal Lump, Anal Pain, Incomplete Evacuation, Urgency

Systematic review: We found that constipation, diarrhoea and abdominal pain were not associated with colorectal cancer. These findings are in keeping with those of other systematic reviews [14, 15, 17, 18].

Primary clinical study: this supported the findings of the systematic review. We found no increased risk for abdominal pain, an abdominal or anal lump, anal pain, incomplete evacuation or urgency.

2.6 General Symptoms: Weight Loss, Fatigue and Anaemia

2.6.1 Weight Loss

Systematic review: 18 papers provided information about the relationship between weight loss and colorectal cancer. Weight loss was associated with colorectal cancer (Table 2.1). Weight loss is expected to occur in 20% of the patients with cancer (sensitivity 0.20; 95% CI 0.05–0.13) compared with 10% of those without cancer (1-specificity 0.08; 95% CI 0.0–0.1). Hence, the likelihood of cancer was more than doubled in people presenting with weight loss (LR+ = 2.5; 95% CI 1.5–4.0). The corresponding likelihood of cancer in people presenting with no weight loss was LR− = 0.9 (95% CI 0.8–1.0).

Our results for weight loss are similar to those reported in other systematic reviews, although the likelihood ratios reported by Ford (LR+ = 1.9; 95% CI 1.3–3.1, and LR− = 0.9; 95% CI 0.8–1.0) based on five studies [14], and Olde Bekkink (LR+ = 1.9; 95% CI 1.0–3.1) [6] were slightly lower than ours. Jellema reporting sensitivity = 0.2 and specificity = 0.89 [15].

Primary clinical study: Weight loss (unintentional) was associated with colorectal cancer. Patients who had lost more than 6 kg in weight were 3.2 times (95% CI 1.9–5.6) more likely to have cancer than those with no weight loss. 11.8% of people in our study had weight loss. Weight loss was more predictive for colorectal cancer in males than females.

2.6.2 Fatigue and Anaemia

Systematic review: we did not assess these in our systematic review. In their systematic review, Ford et al. [14] reported that the likelihood ratios were disappointing (LR+ = 1.38 (0.5–3.9), and LR− = 0.9 (0.7–1.1).

Primary clinical study: People with a history of anaemia were three times (OR 3.0; 95% CI 2.1–4.3) more likely to have colorectal cancer than those with no history. People with fatigue were 1.7 times (OR 1.7 95% CI 1.2–2.3) more likely to have colorectal cancer than those with no history of fatigue. Forty percent of people in the study complained of fatigue, and 10% said they had a history of anaemia.

Anaemia was more predictive of colorectal cancer if the person had up to two other symptoms, irrespective of what these were. It should be stressed that assessment of anaemia in our study was by self-reported recollection of the participants, not documented iron deficiency anaemia.

2.7 Characteristics of Symptoms: Frequency and Time Present

The risks associated with rectal bleeding, rectal mucus and abdominal pain depended on the length of time the symptom had been present and the frequency with which it occurred. For example, the colorectal cancer risk was the highest when the symptom occurred weekly and had been present for less than 12 months for patients with rectal bleeding (over 4 times higher: OR 4.3; 95% CI 2.9–6.3), rectal mucus (3.5 times higher: OR 3.5 95% CI 2.2–5.7), abdominal pain (2 times higher: OR 2.0; 95% CI 1.4–2.9), and incomplete evacuation (almost 2 times higher: OR 1.9; 95% CI 1.3–2.7). For change in bowel habit, short duration (<12 months) was associated with almost a two and a half times higher risk (OR 2.4; 95% CI 1.7–3.3). Notably, for each of these symptoms, the risk in those who had the symptom for longer than 12 months was similar to those without the symptom.

Gender was an effect modifier for colorectal cancer risk in patients with abdominal pain. Males with abdominal pain had a higher risk than males with no pain, while females were not at increased risk. However, when the duration of pain was taken into account, this gender effect was no longer significant: both males and females had a higher risk of colorectal cancer when pain occurred weekly and had been present for less than 12 months.

2.8 Summary of Findings: Summary of Findings on Single Symptoms

The symptoms usually considered important for colorectal cancer diagnosis are rectal bleeding, change in bowel habit, abdominal pain, weight loss, diarrhoea and constipation. Of these, in our systematic review only rectal bleeding and weight loss showed any association with cancer, although this association was small (Table 2.1). In our primary clinical study, only rectal bleeding and weight loss were associated with colorectal cancer, albeit with relatively low diagnostic value. Change in bowel habit and rectal mucus had slight associations with colorectal cancer. If these symptoms occurred more frequently and were present for less than 12 months, the association with colorectal cancer was higher. There was evidence that other symptoms were not associated with colorectal cancer.

2.9 Other Risk Predictors

In our primary clinical study, age was significantly associated with colorectal cancer, with the risk increasing with increasing age. Compared to people aged less than 50 years, people older than 70 years had an 8.6 times (OR 8.6; 95% CI 4.4–16.8) higher risk than colorectal cancer. Those aged between 60 and 69 had a 5.8 times (OR 5.8; 95% CI 2.9–11.5) higher risk, and those between 50 and 59 had a 3.8 times (OR 3.8; 95% CI 1.9–7.6) higher risk.

The increased incidence of colorectal cancer in higher age groups is well established. However, although not reflected in the findings of our study, it has recently become evident that colorectal cancer is becoming more common in people less than 50 years old [19, 20].

The number of symptoms a person reported was associated with a higher risk of colorectal cancer, with those reporting 5–11 symptoms having the highest risk. Smoking was also associated with a higher colorectal cancer risk.

Use of non-steroidal anti-inflammatory medications, having a higher level of education, being female or having had a colonoscopy within 10 years were all associated with lower risk of colorectal cancer. Almost 70% of cancers were in the 41% of people who had not had a colonoscopy in the previous 10 years.

A family history or personal history of polyps are accepted risk factors for an increased risk of colorectal cancer [21, 22]. In our study, these were associated with a lower risk of colorectal cancer. We postulate that in our study this was because many of these participants had had prior colonoscopy with removal of adenomas when present. The reasons for referral of patients in our study were heterogenous and included referral for symptoms evaluation, surveillance and screening.

We found no increased association with body mass index (BMI), use of aspirin, or a history of any other bowel disease, such as anal fissure, inflammatory bowel disease, haemorrhoids, previous bowel resection and diverticular disease.

2.10 Combination of Symptoms and Risk Factors

In a clinical setting, symptoms are seldom reviewed in isolation, and all available information is included in making a diagnosis and plan for further investigation and management. We therefore assessed all the symptoms and risk factors in a multivariate model and also assessed their incremental value.

The association noted for symptoms on their own was no longer evident for some symptoms when all symptoms and risk factors were taken into account together. Although family history of colorectal cancer, history of colorectal polyps, irritable bowel symptom syndrome all decreased the risk of cancer and smoking increased the risk when assessed individually, none of these remained significant risk factors in the multivariable risk model. This implies that these associations were not due directly to the factors themselves, but are in part explained by their association with other factors. The following factors were found to increase the risk of colorectal cancer in the multivariate model (Table 2.2): Rectal bleeding, rectal mucus, and abdominal pain—all occurring weekly and having been present for less than 12 months; increasing age, being male; and history of anaemia. Having had a colonoscopy in the previous 10 years, use of non-steroidal anti-inflammatory medication and aspirin, decreased the risk.

The risk associated with increased age was greater that for symptoms. Using estimates of sensitivity and specificity across all values of the probability of colorectal cancer to construct a ROC curve for each model, we compared the accuracy of each model using the AUC (area under the curve). With only symptoms found to be significant in the model, the AUC was 0.69, whereas it was 0.67 with only age in the model. Adding gender to the model increased the AUC to 0.76, and this increased further to 0.79 when a history of diverticular disease and use of non-steroidal anti-inflammatory medication and aspirin were included.

The risk determined by taking all the symptoms and risk factors into account discriminates well between those with and without cancer, and can be used to calculate the predicted probability for colorectal cancer for any individual based on their age, medical history and symptoms. For example, a female, younger than 50 years with abdominal pain present for longer than 12 months has a cancer risk of 0.1%, compared to a 27% risk in a 70-year-old man with rectal bleeding present for less than 12 months and occurring frequently.

2.11 Implications for Clinical Practice

It is common in clinical practice to perform a colonoscopy in patients with symptoms, often with the aim of detecting or ruling out colorectal cancer [23]. Evaluating symptoms individually, symptoms such as urgency, anal pain, abdominal lump and anal lump do not indicate an increased risk of colorectal cancer. Some bowel symptoms such as rectal bleeding, change in bowel habit and weight loss are associated with colorectal cancer, but not with high diagnostic value. Rectal mucus and abdominal pain are also associated with colorectal cancer but only for those people who have their symptoms at least weekly and for less than 12 months.

However, as occurs more commonly in clinical practice, symptoms are not evaluated in isolation of other factors or of each other. In this situation, rectal bleeding, rectal mucus, and abdominal pain—all occurring weekly and having been present for less than 12 months, increasing age, being male, and history of anaemia all increase the colorectal cancer, while having had a colonoscopy in the previous 10 years, use of non-steroidal anti-inflammatory medication and aspirin, decrease the risk.

With symptoms occurring much more frequently than cancers, and with the relatively low predictive value of symptoms, many patients with symptoms would have to undergo a colonoscopy to find one cancer. The predicted probability of colorectal cancer influences this. If the predicted value of colorectal cancer is <0.5%, 344 people would have to have a colonoscopy to detect one cancer. However, at the other extreme, if the predicted probability of cancer is more than 20%, only three people would need to have a colonoscopy to detect one cancer. Over 40% of people without cancer would be in the group with less than 0.5% predicted probability, while only about 5% of the cancers would be in this group. In our study, 95% of cancers could have been detected by doing only 60% of the colonoscopies, which highlights that a tool for better predicting when to undertake colonoscopy would be useful.

Increasing age is a known risk factor for colorectal cancer. Comparison of the predictive value of age alone to that of symptoms considered jointly, shows that the addition of symptoms provides little additional accuracy. Thus, even though the incidence of colorectal cancer is increasing in younger people, it still occurs much more commonly with increasing age and the number needed to investigate to find one cancer in young people remains high.

The lack of clinical usefulness of most symptoms is also confirmed by the positive likelihood ratio of the symptoms. To provide strong evidence for ruling in disease, a positive likelihood ratio should be greater than 10 [24]. Faecal occult blood tests have been shown to have positive likelihood ratios of up to 47.4 [25]. In our systematic review, weight loss was the symptom with the highest positive likelihood ratio of 2.5. This means that a person with weight loss has less than a threefold increase in colorectal cancer risk. However, weight loss is generally a non-specific symptom, and in most of the studies included in this meta-analysis was analysed in a population already selected for being of sufficiently high risk of colorectal cancer to warrant investigation for colorectal cancer. Apart from weight loss and rectal bleeding, the positive likelihood ratio of other symptoms was around one.

The usefulness of bowel symptoms for the diagnosis of colorectal cancer also needs to be considered in the context of other tests available. In a systematic review of immunochemical faecal occult blood tests, the median OR for a positive test was 20.2 [25]. This is several times higher than the highest OR for any symptom—bleeding, occurring weekly and present for less than 12 months had an OR of 4.3.

Given the frequency of symptoms in the population and the relative high incidence of colorectal cancer, it is perhaps not surprising that people who are investigated for symptoms, irrespective of the symptom or indeed of its inherent accuracy in predicting the disease, may be found to have cancer. However, symptoms by themselves offer little diagnostic value, and even less additional value when added to other known risk factors such as age, or easily available screening tests such as faecal occult blood tests.

2.12 Medicolegal and Other Influences on the Provision of Colonoscopy

There are many drivers of the demand for colonoscopy. These may be consumer driven or come from primary care physicians or the medical and surgical specialists who provide colonoscopy. One such driver is the practice of defensive medicine. This is defined as a doctor's deviation from what is accepted as good clinical care in order to mitigate criticism, complaints, or legal action by patients [26]. Unnecessary investigations and procedures may be ordered when the practitioner knows that these are not warranted based on the patient's presenting symptoms or are not in accord with local practice guidelines for screening or surveillance, but are done to avoid complaints. A survey of practices of Japanese gastroenterologists [27], reported that 5% of these often ordered more tests than medically indicated and 16% often recommended invasive procedures such as biopsy solely for defensive reasons. According to a survey of gastroenterologists conducted by Eli [28] some practitioners found such defensive medicine practices reassuring. This may be due in part to rising litigation rates in parts of the world, including the UK, Australia and Japan. In the US, 88% of doctors will have at least one lawsuit made against them during their career (quoted in Elli [28]).

There are many other drivers of doctors' test ordering behaviour. In countries where colorectal cancer is common, there may be heightened community recognition of the disease due to community awareness campaigns, public health advertising and screening programs. Much community information is centred on having symptoms evaluated, irrespective of the evidence base for such advice. Little wonder patients then have expectations that a procedure, usually colonoscopy, should be done and in many cases, repeated at short intervals.

Pressure to provide colonoscopy to such patients is driven not only by patient expectation, but by primary care physician (PCP) expectation also. Irrespective of PCPs awareness of the relevance and context of symptoms, by referring patients for further evaluation or colonoscopy, PCPs are providing the service the patient wants while also covering their own perceived medicolegal risk. For example, 45% of claims against Australian GPs are for diagnostic error [29]. Gastroenterologists have reported that they have been requested to perform additional "defensive" tests and procedures by referring practitioners, both general practitioners and specialists [28].

It is difficult for a specialist gastroenterologist or colorectal surgeons to decline the request of such a referred patient on the basis that most symptoms are not predictive of the presence of colorectal cancer. These specialists will know that although not predictive, a small proportion of patients will have bowel cancer, whether they have relevant symptoms or not. In our CRISP study, 1.9% of participants had colorectal cancer, including some who had apparent low risk. Moreover, a substantial proportion had neoplastic polyps, which are overwhelmingly asymptomatic. Endoscopic removal of these is known to confer a risk reduction of future colorectal cancer [30]. Indeed, it is increasingly perceived by gastroenterologists that colonoscopy is a powerful tool that is reducing the occurrence of bowel cancer. As such,

many, if not most, are willing to engage in "de facto" screening of patients presenting with symptoms even when the symptoms have no close correlation with the likelihood of colorectal cancer at presentation, knowing that removal of adenomas is of value to the patient. In countries where average risk, age related screening colonoscopy is funded, there may be less need to use (non-predictive) symptoms as the indication for colonoscopy. In some jurisdictions, where the provider of colonoscopies receives a fee for service, that incentives may be another driver of the provision of services.

Added to all these pressures to provide colonoscopy is the possibility in some countries of successful litigation by a patient if a practitioner declines to undertake a requested test and a diagnosis of colorectal cancer is delayed. In Australia, for example, the judiciary may not be swayed by adherence to medical guidelines and these provide no certain protection to the defendant. Moreover, some judges may be inclined to regard medical insurance funds as a social insurance to compensate patients for adverse outcomes, irrespective of fault. Until, and unless bowel cancer screening includes colonoscopy (in addition to faecal occult blood tests) as a widely available procedure to the whole at-risk population in a co-ordinated rather than ad hoc manner, it is inevitable that lower value colonoscopy screening will be done by some doctors who practice defensive medicine. If there is a lack of protection in the courts for doctors who practice evidenced based medicine and adherence to guidelines this will only be exacerbated.

Appendix

Systematic Review: Summary of Methodology

We conducted a comprehensive search of the health literature for all studies evaluating symptoms and colorectal cancer. We searched MEDLINE and complete EMBASE, using a list of symptoms and diagnoses as MeSH headings, and included all papers in English and foreign languages. The search, done in 2006, was done on two separate occasions, 6 months apart, and where discrepancies existed, the results combined. Once papers were selected for inclusion, we reviewed all the references in these as well as from review papers identified. We also reviewed references from citations of the selected papers.

For inclusion, papers had to provide sufficient data, either readily available or able to be calculated, about both the symptom and diagnosis, in order to assess test performance categories (sensitivity and specificity calculated from 2×2 contingency tables).

The search yielded 7928 articles. The titles of these were reviewed, and if thought to be relevant, the abstract was read. We retrieved 177 papers for full review. From these, we identified 62 eligible papers that provided relevant information. There was a wide range of symptoms included in the papers, with many papers providing information on several symptoms.

We extracted information about all symptoms, as well as combination of symptoms, if they were provided. We also extracted data about methodology, quality and

population characteristics. Items assessed included the clinical setting of the study, its primary purpose, whether participants all had a least one symptom or whether some were asymptomatic, and whether each participant could have only one or more than one symptoms reported, and study design items (prospective or retrospective data collection, year of publication, consecutive patient recruitment, study design, reference standard used).

Statistical analysis: Study specific estimates of sensitivity and specificity were analysed using the hierarchical summary ROC (HSROC) model of Rutter and Gatsonis [31]. This mixed model takes separate account of the uncertainty in the estimates of sensitivity and specificity within each study, and includes random study effects for both test accuracy and positivity criterion (proxy for threshold), thereby taking account of unexplained heterogeneity between studies. Study level covariates were fitted to assess whether test accuracy was associated with study or patient characteristics. More detailed descriptions of the methods are provided in the publication [13].

Quality of papers: Although some studies were of high quality, many were not. In some studies, inclusion and exclusion criteria were not stated, the same reference standard was not used for all patients in a study, and patients were not recruited consecutively (or it was unknown if this was the case). Symptoms were not elicited or interpreted consistently in the studies. There was also no consistent reference standard used in all studies (fewer than half the papers used colonoscopy as the reference standard).

Primary Clinical Study (the CRISP Study): Summary of Methodology

Patients were recruited between April 2004 and December 2006 from the practices of 54 gastroenterologists and 27 colorectal surgeons in NSW, Australia. All patients were over 18 years. A detailed history of bowel symptoms was obtained from self-administered questionnaire, which we had validated previously, and has been shown to be repeatable within patient and between patient and doctor [32].

All patients over the age of 18 years who were booked to undergo colonoscopy, irrespective of the indication for the procedure, were eligible to participate. We did not collect information about the indication. Questionnaires were completed within 6 months or less prior to the colonoscopy.

Elicitation of symptoms: Information was elicited about the following 11 symptoms: abdominal and anal pain, change in bowel habit, urgency, rectal bleeding, incomplete evacuation, rectal mucous, fatigue, weight loss, abdominal and anal lumps. These had an initial main question asking about the presence of the symptom, its characteristics, including severity, duration and timing. If the symptom was present, the participant was directed to further sub-questions about detail of that symptom, and whether the presence of the symptom alone would prompt seeking medical advice. The questionnaire also included questions about history of previous

bowel conditions (including bowel resection), anaemia, smoking, use of aspirin and non-steroidal anti-inflammatory medications, family history of colorectal cancer and demographic information.

Outcomes: We obtained the colonoscopy results of all patients who participated in the study. The colonoscopy procedure, histology and follow up of findings were done blinded to the symptom questionnaire results. We included only patients who had complete examinations of their colon in the final analysis. We considered examinations complete if the caecal pole or beyond was visualised at colonoscopy, or where this did not occur, if we received information about follow up investigations that evaluated the whole large bowel.

Statistical analysis: The prevalence of colorectal cancer for each of the subgroups defined by symptoms, demographics and other health information was calculated. Logistic regression was used to identify which symptoms were associated with cancer, individually, and a multiple logistic regression model was used to assess symptoms in combination, with all interactions statistically significant from previous models included. Backwards elimination was then used to simplify the model using likelihood ratio tests with $p < 0.05$ as the criterion for significance. Additional models were fitted to assess the incremental value of variables found to be statistically significant in the final multivariable model. More detailed description is given in the paper about this study [16].

References

1. Pernu J. An epidemiological study of the digestive organs and respiratory system. Ann Med Intern Fenniae Suppl. 1960;49(Suppl 33):1–117.
2. Majumdar SR, Fletcher RH, Evans AT. How does colorectal cancer present? Symptoms, duration, and clues to location. Am J Gastroenterol. 1999;94(10):3039–45.
3. Mulcahy HE, O'Donoghue DP. Duration of colorectal cancer symptoms and survival: the effect of confounding clinical and pathological variables. Eur J Cancer. 1997;33(9):1461–7.
4. John SK, George S, Primrose JN, Fozard JB. Symptoms and signs in patients with colorectal cancer. Colorectal Dis. 2011;13(1):17–25.
5. Chapuis PH, Goulston KJ, Dent OF, Tait AD. Predictive value of rectal bleeding in screening for rectal and sigmoid polyps. Br Med J Clin Res Ed. 1985;290(6481):1546–8.
6. Olde Bekkink M, McCowan C, Falk GA, Teljeur C, Van de Laar FA, Fahey T. Diagnostic accuracy systematic review of rectal bleeding in combination with other symptoms, signs and tests in relation to colorectal cancer. Br J Cancer. 2010;102(1):48–58.
7. Dent OF, Goulston KJ, Zubrzycki J, Chapuis PH. Bowel symptoms in an apparently well population. Dis Colon Rectum. 1986;29(4):243–7.
8. Goulston K, Chapuis P, Dent O, Bokey L. Significance of bowel symptoms. Med J Aust. 1987;146(12):631–3.
9. Cha JM, Kozarek RA, La Selva D, Gluck M, Ross A, Chiorean M, et al. Findings of diagnostic colonoscopy in young adults versus findings of screening colonoscopy in patients aged 50 to 54 years: a comparative study stratified by symptom category. Gastrointest Endosc. 2015;82(1):138–45.
10. NHS Cancer Screening Programmes. Bowel cancer: the facts (leaflet no 273372). 2016. Department of Health. www.gov.uk/phe/screening-leaflets.
11. Cancer Research UK. Bowel cancer: symptoms. http://www.cancerresearchuk.org/about-cancer/bowel-cancer/symptoms. Accessed February 2017.

12. The Jodie Lee Foundation. Bowel cancer: act quickly on symptoms. http://jodileefoundation.org.au/bowel-cancer/symptoms?gclid=COndtI3io9MCFYWXvAodPcYNTw. Accessed February 2017.
13. Adelstein B-A, Macaskill P, Chan SF, Katelaris PH, Irwig L. Most bowel cancer symptoms do not indicate colorectal cancer and polyps: a systematic review. BMC Gastroenterol. 2011;11:65.
14. Ford AC, Veldhuyzen van Zanten SJ, Rodgers CC, Talley NJ, Vakil NB, Moayyedi P, et al. Diagnostic utility of alarm features for colorectal cancer: systematic review and meta-analysis. Gut. 2008;57(11):1545–53.
15. Jellema P, van der Windt DAWM, Bruinvels DJ, Mallen CD, van Weyenberg SJB, Mulder CJ, et al. Value of symptoms and additional diagnostic tests for colorectal cancer in primary care: systematic review and meta-analysis. BMJ. 2010;340:c1269.
16. Adelstein BA, Irwig L, Macaskill P, Turner RM, Chan SF, Katelaris PH. Who needs colonoscopy to identify colorectal cancer? Bowel symptoms do not add substantially to age and other medical history. Aliment Pharmacol Ther. 2010;32(2):270–81.
17. Astin M, Griffin T, Neal RD, Rose P, Hamilton W. The diagnostic value of symptoms for colorectal cancer in primary care: a systematic review. Br J Gen Pract. 2011;61(586):e231–43.
18. Del Giudice ME, Vella ET, Hey A, Simunovic M, Harris W, Levitt C. Systematic review of clinical features of suspected colorectal cancer in primary care. Can Fam Physician. 2014;60(8):e405–15.
19. Young JP, Win AK, Rosty C, Flight I, Roder D, Young GP, et al. Rising incidence of early-onset colorectal cancer in Australia over two decades: report and review. J Gastroenterol Hepatol. 2015;30(1):6–13.
20. Siegel RL, Fedewa SA, Anderson WF, Miller KD, Ma J, Rosenberg PS, et al. Colorectal Cancer Incidence Patterns in the United States, 1974-2013. J Natl Cancer Inst. 2017;109(8):01.
21. Butterworth AS, Higgins JP, Pharoah P. Relative and absolute risk of colorectal cancer for individuals with a family history: a meta-analysis. Eur J Cancer. 2006;42(2):216–27.
22. Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Speizer FE, Willett WC. A prospective study of family history and the risk of colorectal cancer. N Engl J Med. 1994;331(25):1669–74.
23. Lieberman DA, Holub J, Eisen G, Kraemer D, Morris CD. Utilization of colonoscopy in the United States: results from a national consortium. Gastrointest Endosc. 2005;62(6):875–83.
24. Deeks JJ, Altman DG. Diagnostic tests 4: likelihood ratios. BMJ. 2004;329(7458):168–9.
25. Soares-Weiser K, Burch J, St John J, Smith S, Westwood M, Kleijnen J. Diagnostic accuracy and cost-effectiveness of faecal occult blood tests used in screening for colorectal cancer: a systematic review. York: Centre for Reviews and Dissemination; 2007 February.
26. Ortashi O, Virdee J, Hassan R, Mutrynowski T, Abu-Zidan F. The practice of defensive medicine among hospital doctors in the United Kingdom. BMC Med Ethics. 2013;14:42.
27. Hiyama T, Yoshihara M, Tanaka S, Urabe Y, Ikegami Y, Fukuhara T, et al. Defensive medicine practices among gastroenterologists in Japan. World J Gastroenterol. 2006;12(47):7671–5.
28. Elli L, Tenca A, Soncini M, Spinzi G, Buscarini E, Conte D. Defensive medicine practices among gastroenterologists in Lombardy: between lawsuits and the economic crisis. Dig Liver Dis. 2013;45(6):469–73.
29. Bird S. Diagnostic tests and litigation. Aust Prescriber. 2012;35(4):106.
30. Zauber AG, Winawer SJ, O'Brien MJ, Lansdorp-Vogelaar I, van Ballegooijen M, Hankey BF, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med. 2012;366(8):687–96.
31. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. Stat Med. 2001;20(19):2865–84.
32. Adelstein B-A, Irwig L, Macaskill P, Katelaris PH, Jones DB, Bokey L. A self administered reliable questionnaire to assess lower bowel symptoms. BMC Gastroenterol. 2008;8:8.

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