Systematic review of clinical features of suspected colorectal cancer in primary care

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Abstract

Objective To systematically review the diagnostic accuracy of clinical features associated with colorectal cancer (CRC) presenting in primary care.

Data sources MEDLINE and EMBASE were searched for studies in primary care that provided information on clinical features predictive of CRC. Positive predictive values were used to guide the determination of clinical features associated with increased risk of CRC.

Study selection Systematic reviews or primary studies that provided possible clinical features predictive of CRC were included.

Synthesis Clinical features of patients presenting in primary care that are associated with increased risk of CRC, listed in descending order of association, included palpable rectal or abdominal mass; rectal bleeding combined with weight loss; iron deficiency anemia; rectal bleeding mixed with stool; rectal bleeding in the absence of perianal symptoms; rectal bleeding combined with change in bowel habits; dark rectal bleeding; rectal bleeding and diarrhea; and change in bowel habits. Being male and increasing age were also, in general, associated with increased risk of CRC.

Conclusion Recognition of clinical features associated with increased risk of CRC by FPs might help with earlier identification and referral among patients presenting in primary care. This review might help inform providers and CRC diagnostic assessment programs about indications for assessment and further investigation.

EDITOR'S KEY POINTS
- Colorectal cancer (CRC) is a leading cause of cancer death in Canada. Early detection and management can lead to considerable reductions in mortality. For FPs and other primary care providers it is often difficult to distinguish the early presentation of CRC from other benign conditions.

- This systematic review and objective approach to stratifying clinical features into low and increased levels of CRC risk helped in the development of recommendations for symptomatic patients who should be referred at least as quickly as asymptomatic patients with positive fecal occult blood test screening results.

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Revue systématique des caractéristiques cliniques du cancer colorectal suspecté en contexte de soins primaires

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Résumé

Objectif Faire une revue systématique de la valeur diagnostique des caractéristiques cliniques associées au cancer colorectal (CCR) observé en première ligne.

Sources des données On a consulté MEDLINE et EMBASE à la recherche d'études effectuées en première ligne qui contenaient des informations sur les caractéristiques cliniques prédictives de CCR. La présence d'une valeur prédictive positive pour ces caractéristiques a permis d'établir celles qui sont associées à un risque augmenté de CCR.

Choix des études On a retenu les revues systématiques ou les études primaires qui portaient sur des caractéristiques cliniques pouvant être prédictives de CCR.

Synthèse Chez les patients du milieu des soins primaires, les caractéristiques cliniques associées à un risque accru de CCR sont, par ordre décroissant de probabilité, une masse rectale ou abdominale palpable; un saignement rectal avec amaigrissement; une anémie ferriprive; la présence de sang mélangé aux selles; un saignement rectal sans symptômes péri-anaux; un saignement rectal avec changement des habitudes intestinales; un saignement rectal foncé; un saignement rectal avec diarrhée; et un changement des habitudes intestinales. Le fait d'être un homme et d'avoir un certain âge était aussi associé à un risque accru de CCR.

Conclusion Le MF de première ligne qui connaît les caractéristiques cliniques associées à un risque accru de CCR devrait être en mesure d'identifier plus tôt les patients à risque et de les diriger en spécialité. Cette revue pourrait servir à informer les soignants ainsi que les programmes d'évaluation du diagnostic du CCR sur les cas où une évaluation et une investigation additionnelle sont indiquées.

POINTS DE REPÈRE DU RÉDACTEUR

- Au Canada, le cancer colorectal (CCR) est une des principales causes de mortalité due au cancer. Un diagnostic et un traitement précoces peuvent entraîner une diminution importante de la mortalité. Il est souvent difficile pour les MF et pour les autres soignants de première ligne de distinguer un CCR à un stade précoce de certaines affections bénignes.

- Cette revue systématique, complétée par une classification objective des caractéristiques cliniques selon qu'elles représentent un risque de CCR faible ou plus grand, a permis d'élaborer des recommandations pour identifier les patients qui devraient être orientés en spécialité au moins aussi rapidement que les patients asymptomatiques qui ont eu une recherche positive du sang occulte dans les selles.

Colorectal cancer (CRC) is one of the most common types of cancer in Canada.[1] There is strong evidence that screening using fecal occult blood testing (FOBT) reduces mortality from CRC and it should be strongly encouraged.[2] Although many jurisdictions across Canada have introduced population-based screening programs, screening rates are still low.[3] Patients who have either not been screened or who have interval signs or symptoms of CRC despite regular screening will rely on their FPs or other primary care providers to detect CRC. Cancer Care Ontario's Provincial Primary Care and Cancer Network has collaborated with the Program in Evidence-based Care to develop this updated systematic review and address the following question: What signs, symptoms, and other clinical features of patients who present in primary care are predictive of CRC?

DATA SOURCES

As a foundation, the authors chose a priori to update the literature review used to support the New Zealand Guidelines Group (NZGG) 2009 guidelines and the National Institute for Health and Care Excellence (NICE) 2005 guidelines.[4,5] These guidelines were considered to be of high quality based on assessment using the AGREE II (Appraisal of Guidelines Research and Evaluation) tool,[6,7] as well as being comprehensive, recent, and relevant to this topic.

The search strategies from the NZGG 2009 and NICE 2005 guidelines were kindly provided.[4,5] MEDLINE and EMBASE were searched for additional English-language papers published from January 2005 to August 2011. Reference lists of papers and review articles were scanned for further citations. Details about the search strategy are available upon request.

Evidence was selected by a methodologist (E.T.V.) and reviewed by the other authors. Systematic reviews and meta-analyses were assessed for quality using the AMSTAR (Assessment of Multiple Systematic Reviews) tool.[8] The quality of primary studies was assessed using a modified QUADAS (Quality Assessment of Diagnostic Accuracy Studies) tool, which is based on the Cochrane Collaboration method for assessing the methodologic quality of diagnostic studies.[9] Data were not pooled owing to considerable heterogeneity among studies.

Study selection
Systematic reviews or primary studies that provided possible clinical features predictive of CRC were included. An attempt was made to include only studies conducted in primary care. Studies conducted in secondary care settings were included if they provided predictive information about signs or symptoms for suspected CRC. Studies that did not have CRC as the main outcome, case reports, and CRC screening studies were excluded.

A post hoc decision was made to focus on positive predictive values (PPVs). A PPV is the probability that the disease is truly present when the test result is positive. Because PPVs are affected by the prevalence in the population, PPVs from studies conducted in secondary care settings were excluded. Studies that did not provide PPVs or for which the PPVs could not be calculated were excluded. Median PPVs were calculated only if PPVs for a specific clinical feature were reported in at least 4 studies.

Because many jurisdictions consider a positive guaiac FOBT screening result to be an indicator of increased risk of CRC, PPVs relative to a screen-positive FOBT result were used to stratify risk for individual or combinations of signs and symptoms of CRC. The median PPV for the combined guaiac FOBTs evaluated in a review was 5.7%.[10] Furthermore, a recent report evaluating the FOBT used in the ColonCancerCheck program in Ontario showed a PPV of 5.4% for single (1-time) testing in asymptomatic patients.[11] Clinical features with pooled PPVs from our systematic review and from published meta-analyses that were equal to or greater than the PPV for a positive asymptomatic screening FOBT result (5.4%) were considered high risk for CRC. A PPV greater than 5.4% is above the prevalence of CRC in Canada, which is 0.3% for all age groups and both sexes combined, and also above the prevalence in the demographic groups that have the highest prevalence of CRC (men aged 70 to 79 years and women aged 80 and older, each with a prevalence of 2%).[1]
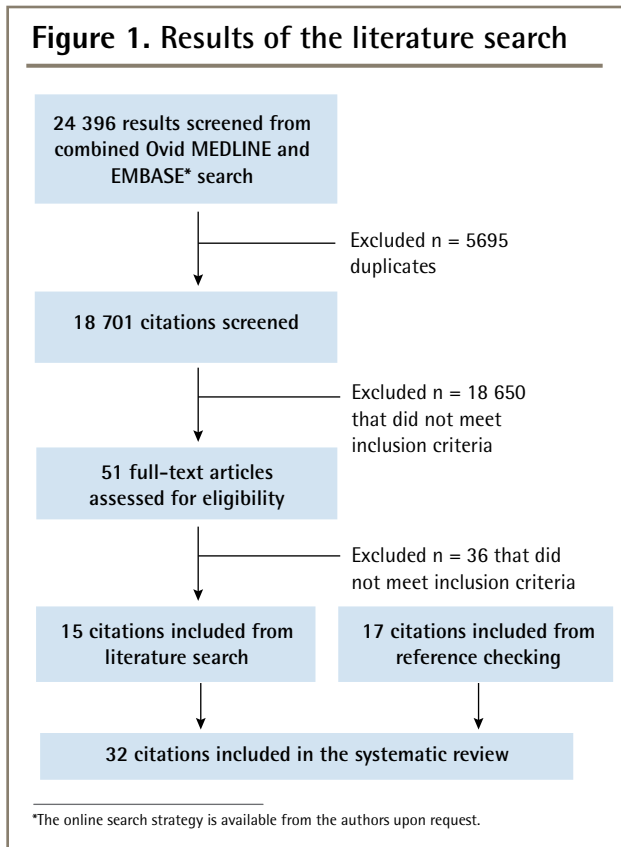
SYNTHESIS

Literature search results
Of 12 013 articles on CRC published since the NICE and NZGG guidelines searches, 51 were deemed relevant (**Figure 1**).[4,5] After full article reviews, 6 systematic reviews and 9 primary studies met the revised inclusion criteria and were retained.[12-26] In addition, 17 primary study articles were found in reference lists.[27-43]

Study design and quality
Reviews. Six systematic reviews, 5 with meta-analyses, investigated the diagnostic accuracy of symptoms or signs of CRC.[12,15,19,20,23,25] **Table 1** shows how the systematic reviews scored on each of the 11 AMSTAR items.[12,15,19,20,23,25] The 5 reviews with meta-analyses had high overall scores. The meta-analyses by Ford et al[15] and Jellema et al[19] focused on primary care referral and therefore were included in this current review despite their inclusion of

Figure 1. Results of the literature search

24 396 results screened from combined Ovid MEDLINE and EMBASE* search

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Excluded n = 5695 duplicates

18 701 citations screened

↓

Excluded n = 18 650 that did not meet inclusion criteria

51 full-text articles assessed for eligibility

↓

Excluded n = 36 that did not meet inclusion criteria

15 citations included from literature search   17 citations included from reference checking

↓

32 citations included in the systematic review

*The online search strategy is available from the authors upon request.

secondary care studies. Jellema et al included 2 secondary care studies that were classified as primary care studies by Ford et al.[15,19] Jellema et al included secondary care studies only if the prevalence of CRC was less than 15%, which was the highest prevalence reported in primary care studies.[19] The meta-analysis by Olde Bekkink et al included studies only from primary care; however, all the studies selected for patients with rectal bleeding.[23] Owing to low AMSTAR scores, the meta-analysis by John et al from 2011 was used only to search the reference list for additional studies.[20]

Primary studies. Relevant primary studies from the NZGG and NICE reviews and those identified in the current literature search and reference lists included 18 prospective studies[14,18,22,24,27,29-37,40-43]; 5 retrospective studies[13,21,26,28,39]; and 3 case-control studies.[16,17,38] The details and factors that might have affected the quality of each of these studies are highlighted in **Table 2**.[13,14,16-18,21,22,24,26-43] Because studies conducted in the UK 2-week referral clinics occurred at the interface between primary and secondary care, they were retained for this current review.[13,28,31]

What signs, symptoms, and other clinical features of patients who present in primary care are predictive of CRC? **Table 3** provides individual and median

PPVs for CRC for each clinical feature from primary studies, as well as pooled PPVs, pooled positive likelihood ratios (PLRs), and diagnostic performance measures including sensitivities and specificities from meta-analyses.[12-15,17-19,21,23-26,28-37,39-43] **Table 4** lists the clinical features of patients presenting in primary care that are associated with increased risk of CRC, listed in descending order of association.

Rectal or abdominal mass: Three studies conducted in the UK 2-week referral clinics found rectal and abdominal masses to be significant predictors of CRC.[13,28,31] The PPV for combined rectal or abdominal masses was 16.7% in one study.[13] Two studies found the PPVs were 80%[28] and 22.6%[31] for rectal masses and 41%[28] and 16.3%[31] for abdominal masses, respectively.

Anemia or iron deficiency anemia (IDA): For anemia defined as a hemoglobin level of less than 100 g/L, 2 different case-control studies by Hamilton et al found PPVs of 2.3% and 2.0% for all ages and both sexes combined.[16,17] When Hamilton et al (2008) and Lawrenson et al (2006) stratified patients by sex and age group, PPVs generally increased with age and were higher in men compared with women within each age group.[16,22] The highest PPVs in the Lawrenson et al study were found among men with anemia aged 70 to 79 (PPV = 3.38%) and among women with anemia aged 80 to 89 (PPV = 2.01%).[22] In the Hamilton et al study, PPVs were higher than 5% in both men or women older than 60 years of age with hemoglobin levels less than 90 g/L and men aged 60 to 69 or older than 79 years with hemoglobin levels of 90 to 99 g/L.[16] In most cases, these PPVs increased to greater than 10% if the patients were also iron deficient.

Six studies[13,26,28,31,37,42] that examined IDA found PPVs ranging from 7.7% to 40.6%, with a median of 11% (**Table 3**).[12-15,17-19,21,23-26,28-37,39-43] Regression analyses in both of the case-control studies by Hamilton et al found lower hemoglobin levels were significantly associated with increased CRC risk (P<.001).[16,17] Furthermore, microcytosis (mean corpuscular volume <80.0 fL) and low ferritin (<20 ng/mL) were both strongly associated with CRC.[16] Panzuto et al (2003) also found IDA (hemoglobin <140 g/L for men and <120 g/L for women, with ferritin <30 μg/L and mean corpuscular volume of <80 fL) to be a significant predictor of CRC (P<.001).[37]

Rectal bleeding: Twenty-one primary studies provided PPVs on rectal bleeding as a single presenting symptom.[13,14,17,18,21,22,24,27-34,36,37,39-41,43] In more than half of the studies of rectal bleeding broadly classified,[29,32-34,36,37,40,41,43] PPVs were greater than or equal to 5% (**Table 3**).[12-15,17-19,21,23-26,28-37,39-43]

Five of 6 studies[13,21,24,30,33,36] found higher PPVs for men (median PPV = 7.5%, range 2.4% to 17%) compared with women (median PPV = 3.9%, range 1.0% to 13%), collapsed across all ages (**Table 3**).[12-15,17-19,21,23-26,28-37,39-43]

Table 1. Evaluation of systematic reviews and meta-analyses using AMSTAR

	ASTIN ET AL,[12] 2011	FORD ET AL,[15] 2008	JELLEMA ET AL,[19] 2010	JOHN ET AL,[20] 2011	OLDE BEKKINK ET AL,[23] 2010	SHAPLEY ET AL,[25] 2010
No. of studies included	23	15	47	85	8	25
No. of patients included	81 464	19 443	NR	NR	2323	NR
AMSTAR items						
• Was an a priori design provided?	Yes	Yes	Yes	Yes	Yes	Yes
• Were there duplicate study selection and data extraction?	Yes	Yes	Yes	Yes	Yes	Yes
• Was a comprehensive literature search performed?	Yes	Yes	Yes	Yes	Yes	Yes
• Was the status of publication (eg, gray literature) used as an inclusion criterion?	Yes	Yes	Yes	Yes	Yes	Yes
• Was a list of studies (included and excluded) provided?	No	Yes	Yes	Yes	Yes	No
• Were the characteristics of the included studies provided?	Yes	Yes	Yes	No	Yes	Yes
• Was the scientific quality of the included studies assessed and documented?	Yes	Yes	Yes	No	Yes	Yes
• Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Yes	Yes	No	Yes	Yes
• Were the methods used to combine the findings of the studies appropriate?	Yes	Yes	Yes	NA	Yes	Yes
• Was the likelihood of publication bias assessed?	No	No	Yes	No	No	No
• Was the conflict of interest stated?	No	No	No	No	No	No
Total AMSTAR points*	8	9	10	5	8	8

AMSTAR—Assessment of Multiple Systematic Reviews, NA—not applicable, NR—not reported.
*Out of a possible total of 11.

Patients 50, 60, and 70 years of age or older with rectal bleeding had median PPVs for CRC of 5.9%, 8.6%, and 7.9%, respectively.[14,18,24,29,30,36,39,40,43] Jellema et al found a pooled PPV of 13% in patients older than 70 years of age.[19] In patients presenting with rectal bleeding, both Lawrenson and colleagues (2006)[22] and Jones and colleagues (2007)[21] observed increasing risk of CRC with increasing age; however, men had higher PPVs compared with women within each age group. Similarly, in a multivariate analysis of 29 007 patients with rectal bleeding, Parker et al (2007) found that the risk of CRC was strongly associated with age and was higher in men than in women.[39] Olde Bekkink et al found that being aged 60 years or older among patients with rectal bleeding almost tripled the posttest probability of CRC (pooled PLR = 2.8, 95% CI 2.0 to 3.9).[23]

Four studies[13,14,28,31] examined rectal bleeding without anal symptoms such as hemorrhoids and peri-anal eczema (median PPV = 10.8%, range 6.9% to 18%) (**Table 3**).[12-15,17-19,21,23-26,28-37,39-43] One study found that rectal bleeding with and without perianal symptoms had PPVs of 2% and 11%, respectively.[14]

In patients with rectal bleeding, the PPV for CRC of dark blood was higher than that for bright red blood within each of the 3 studies that compared shade of blood. The PPVs for dark rectal bleeding were 17.0%, 9.7%, and 9.7% compared with those for bright-red rectal bleeding of 9.9%, 4.0%, and 8.6%, in the 3 studies respectively.[14,33,34] Jellema et al found a pooled PPV of 14% (95% CI 9% to 21%) in patients with dark rectal bleeding.[19] In regression analyses, Ford et al found that the presence of dark rectal blood nearly quadrupled the posttest probability of CRC (PLR = 3.8, 95% CI 2.6 to 5.6).[15]

In 3 of 5 studies that explored location of blood in relation to stool, the PPVs for CRC when blood was mixed with stool (5.4%, 21%, and 14%, respectively)

Table 2. Characteristics of studies exploring signs or symptoms predictive of CRC: *Prospective, retrospective, and case-control studies conducted in primary care.*

STUDY	STUDY TYPE, LENGTH OF STUDY, AND COUNTRY	NO. OF PATIENTS	SPECIFIC INCLUSION AND EXCLUSION CRITERIA	NO. OF PATIENTS WITH CRC (%)	INVESTIGATION USED TO CONFIRM CRC (LENGTH OF FU)	CONSECUTIVE PATIENTS	BLINDING TO INDEX	MISSING DATA EXPLAINED	WITHDRAWALS EXPLAINED
Barwick et al,[13] 2004	Retrospective, 8 mo, UK	144	2WW	14 (9.7)	Various, including BE, SIG, US, CS	NR	No	NR	Yes
Bat et al,[27] 1992	Prospective, NR, Israel	101	≥80 y with rectal bleeding	29 (29.7)	CS	NR	No	No	No
Chohan et al,[28] 2005	Retrospective, 18 mo, UK	462	2WW	64 (13.9)	Histopathology	Yes	No	Yes	Yes
Du Toit et al,[29] 2006	Prospective, >10 y, UK	265	Age ≥45 y with rectal bleeding	15 (5.7)	Mostly SIG with BE, SIG, or CS (>10 y)	Yes	No	No	Yes
Ellis and Thompson,[14] 2005	Prospective, 18 mo, UK	319	Rectal bleeding	11 (3.4)	SIG and BE or CS (18 mo)	Yes	NR	Yes	Yes
Fijten et al,[30] 1995	Prospective, 20 mo, Netherlands	269	Rectal bleeding	9 (3.3)	CS, radiography, SIG, proctoscopy, US (>12 mo, mean 20 mo)	Yes	Yes	NR	Yes
Flashman, et al,[31] 2004	Prospective, 1 y, UK	695	2WW	65 (9.4)	NR	Yes	No	Yes	Yes
Hamilton et al,[16] 2008	Case control, NR, UK	3183 cases, 10 514 controls	Hb measured in year before diagnosis	3183 (100.0)	Electronic records	No	NR	Yes	NR
Hamilton et al,[17] 2005	Case control, NR, UK	349 cases, 1744 controls	NA	349 (100.0)	Cancer registry	No	Yes	Yes	Yes
Heintze et al,[18] 2005	Prospective, 1 y, Germany	422	Rectal bleeding	17 (4.0)	CS, SIG, rectoscopy	No	Yes	Yes	Yes
Helfand et al,[32] 1997	Prospective, NR, United States	201	Rectal bleeding	13 (6.5)	SIG plus BE (6-12 mo)	No	No	Yes	Yes
Jones et al,[21] 2007	Retrospective, 7 y, UK	7523 men, 7766 women	Rectal bleeding	184 (2.4) men, 154 (2.0) women	NR from research database	No	No	Yes	Yes
Lawrenson et al,[22] 2006	Prospective, NR, UK	2 793 468	Age 40-89 y	9143 (0.3)	Medical database (1 y)	Yes	No	No	Yes
Mant et al,[33] 1989	Prospective, >11 mo, Australia	145	Age >40 y with rectal bleeding	16 (11.0)	Most CS, some SIG and BE, histopathology	Yes	No	NR	Yes
Metcalf et al,[34] 1996	Prospective, NR, UK	99	Age >40 y with rectal bleeding	8 (8.1)	CS and histopathology	Yes	No	Yes	Yes
Muris et al,[35] 1993	Prospective, >15 mo, Netherlands	578	Abdominal pain	3 (0.5)	X-ray scan, US (15 mo)	Yes	NR	No	Yes
Nørrelund and Nørrelund,[36] 1996	Prospective; study 1: 3 y, study 2: 2 y; Denmark	Study 1: 208, study 2: 209	New rectal bleeding	Study 1: 32 (15.4), study 2: 22 (10.5)	BE and CS, histopathology, (study 1: 32-57 mo, study 2: 22-36 mo)	Yes	NR	No	Yes
Panzuto et al,[37] 2003	Prospective, 2 mo, Italy	280	Exclude previous CRC, recent large bowel examination	41 (14.6)	CS or BE	Yes	No	Yes	Yes
Park et al,[38] 2009	Nested case control, NR, UK	159 cases, 771 controls	NA	159 (100.0)	National cancer registry (average 12 y)	No	NR	NR	Yes
Parker et al,[39] 2007	Retrospective, 5 y, UK	29 007	Age ≥25 y with rectal bleeding	645 (2.2)	PC medical database (2 y)	Yes	No	Yes	Yes
Robertson et al,[24] 2006	Prospective, 4 y, UK	604	Rectal bleeding	22 (3.6)	SIG and hospital records (>4 y)	No	No	Yes	Yes
Sánchez et al,[40] 2005	Prospective, >3 mo, Spain	126	Rectal bleeding	6 (4.8)	CS	Yes	No	Yes	Yes
Steine et al,[41] 1994	Prospective, 9 mo, Norway	1852	NA	55 (3.0)	BE	Yes	Yes	Yes	Yes
Stellon and Kenwright,[42] 1997	Prospective, >5 y, UK	26	>50 y with IDA	2 (7.7)	SIG with or without BE	Yes	No	Yes	Yes
Wauters et al,[43] 2000	Prospective, 2 y, Belgium	386	Rectal bleeding	27 (7.0)	Histopathology (18-30 mo)	Yes	NR	Yes	NR
Yates et al,[26] 2004	Retrospective, 4 y, UK	431	New IDA	37 (8.6)	Various (≥12 mo)	Yes	No	Yes	Yes

2WW—2-wk wait program, BE—barium enema, CRC—colorectal cancer, CS—colonoscopy, FU—follow-up, Hb—hemoglobin, IDA—iron deficiency anemia, NA—not applicable, NR—not reported, PC—primary care, SIG—sigmoidoscopy, US—ultrasound, UK—United Kingdom.

Table 3. Clinical features of CRC: *Summary of findings. Empty cells indicate that the study did not examine the sign or symptom.*

PPV, % (95% CI)

STUDY	IDA	RB	RB AND MALE	RB AND FEMALE	RB AND ≥50 OR ≥55 Y	RB AND ≥60 OR ≥65 Y	RB AND ≥70 OR ≥75 Y	DARK RB	RB MIXED WITH STOOL	RB AND NO PERIANAL SYMPTOMS	RB AND ABD PAIN	RB AND WT LOSS	RB AND CBH	CBH OR DIARRHEA*	WT LOSS	ABD PAIN
Primary studies																
• Barwick et al,[13] 2004†	11		16 (9-28)	5 (2-12)						6.9 (14-24)					5	7
• Chohan et al,[28] 2005†	34 (21-50)									18				14 (9.5-19)		
• Du Toit et al,[29] 2006		5.7 (3.4-9.2)			6.1 (3.6-10)	8.6 (5-15)	7.9 (3.6-16)									
• Ellis and Thompson,[14] 2005		3.4 (3.6-16)											9.2 (4.7-15.9)			
• Fitjen et al,[30] 1995		3.3 (1.7-6.3)	5.9 (2.9-12)	1.0 (0.3-5.1)		5.2 (2.6-10)		9.7 (3.2-26)	3.0 (0.4-19)	11 (5.4-22)	2.2 (0.5-6.4)	9.5 (2.7-22.6)				
• Flashman et al,[31] 2004†	10.9 (5-22)					20 (10-35)			14 (3.6-43)	10.6 (6.7-16)						
• Hamilton et al,[17] 2005†		2.4 (1.9-3.2)									3.1 (1.9-5.3)	4.7		0.9* (0.7-1.1)	1.2 (0.9-1.6)	1.1 (0.9-1.3)
• Heintze et al,[18] 2005		4.0 (2.5-6.4)			5.6 (3.4-9.1)											
• Helfand et al,[32] 1997		6.5 (3.8-11)														
• Jones et al,[21] 2007		2.2 (2.0-2.5)	2.4 (2.1-2.8)	2.0 (1.7-2.3)												
• Mant et al,[33] 1989		10 (6.3-16)	9.1 (4.4-18)	13 (7-24)				17 (6.7-38)	21 (11-36)		9.3 (2.6-22.1)	14.3 (1.8-42.8)	10.7 (4.0-21.9)			
• Metcalf et al,[34] 1996		8.1 (4.1-15)						9.7 (3.2-26)	11 (4.6-24)		7.1 (1.5-19.5)	13.3 (1.7-40.5)	10.3 (2.9-24.2)			
• Muris et al,[35] 1993							31									0.5 (0.1-1.5)
• Norrelund and Norrelund,[36] 1996		14 (11-19)	17 (12-24)	13 (9-18)							23 (16-33)	22.7 (7.8-45.4)	27 (19-36)			
• Panzuto et al,[37] 2003†	40.6 (28.9-53.1)	16 (10-24)												12 (6.4-21)	35.7 (9.3-18.6)	13.5 (9.3-18.7)
• Parker et al,[39] 2007		2.2 (2.1-2.4)			4.0 (3.7-4.3)	4.6 (4.2-5.1)	4.9 (4.3-5.6) 7.5 (3.8-14)									
• Robertson et al,[24] 2006		3.6 (2.4-5.5)	4.8 (2.8-8)	2.7 (1.4-5.1)	5.7 (3.7-8.7)			7.4 (3.9-14)	5.4 (3.4-8.5)		1.7 (0.5-4.4)	4.8 (1.0-13.5)				
• Sánchez et al,[40] 2005		4.8			9.5											
• Steine et al,[41] 1994		5.9 (3.7-9.3)												3.0 (2.1-4.5)	4.8 (3-7.6)	2.1 (1.4-3.0)
• Stellon and Kenwright,[42] 1997	7.7															
• Wauters et al,[43] 2000		7.0 (4.6-10)			11 (7-15)	13 (9-19)	15 (9-22)					16 (4.5-36)				
• Yates et al,[26] 2004†	8.6 (6.1-11.6)															

Table 3 continued from page e411

STUDY	IDA	RB	RB AND MALE	RB AND FEMALE	RB AND ≥50 OR ≥55 Y	RB AND ≥60 OR ≥65 Y	RB AND ≥70 OR ≥75 Y	DARK RB	RB MIXED WITH STOOL	RB AND NO PERIANAL SYMPTOMS	RB AND ABD PAIN	RB AND WT LOSS	RB AND CBH	CBH OR DIARRHEA*	WT LOSS	ABD PAIN
Median PPV (95% CI) across primary studies	11	5.3	7.5	3.9	5.9	8.6	7.9	9.7	11	10.8	5.1	13	10.5	7.5	4.9	2.1
Meta-analyses																
Pooled PPV, % (95% CI)																
• Astin et al,[12] 2011	9.7 (3.5–26.8)				8.1 (6.0–10.8)						7.6 (3.0–19.2)	13.4 (8.2–21.9)	11.8 (6.8–20.4)			3.3 (0.7–15.7)
• Jellema et al,[19] 2010†	13* (11–34)	7 (5–12)			10 (7–13)	9 (8–10)	13 (8–31)	14 (9–21)	6 (4–10)		5* (0–23)	9* (5–23)	9* (5–50)			
• Shapley et al,[25] 2010		4.6 (3.7–5.5)					5.5 (3.9–7.2)									
Pooled PLR (95% CI)																
• Astin et al,[12] 2011		5.3 (1.7–17.1)									1.0 (0.6–1.7)	1.9 (1.3–2.8)	1.8 (1.3–2.5)	2.4 (1.6–3.8)	3.5 (2.1–5.8)	2.5 (1.1–5.6)
• Ford et al,[15] 2008	1.4 (0.8–2.7)	1.3 (1.2–1.5)						3.8 (2.6–5.6)						1.3 (1.1–1.6)	2.0 (1.3–3.1)	
• Olde Bekkink et al,[23] 2010†	3.7 (1.3–10.4)		1.2 (1.0–1.5)			2.8 (2.0–3.9)		1.4 (0.6–3.3)	1.9 (0.8–5.5)		0.9 (0.2–1.6)	1.9 (1.0–3.1)	1.9 (0.5–3.6)			
Pooled sensitivity (95% CI)																
• Astin et al,[12] 2011		17 (16–18)									33 (24–43)	19 (12–28)	58 (49–67.3)		11 (11–12)	31 (30–32)
• Ford et al,[15] 2008	17 (5.5–33)	64 (55–73)								15 (3–34)				41 (23–60)	22 (14–31)	
• Jellema et al,[19] 2010g	13 (11–34)		62 (44–78)		91 (86–96)	83 (73–93)	50 (36–63)	35 (25–41)	51 (9–77)		35 (0–40)	20 (13–44)	52 (10–100)			
• Olde Bekkink et al,[23] 2010†	17 (5–35)		58 (48–67)			66 (45–83)		22 (13–34)	40 (4–93)		25 (4–62)	17 (6–37)	62 (18–94)			
Pooled specificity (95% CI)																
• Astin et al,[12] 2011		98 (98–99)									63 (60–65)	89 (87–90)	63 (60–65)	69 (58–78)	96 (96–96)	91 (91–92)
• Ford et al,[15] 2008	90 (87–92)	52 (42–63)								96 (93–98)					89 (81–95)	
• Jellema et al,[19] 2010	92 (92–94)		55 (46–57)		36 (39–46)	55 (52–88)	79 (72–83)	85 (69–87)	71 (49–95)		59 (49–91)	89 (85–94)	61 (55–93)			
• Olde Bekkink et al,[23] 2010†	95 (93–96)		52 (48–56)			76 (68–83)		84 (69–93)	81 (23–98)		73 (52–89)	91 (83–96)	68 (53–80)			

ABD—abdominal, CBH—change in bowel habits, CRC—colorectal cancer, Hb—hemoglobin, IDA—iron deficiency anemia, PLR—positive likelihood ratio, PPV—positive predictive value, RB—rectal bleeding, WT—weight.

*Values for diarrhea were used when data on CBH were not available.

†Definitions of anemia: Barwick et al[13] and Chohan et al[28] used IDA and Hb <100 g/L; Flashman et al[31] used IDA and Hb <110 g/L for men and Hb <100 g/L for women; Hamilton et al[17] used Hb <99 g/L; Panzuto et al[37] used IDA and Hb <140 g/L for men and Hb <120 g/L for women; Yates et al[26] used IDA and Hb <120 g/L for men and <110 g/L for women; Olde Bekkink et al[23] used Hb <133 g/L for men and Hb <120 g/L for women.

‡Where data are not homogeneous, median and range are provided.

§Median and range are provided for all.

Table 4. Clinical features that indicate increased risk of CRC

CLINICAL FEATURE	MEDIAN PPV, % (RANGE)
Palpable rectal or abdominal mass	NA*
Rectal bleeding combined with weight loss	13.0 (4.7–23)
Iron deficiency anemia	11.0 (7.7–41)
Rectal bleeding mixed with stool	11.0 (3.0–21)
Rectal bleeding in the absence of perianal symptoms	10.8 (6.9–18)
Rectal bleeding combined with change in bowel habits	10.5 (9.2–27)
Dark rectal bleeding	9.7 (7.4–17)
Rectal bleeding and diarrhea	9.0 (3.4–19)
Rectal bleeding and age ≥60 or ≥65 y	8.6 (4.6–20)
Rectal bleeding and age ≥70 or ≥75 y	7.9 (4.9–31)
Change in bowel habit or diarrhea	7.5 (0.94–14)
Rectal bleeding and male	7.5 (2.4–17)
Rectal bleeding and age ≥50 or ≥55 y	5.9 (4–11)
Rectal bleeding (undefined)	5.3 (2.2–16)
Rectal bleeding and abdominal pain	5.1 (1.7–23)
Rectal bleeding, first episode	5.0 (2.2–14)

CRC—colorectal cancer, NA—not available, PPV—positive predictive value.
*Median not available; individual studies reported PPVs >15%.

were higher compared with the PPVs for blood separate from stool (1.9%, 6.6%, and 7%, respectively).[24,30,33] Jellema et al found a pooled PPV of 6% in patients with rectal bleeding mixed with stool.[19] In contrast, Ellis and Thompson found a PPV of 3.0% for rectal blood mixed with stool compared with 4.3% for rectal bleeding not mixed with stool.[14] In regression analyses, blood mixed with stool was a significant predictor of CRC.[24,30]

Robertson et al (2006) found higher PPVs when rectal blood was both mixed with stool and dark (10%), compared with when it was neither dark nor mixed with stool (1.9%).[24]

Change in bowel habits: Two studies investigated undefined or undifferentiated change in bowel habits,[37,41] 3 studies investigated diarrhea,[17,28,37] and 2 studies examined constipation[17,37] as predictors of CRC (**Table 3**).[12-15,17-19,21,23-26,28-37,39-43] In one study, the PPVs of change in bowel habits appeared to increase with age; however, for men PPVs were greater than 5% beginning at age 60 years, whereas for women the PPV never exceeded 4.09% even in the oldest age group.[22]

In regression analysis, change in bowel habits, including constipation or diarrhea, was found to be a significant predictor of CRC in 3 studies.[17,30,36] A study examining the association between the characteristics of changes in bowel habits and risk of CRC found that loose stools significantly increased the risk of CRC compared with

soft stools, after adjusting for age, sex, and lifestyle variables.[38] Frequency of bowel movement, stool quantity, feelings of discomfort, and laxative use were not significantly associated with risk of CRC.

Weight loss: The median PPV among the 4 studies[13,17,37,41] that looked at weight loss as a predictor of CRC was 4.9% (range 1.2% to 35.7%) (**Table 3**).[12-15,17-19,21,23-26,28-37,39-43] In regression analysis, loss of weight was found to be a significant predictor of CRC in 2 of these studies.[17,41] Significantly high PLRs for weight loss were found by Astin et al (PLR=3.5, 95% CI 2.1 to 5.8) and by Ford et al (PLR=2.0, 95% CI 1.3 to 3.1).[12,15]

Abdominal pain: In 5 studies[13,17,35,37,41] that explored abdominal pain or bloating as a predictor of CRC, the PPVs ranged from 0.5% to 13.5%, with a median of 2.1% (**Table 3**).[12-15,17-19,21,23-26,28-37,39-43] In regression analysis, abdominal pain and tenderness were each reported as significant predictors by Hamilton et al (*P*<.001).[17]

Rectal bleeding in combination with other symptoms and signs: In studies that examined the combination of rectal bleeding and change in bowel habits or diarrhea, or rectal bleeding and weight loss,[14,17,24,28,30,31,33,34,36,43] higher PPVs for the combination of symptoms compared with rectal bleeding alone were reported (median PPV for rectal bleeding=5.3%; median PPV for rectal bleeding and weight loss=13%; median PPV for rectal bleeding and change in bowel habits=10.5%) (**Table 3**).[12-15,17-19,21,23-26,28-37,39-43] The median PPV of rectal bleeding and diarrhea, derived from 7 studies, was 9% (data not shown).[14,17,24,28,30,31,34] In 3 studies, higher PPVs were seen for the combination of rectal bleeding and diarrhea compared with rectal bleeding and constipation.[14,17,34] Astin et al found that the probability of CRC almost doubled when there was a change in bowel habits (PLR=1.8, 95% CI 1.3 to 2.5) or weight loss (PLR=1.9, 95% CI 1.3 to 2.8) in patients with rectal bleeding.[12]

In only 2 of 6 studies, the combination of rectal bleeding and abdominal pain as presenting symptoms had a higher PPV compared with rectal bleeding alone.[17,24,30,33,34,36] Both Astin et al[12] and Olde Bekkink et al[23] also found low PLRs for abdominal pain in patients with rectal bleeding (**Table 3**).[12-15,17-19,21,23-26,28-37,39-43]

The PPVs in 2 studies that specifically reported on rectal bleeding and hemorrhoids were 3.1% and 3.3%.[24,33] Fijten et al reported a PPV of 18% in patients who presented with rectal bleeding and perianal eczema.[30]

In a meta-analysis by Olde Bekkink et al, IDA in patients with rectal bleeding had one of the highest PLRs (PLR=3.7, 95% CI 1.3 to 10.4) compared with all other signs or symptoms examined.[23]

DISCUSSION

Clinical features of patients presenting in primary care that might raise a suspicion of CRC were evaluated. Signs

and symptoms presenting in primary care that were considered to be associated with increased risk of CRC (listed in descending order of associated risk) included a palpable rectal or abdominal mass; rectal bleeding combined with weight loss; IDA; rectal bleeding mixed with stool; rectal bleeding in the absence of perianal symptoms; rectal bleeding combined with change in bowel habits; dark rectal bleeding; rectal bleeding and diarrhea; and change in bowel habits. A combination of clinical features, increasing age, and male sex generally increased the risk of CRC.

Limitations

The current literature search was an update of the searches completed for the NICE and NZGG guidelines.[4,5] We trusted that the original searches were equally extensive and that relevant articles were not missed. This review is limited to only those studies published in English. The consistency of results seen among primary studies, meta-analyses, and systematic reviews provides some reassurance that irretrievable literature would be unlikely to show contradicting evidence.

We were limited by the number of rigorous prospective studies that assessed signs or symptoms of CRC. Some studies did not recruit consecutive patients or were not blinded to the patients' diagnoses. There were also studies that did not adequately explain missing data, data that could not be interpreted, or the reasons for patient withdrawals. In addition, the reference standard of colonoscopy for detecting CRC was not always used. It was difficult to pool data owing to this considerable heterogeneity among studies. Furthermore, some studies selected patients with specific signs or symptoms such as rectal bleeding and, therefore, might not be representative of a primary care population.

As electronic medical records in primary care practices become more widely used, opportunities for rigorous large-sample prospective studies exploring the presentation of clinical features of cancers presenting in primary care will likely become increasingly more feasible.

Conclusion

This systematic review and objective approach to stratifying clinical features into low and increased levels of CRC risk helped assist in the development of recommendations for symptomatic patients who should be referred at least as quickly as asymptomatic patients with positive FOBT screening results.[44] This information might also be of value for informing indications for expedited assessment and investigation in CRC diagnostic assessment programs. Knowledge dissemination of clinical features that should raise suspicion of CRC could help with earlier identification and referral by primary care physicians, in addition to those patients identified through routine CRC screening. 🍁

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