Louise Olsson
Editor

Timely Diagnosis of Colorectal Cancer

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Preface

An overwhelming majority of colorectal cancer patients worldwide are diagnosed via the clinical route. Screening programmes are not implemented in all countries, compliance rates are far from complete, and the screening test itself is likely not to be fully sensitive. The aim of this book is therefore to target the searchlight, not on screening but on the important and difficult task of diagnosing colorectal cancer in symptomatic patients.

The design of the diagnostic process, or simply ordinary clinical work to diagnose disease, naturally involves those who are finally found to harbour a cancer. But it also involves a large number of patients who seek an explanation of their symptoms, potentially associated with bowel cancer. The challenge, in spite of all the alternative benign explanations, is to establish the diagnosis of colorectal cancer in a timely manner.

In our era of abundant information, and some disinformation, on the Internet, the acceptance of all but a very prompt investigation of symptoms possibly associated with serious diseases like cancer is decreasing. The claims from patients to rule out colorectal cancer very early on will probably get more pronounced. In addition, many countries face ageing populations, with an increasing risk of both gastrointestinal symptoms and colorectal cancer.

This book will be of interest to all professionals who struggle with these issues. Whether you are a qualified clinician, perhaps with a special interest in colorectal cancer, or a dedicated clinical researcher, the chapters will provide you with knowledge and inspiration at a cutting-edge level. Together they evoke some optimism for the way forward.

Non-invasive tests for an optimal selection of patients and further adequate examinations of the large bowel are crucial to sustain the increasing demands. You will find a hopeful chapter on the merits of faecal immunochemical tests, and a balanced discussion on computed tomographic colonography and colonoscopy. A new idea worth further exploration is the ability to make better use of already collected haemoglobin values by using computerized algorithms for trend analyses. The low predictive value of bowel symptoms is highlighted separately and, on the other hand, there is a valuable account of standardized colorectal cancer pathways based on the referral of alarm symptoms. You will also find two very thought-provoking chapters on a poor general awareness of colorectal cancer and on the psychological implications of diagnostic delay.

Let's hope the book will bring about many further optimizing ideas on how to proceed in the future. After all, a timely diagnosis is associated not only with a swift procedure, but also with a high clinical quality in the management of patients. Welcome to some rewarding hours of reading, and to share my appreciation of the authors. I also wish to express my gratitude to Evgenia Koutsouki at Springer for her professional support. Thank you all!

Stockholm, Sweden Louise Olsson

Contents

Awareness of Colorectal Cancer: Recognition of Symptoms and Risk Factors by Socio-demographic Characteristics

1

Maja Niksic and Lindsay J.L. Forbes

Key Points

- Only about 10% of participants, in a large survey of the English population, were aware that colorectal cancer is the third most common type of cancer in men and women.
- Almost half of participants could not recall any symptom (46%) or any risk factor (44%) for colorectal cancer.
- Awareness about cancer symptoms and risk factors varied greatly between different demographic groups, but the lowest awareness overall was observed among the most socio-economically deprived people.
- Over a third of participants (38%) reported that they would delay help-seeking for more than 2 weeks for "unexplained weight loss", but only 5% reported this for "unexplained bleeding".
- The results suggest an urgent need to improve public awareness of colorectal cancer symptoms symptoms and encourage early presentation.

1.1 Introduction

Colorectal cancer is the third most common malignant tumour diagnosed in males and the second in females, with over 1.3 million new cases and 694,000 deaths estimated to have occurred worldwide in 2012 [1]. In England it is the third most common type of cancer in both men and women [2]. In comparison with similar high-income countries such as Australia, Canada, Denmark, Norway, and Sweden,

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England has the lowest survival from colorectal cancer [3, 4]. Possible reasons for this finding include lack of awareness of cancer symptoms and late diagnosis [5–7]. A recent study reported that higher cancer symptom awareness is associated with better cancer survival, highlighting the need for effective early presentation campaigns [8].

Many people are not aware of early symptoms of colorectal cancer. Yardley et al. [9] reported that 69% of the general population in the UK was not able to identify a single symptom of colorectal cancer. Among patients attending a colorectal clinic in England, only 37% of patients could name a bowel cancer symptom [10]. This suggests that awareness of colorectal cancer symptoms was low, even among people who experienced some of the symptoms. Based on a national survey of 1520 people, Power et al. [11] concluded that people in England have relatively poor recognition of early symptoms of colorectal cancer, particularly when open-ended (unprompted recall) questions were used. Average recall was less than one symptom per person. "Change in bowel habit" was mentioned by only 23% of participants, "blood in stools" by 15%, less than 10% of participants mentioned any other symptom, and 25% stated they did not know any symptom of colorectal cancer. Although recognition of symptoms was better if prompted with a list of symptoms rather than with an open-ended question, men, younger participants, and the most socio-economically disadvantaged groups were least likely to recognise early cancer symptoms. More than 76% of participants recognised that a change in bowel habit, bleeding from the back passage, blood in stools and pain in abdomen could be symptoms of colorectal cancer.

Women and the socio-economically disadvantaged people had the lowest knowledge of risk factors for colorectal cancer [11]. For example, only 9% of people recalled that being overweight was a risk factor, and 37% recognised this factor from the list; 19% of people recalled that drinking alcohol was a risk factor, and 46% recognised it from the list; while older age was recalled by only 3% of people, 45% recognised this factor from the list. Similar results were reported in another study, where recall and recognition of colorectal cancer symptoms and risk factors was even lower [12]. One of the limitations of previous studies is that they have included few people from the oldest, youngest and most socio-economically disadvantaged groups, and the analyses were often not adjusted for potential confounding factors.

A systematic review concluded that poor recognition of symptoms of colorectal cancer and their seriousness increased delay in seeking medical help [13]. The researchers found no association between delay in help-seeking and patients' age, gender and socioeconomic position. In contrast, Robb et al. [14] found that people with lower socio-economic position (SEP) reported that they would take longer before seeking help for early symptoms of colorectal cancer and other common cancers than those with higher SEP. It seems that delay in help-seeking is more likely in patients diagnosed with colorectal cancer, than, for example, breast or bladder cancer [15]. However, not all symptoms appear to be linked with delay. Unexplained bleeding, especially rectal bleeding was linked with delay in help-seeking [15, 16], while change in bowel habit was reported to be a risk factor for delay in some studies [15, 17] but not in others [16, 18]. It is not clear which risk

factors are associated with delay in help-seeking, and how long it takes to visit a GP after noticing some of the most common symptoms of colorectal cancer.

To address these issues, we aimed to assess public awareness of symptoms of colorectal cancer, anticipated time to help-seeking in relation to these symptoms, knowledge about the most common types of cancer and risk factors for diagnosis of colorectal cancer in the English population, and whether these vary by socio-demographic factors.

1.2 Materials and Methods

We collated a uniquely large data set (n = 47,270), which allowed us to examine recall and recognition of cancer symptoms, risk factors and anticipated time to help-seeking with high statistical power, even after controlling for potential confounding factors. The data set included 18 cross-sectional surveys carried out across England during 2009/2011, which used the Cancer Research UK Cancer Awareness Measure (CAM) [19]. This is the first validated measure of public cancer awareness. The response rate was 51%. A more detailed description of the surveys and data collection procedure can be found elsewhere [20].

To explore whether participants are aware of the most common cancers in men and women, we asked the following questions: *"What do you think is the most/second most/third most common cancer in women?"*, and *"What do you think is the most/second most/third common cancer in men?"*. Awareness of cancer symptoms was measured with two types of questions, unprompted (open) and prompted (interviewer reads the list of possible answers). The unprompted question about cancer symptom was*: "There are many warning signs and symptoms of cancer. Please name as many as you can think of"*. Cancer symptom awareness was also measured using the prompted question: "*The following may or may not be warning signs of cancer. We are interested in your opinion. Do you think X is a warning sign for cancer?" (Yes/No/Don't know).* For the purpose of this analysis we used four symptoms, which were associated with colorectal cancer: *"unexplained pain", "unexplained bleeding", "persistent change in bowel or bladder habits"*, and *"unexplained weight loss"*. As this was a generic measure of public cancer awareness, the four symptoms used in this study were not exclusively linked to colorectal cancer. We do not know if participants had in mind specific type of pain (e.g. in one area of their body) or generic pain, or whether the bleeding they considered was occult or rectal. However, it is still relevant to know whether people have general awareness about these symptoms, which might be early symptoms of colorectal cancer.

To explore when a participant would seek help for one of these four symptom that they thought could be suggestive of cancer, we asked*: "If you had a symptom (X) that you thought might be a sign of cancer how soon would you contact your doctor to make an appointment to discuss it?"* We defined prompt presentation as "two weeks or less" and delay as "more than two weeks", as in previous studies [7, 14, 15].

Knowledge of risk factors for diagnosis of colorectal cancer was also assessed using open (unprompted) and closed (prompted) questions. The unprompted questions assessed which risk factors can participants recall unaided, using the following sentence: *"What things do you think affect a person's chance of getting cancer?"* The prompted questions were assessed using the following sentence: *"These are some of the things that can increase a person's chance of developing cancer. How much do you agree that each of these can increase a person's chance of developing cancer?" (Yes often/Yes sometimes/No/Don't know).*

For the purpose of this analysis we used the following risk factors associated with colorectal cancer: *"smoking any cigarettes at all", "exposure to another person's cigarette smoke", "drinking more than 1 unit of alcohol a day", "eating less than 5 portions of fruit and vegetables a day", "eating red or processed meat once a day or more", "being overweight (BMI over 25)", "being over 70 years old", "having a close relative with cancer", and "doing less than 30 minutes of moderate physical activity 5 times a week".* In all analyses we considered "No" and "Don't know" responses as lack of awareness about risk factors or cancer symptoms.

1.2.1 Analysis

Descriptive statistics were calculated for participants' socio-demographic characteristics (age groups, gender, marital status, education level, employment status, and SEP) in relation to recognition of four cancer symptoms, anticipated time to help-seeking, risk factors for developing cancer and knowledge about the three most common types of cancer in men and women. Age groups were defined based on previous literature and classifications that were used in different surveys across England, which were included in the data set. Marital status was defined using the following categories: married—including participants who were either married, living with a partner or in a civil partnership, single—including participants who were either not in a relationship or never married, separated—including participants who were either separated, divorced or widowed, and missing category—included those who stated that they "don't know" or "prefer not to say" their relationship status. Socio-economic position (SEP) was defined using five categories—from the most affluent to the least affluent. This was an area-based measure, estimated using information about participants' postcode of residence that we matched with the income domain of the Indices of Multiple Deprivation (IMD) [21], as previously described [20]. All analyses were done using Stata 14.0 [22]. This approach is frequently used to estimate SEP [15, 23, 24].

We assessed whether recognition of four cancer symptoms and anticipated delay in help-seeking in relation to these varied between socio-demographic groups using Kruskal-Wallis tests. We examined the association between socio-demographic factors (independent variables) and recognition of four cancer symptoms (dependent variables), using logistic regression models. In the multivariable logistic regression model we controlled for *a priori* confounders defined in previous studies; age group, gender and area income deprivation. To be able to control for these confounders, we excluded from the full data set (n = 49,270)

participants with missing information on gender (n = 58), age (n = 2431), and socio-economic position (n = 8151). The excluded observations were missing completely at random. However, we found patterns in missing observations on marital status, educational attainment and employment, suggesting that these data were not missing completely at random and could not be excluded from the data set. Therefore, we also presented logistic regression results for participants with missing data on these socio-economic variables. Despite deleted observations, our sample size remained large (n = 38,630).

1.3 Results

Socio-demographic characteristics of the sample are shown in Table 1.1. In general, the distribution of these characteristics in our sample was similar to that of the general population of England [25]. There were slightly more women in our sample

Table 1.1 Socio-demographic characteristics of the study sample

Sample	Sample n (%)
Total	38,630 (100)
Gender	
Women	21,606 (56)
Men	17,024 (44)
Missing	0 (0)
Age (years)	
15–54	24,312 (63)
55–74	12,028 (31)
75+	2290 (6)
Missing	0 (0)
Marital status	
Married	16,884 (44)
Single	7631 (20)
Separated	6075 (16)
Missing	8040 (21)
Education	
With degree	6932 (18)
Without degree	23,661 (61)
Missing	8037 (21)
Employment	
Employed	15,601 (40)
Not employed	7211 (19)
Retired	8051 (21)
Missing	7767 (20)
Quintile of area income deprivation	
1 (least deprived)	4595 (12)
2	5490 (14)
3	8118 (21)
4	8316 (22)
5 (most deprived)	12,111 (31)
Missing	0 (0)

(56%), the majority of our participants were married (44%), between 35 and 54 years of age (37%), without a university degree (61%), currently employed (40%), and slightly more lived in some of the most socio-economically deprived areas in England (31%).

1.3.1 Knowledge About the Most Common Types of Cancer

The correct answers were that in England the first, second and third most common types of cancer are: prostate, lung and colorectal cancer in men, and breast, lung and colorectal cancer in women [2]. This is very similar to cancer incidence worldwide, where lung, prostate and colorectal cancer in men, and breast, colorectal and lung cancer in women take the first, second and third place, respectively [1].

Knowledge about the most common types of cancer among men and women was poor. Only 12% of participants correctly reported that colorectal cancer is the third most common cancer in men, and only 9% correctly reported this for women (Fig. 1.1). Only 10% of participants correctly reported that lung cancer is the second most common cancer in men, while only 8% were aware that this is also the second most common cancer in women. The majority of participants correctly reported that breast cancer is the first most common cancer in women (67%), but only a third (33%) were aware that prostate cancer is the most common type of cancer in men (Fig. 1.1). About a third of participants thought colorectal cancer was in the top three cancers (36%).

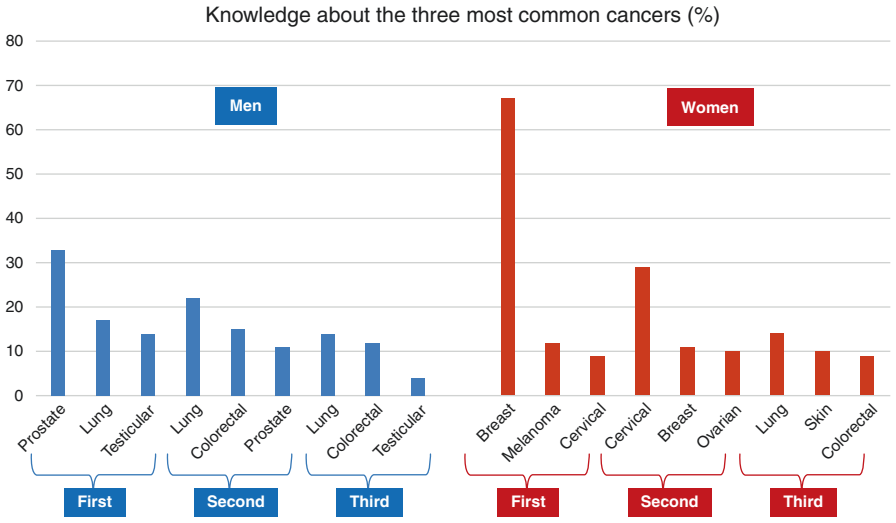

Fig. 1.1 Frequencies of reported most common types of cancer in men and women (%)

1.3.2 Awareness of Colorectal Cancer Symptoms

Almost a half of participants in our sample (46%) could not recall any of the four common symptoms of colorectal cancer: unexplained bleeding, change in bowel habit, unexplained weight loss or unexplained pain. Only 3% of participants were able to recall all these symptoms. When participants were asked to recognise the symptoms from the list (prompted), their results were better as 61% of participants recognised all four symptoms of colorectal cancer. Participants recognised on average 3 (mean: 3.3; SD: 1.0), and recalled less than one symptom out of a possible four (mean: 0.9; SD: 1.0).

Participants most frequently recalled "unexplained bleeding" (26%); and least frequently recalled "change in bowel habit" (14%) (Table 1.2). They most frequently recognised "change in bowel habit" (86%); and least frequently recognised 'unexplained persistent pain' (78%) as potential symptoms of colorectal cancer. There were statistically significant differences between socio-demographic groups in cancer symptom awareness (Table 1.2). Overall, participants who least frequently recalled and recognised the four cancer symptoms were men, the youngest, participants with low SEP, currently unemployed and single. For example, 'unexplained bleeding' was recalled by 23% of men (vs. 28% women), 18% of participants between 15 and 34 years old (vs. 31% of 55–74 year-olds), 23% of those with the lowest SEP (vs. 28% of the highest SEP), 25% of participants without a university degree (vs. 31% with a degree), 22% of the unemployed (vs. 27% of the employed), and 18% of single participants (vs. 28% of married ones).

These results persisted in the multivariable logistic regression analysis, where age group, gender, marital status, educational level, employment status, and SEP were all associated with recognition of each cancer symptom (Table 1.3). Women were more likely than men to recognise cancer symptoms, except "unexplained persistent pain". For example, the odds of recognising "unexplained bleeding" were about 50% higher in women than men (OR = 1.49; 95% confidence interval (CI): 1.41–1.58). The youngest participants were least likely to recognise each of the symptoms, with the exception of an "unexplained, persistent pain" which was least likely recognised by 75+ year-olds (OR = 0.70; 95%CI: 0.63–0.77). Participants aged between 55 and 74 were most likely to recognise each of the four possible symptoms of cancer. There was a strong trend suggesting that the lower the SEP, the less likely the participants were to recognise the symptoms.

Participants who were single were least likely to recognise "unexplained persistent pain" (OR = 0.89; 95%CI: 0.84–0.96), while the other three symptoms were least likely to be recognised by participants with missing data. However, when we excluded those who have not provided data on marital status from the analysis, single participants were statistically significantly less likely to recognise all symptoms than married participants. We observed similar pattern with educational attainment and employment status. When we excluded participants with missing

Table 1.2 Recognition of symptoms of colorectal cancer and anticipated delay >2 weeks to help-seeking % (n)

Recognition of four symptoms of colorectal cancer and anticipated time to help-seeking % (n)												
	Unexplained bleeding		Anticipated delay > weeks	Change in bowel habit		Anticipated delay > weeks	Unexplained pain		Anticipated delay > weeks	Unexplained weight loss		Anticipated delay > weeks
	Unprompted	Prompted		Unprompted	Prompted		Unprompted	Prompted		Unprompted	Prompted	
All participants	26 (9951)	85 (32,811)	5 (1793)	14 (5577)	86 (33,240)	19 (7193)	24 (9130)	78 (30,135)	12 (4567)	23 (9000)	84 (32,301)	38 (14,281)
Gender												
Men	*23 (3951)	*82 (13,971)	5 (812)	*13 (2312)	*84 (14,314)	13 (2100)	*23 (3848)	78 (13,317)	*13 (2100)	*22 (3760)	*81 (13856)	*37 (6153)
Women	28 (6000)	87 (18,840)	5 (981)	15 (3265)	88 (19,026)	12 (2467)	24 (5282)	78 (16,818)	12 (2467)	24 (5240)	85 (18,445)	39 (8128)
Age group												
15–34	*18 (1848)	*78 (7856)	*5 (479)	*9 (879)	*79 (7983)	*19 (1834)	*21 (2097)	*77 (7683)	*11 (1138)	*21 (2082)	*76 (7604)	*40 (3940)
35–54	27 (3825)	86 (12,293)	5 (746)	13 (1914)	87 (12,449)	21 (2890)	24 (3446)	79 (11,263)	13 (1827)	25 (3527)	85 (12,149)	40 (5628)
55–74	31 (3736)	89 (10,763)	4 (480)	20 (2431)	92 (10,935)	19 (2171)	26 (3071)	79 (9520)	12 (1380)	24 (2915)	89 (10,673)	36 (4045)
75+	24 (542)	83 (1899)	4 (88)	15 (353)	86 (1973)	13 (298)	22 (516)	73 (1669)	10 (222)	21 (476)	82 (32,301)	30 (668)
Quintile of area income deprivation												
1 (most affluent)	*28 (1294)	*88 (4063)	*6 (268)	*17 (771)	*90 (4131)	*24 (1088)	*26 (1191)	*81 (3720)	*15 (697)	*21 (983)	*85 (3925)	*44 (2009)
2	28 (1557)	88 (4854)	5 (281)	17 (928)	90 (4935)	21 (1143)	24 (1309)	81 (4437)	13 (720)	21 (1145)	86 (4752)	41 (2186)
3	27 (2183)	86 (7027)	5 (416)	16 (1322)	88 (7148)	20 (1582)	25 (2014)	80 (6513)	13 (1033)	23 (1883)	85 (6913)	40 (3124)
4	25 (2111)	83 (6844)	4 (369)	14 (1216)	85 (7076)	18 (1426)	24 (1988)	77 (6380)	11 (922)	27 (2227)	82 (6829)	34 (4005)
5 (most deprived)	23 (2806)	92 (9923)	4 (459)	11 (1340)	83 (10,050)	17 (1954)	22 (2628)	75 (9085)	10 (1195)	23 (2762)	82 (9882)	38 (14,281)
Education												
With degree	*31 (2198)	*89 (6177)	5 (356)	*19 (1328)	*91 (6282)	*24 (1618)	*30 (2100)	*84 (5836)	*14 (970)	*31 (2146)	*88 (6071)	*44 (2999)
No degree	25 (5831)	85 (20,186)	5 (1101)	14 (3210)	87 (20,629)	18 (4159)	22 (5213)	76 (18,117)	12 (2721)	22 (5284)	84 (19,939)	35 (8051)
Missing	24 (1922)	80 (6448)	4 (336)	13 (1039)	80 (6429)	19 (1416)	23 (1817)	77 (6182)	11 (876)	19 (1570)	78 (6291)	42 (3231)

Employment												
Employed	*27 (4235)	*87 (13,613)	*5 (790)	*15 (2331)	*89 (13,840)	*21 (3180)	*25 (3948)	*80 (12,422)	*13 (2021)	*26 (4093)	*85 (13,289)	*40 (6092)
Unemployed	22 (1561)	80 (5798)	5 (385)	10 (728)	82 (5939)	19 (1307)	21 (1488)	75 (5422)	12 (839)	22 (1605)	81 (5829)	35 (2474)
Retired	30 (2437)	89 (7162)	4 (278)	21 (1723)	91 (7357)	17 (1294)	26 (2117)	78 (6295)	11 (832)	24 (1980)	88 (7118)	33 (2466)
Missing	22 (1718)	80 (6238)	4 (340)	10 (795)	80 (6204)	18 (1412)	20 (1577)	77 (5996)	11 (875)	17 (1322)	78 (6065)	43 (3249)
Marital status												
Married	*28 (4807)	*88 (14,864)	*4 (719)	*17 (2815)	*90 (15,169)	19 (3140)	*26 (4327)	*79 (13,373)	*12 (1952)	*25 (4200)	*87 (14,692)	*37 (6093)
Single	18 (1413)	80 (6122)	6 (438)	8 (594)	82 (6301)	19 (1443)	19 (1423)	76 (5837)	13 (967)	22 (1703)	79 (6019)	37 (2739)
Separated	28 (1718)	88 (5364)	5 (290)	17 (1044)	90 (5442)	19 (1129)	25 (1529)	77 (4707)	13 (725)	24 (1491)	87 (5288)	36 (2064)
Missing	25 (2013)	80 (6461)	4 (346)	14 (1124)	80 (6428)	19 (1481)	23 (1851)	77 (30,135)	12 (923)	20 (1606)	78 (6302)	43 (3385)

*Values were significant at 95% Confidence Interval ($p<0.05$), using Kruskal-Wallis tests

Table 1.3 Recognition of symptoms of colorectal cancer by socio-demographic group, in models adjusted for age group, gender and area income deprivation (n = 38,630)

*Recognition of symptoms OR (95%CI, *p-value < 0.05)*				
	Unexplained bleeding	Change in bowel/ bladder habit	Unexplained persistent pain	Unexplained weight loss
Gender[a]				
Men	1.00	1.00	1.00	1.00
Women	1.49* (1.41–1.58)	1.40* (1.32–1.49)	0.97 (0.93–1.02)	1.33* (1.26–1.40)
Age group[a]				
15–34	0.43* (0.40–0.46)	0.40* (0.37–0.43)	0.88* (0.82–0.94)	0.40* (0.37–0.43)
35–54	0.73* (0.67–0.79)	0.68* (0.63–0.74)	0.99 (0.93–1.05)	0.72* (0.67–0.78)
55–74	1.00	1.00	1.00	1.00
75+	0.56* (0.49–0.63)	0.61* (0.53–0.69)	0.70* (0.63–0.77)	0.56* (0.50–0.64)
Quintile of area income deprivation[a]				
1 (most affluent)	1.00	1.00	1.00	1.00
2	0.98 (0.87–1.11)	0.98 (0.86–1.21)	0.98 (0.89–1.09)	1.08 (0.96–1.21)
3	0.84* (0.75–0.94)	0.83* (0.73–0.93)	0.94 (0.86–1.04)	0.98 (0.88–1.09)
4	0.67* (0.60–0.75)	0.65* (0.58–0.73)	0.77* (0.70–0.84)	0.80* (0.72–0.88)
5 (most deprived)	0.60* (0.54–0.67)	0.56* (0.50–0.62)	0.70* (0.64–0.76)	0.77* (0.69–0.85)
Marital status[b]				
Married	1.00	1.00	1.00	1.00
Single	0.73* (0.67–0.78)	0.70* (0.64–0.77)	0.89* (0.84–0.96)	0.75* (0.69–0.80)
Separated	0.97 (0.88–1.07)	0.89* (0.80–0.98)	0.95 (0.88–1.02)	0.92 (0.84–1.01)
Missing	0.61* (0.57–0.66)	0.49* (0.46–0.53)	0.90* (0.84–0.96)	0.61* (0.56–0.65)
Education[b]				
With degree	1.00	1.00	1.00	1.00
No degree	0.70* (0.64–0.76)	0.67* (0.61–0.73)	0.64* (0.59–0.69)	0.74*(0.68–0.80)
Missing	0.51* (0.46–0.56)	0.42* (0.38–0.46)	0.64* (0.59–0.69)	0.52* (0.47–0.57)
Employment[b]				
Employed	1.00	1.00	1.00	1.00
Unemployed	0.65* (0.60–0.71)	0.66* (0.61–0.72)	0.82* (0.77–0.88)	0.81* (0.75–0.87)
Retired	0.94 (0.84–1.05)	1.06 (0.94–1.19)	0.98 (0.90–1.07)	1.04 (0.94–1.16)
Missing	0.60* (0.55–0.64)	0.50* (0.46–0.54)	0.87* (0.82–0.93)	0.63* (0.58–0.67)

[a]These estimates were derived from a model including gender, age and quintile of area income deprivation. Each model was adjusted for the other two co-variables, respectively

[b]These estimates were derived from a model including gender, age and area income deprivation adjustment, as well as one of the three co-variables: marital status, education, employment

data on these variables from the analysis, unemployed participants and those without a university degree were less likely to recognise all cancer symptoms than the employed and those with a degree (Table 1.3). Participants with the lowest SEP were least likely to recognise all cancer symptoms, and the lower their SEP the less likely they were to recognise the symptoms. For example, the most socio-economically deprived participants were about half as likely as the most affluent to

recognise "change in bowel habit" (OR = 0.56; 95%CI: 0.50–0.62) as a possible early symptom of cancer.

1.3.3 Anticipated Delay in Help-Seeking

Over a third of participants reported that they would delay help-seeking for more than 2 weeks for "unexplained weight loss" (38%), but only 5% of them reported that they would do the same for "unexplained bleeding" (Table 1.2). Approximately a fifth of all participants reported that they would delay help-seeking if they experienced a "change in bowel habit". There were statistically significant differences between some socio-demographic groups in anticipated delay in help-seeking, although these differences were not large (Table 1.2). We did not observe a clear trend for anticipated delay in help-seeking between men and women. Women slightly more frequently reported that would delay more than 2 weeks for seeking help for "unexplained weight loss", while men were more likely to delay help-seeking for "unexplained persistent pain". More participants from younger age groups (15–34, and 35–54) reported that they would delay seeking medical help for all symptoms longer than 2 weeks, in comparison with participants from the two older age groups. More participants from the most affluent SEP reported that they would delay help-seeking than those from the least affluent SEP. For example, 44% of the most affluent participants stated that they would delay more than 2 weeks to seek help for "unexplained weight loss" in comparison with 34% of the less privileged. Although differences in terms of education were small they were statistically significant for: "unexplained persistent pain", "unexplained weight loss", and "change in bowel habit", which participants with a degree were most likely to delay discussing with their GP. There were slightly more employed participants who reported that they would delay visiting their GP for "unexplained persistent pain" and "change in bowel habit", then unemployed or retired participants. There were no clear patterns in anticipated delay in help-seeking in terms of marital status.

1.3.4 Risk Factors

Almost a half of participants in our sample (44%) could not recall any of the seven risk factors for colorectal cancer, and only 2% of participants were able to recall all seven risk factors. The results were not much better when participants were asked to recognise the risk factors from a list. Only 8% of participants recognised all seven risk factors and 7% were not able to recognise any of the risk factors, from prompted questions. Participants recognised on average 3 (mean: 3.3; SD: 2.0), and recalled one risk factor out of a possible seven (mean: 1.1; SD: 1.5).

Approximately a third of all participants (35%) were able to remember (recall) that "drinking >1 unit of alcohol a day" might be a risk factor of colorectal cancer

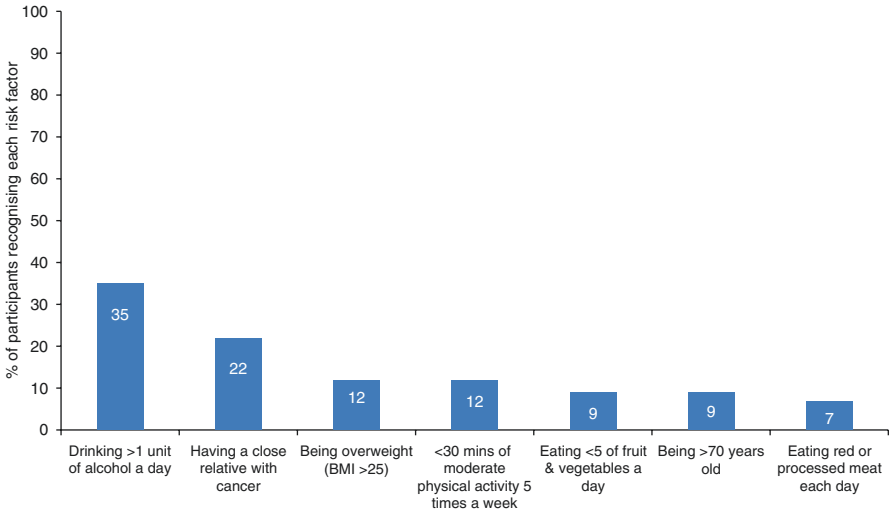

Fig. 1.2 Frequency of recall of risk factors for colorectal cancer

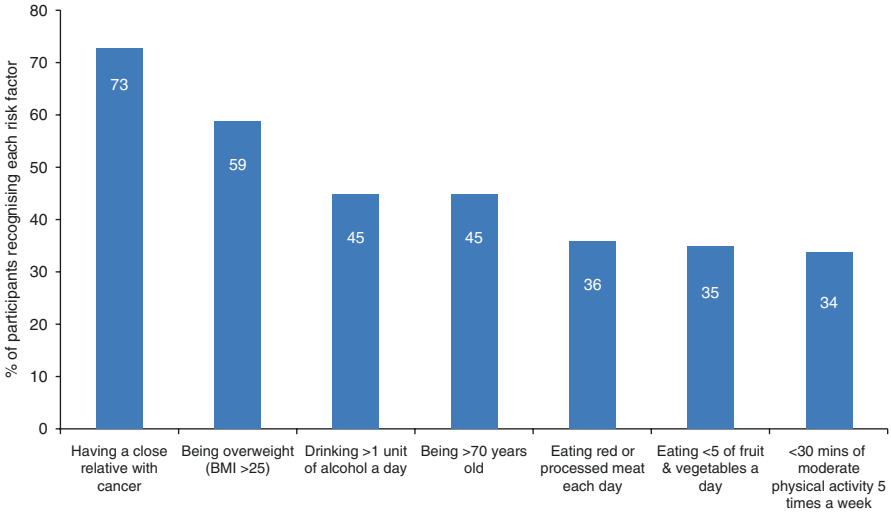

Fig. 1.3 Frequency of recognition of risk factors for colorectal cancer (prompted questions)

(Fig. 1.2). Participants were least likely to recall "eating red or processed meat each day" might be a risk factor of colorectal cancer (7%).

In terms of additional risk factors participants mentioned the following: diet (26%), genes (16%), stress (12%), a high fat diet (10%), a low fibre diet (10%) and all other factors were mentioned by less than 10% of participants. Interestingly, 12% of participants stated that they are not aware of any cancer risk factor, while 22% reported that "nothing" could be called a risk factor for cancer.

Table 1.4 Recognition of risk factors for colorectal cancer using prompted questions (% (n))

Recognition of risk factors of colorectal cancer % (n)							
	Drinking >1 unit of alcohol a day	Eating <5 of fruit and vegetables a day	Eating red or processed meat each day	Being overweight (BMI >25)	Being >70 years old	Having a close relative with cancer	<30 min of moderate physical activity five times a week
All participants	45 (16,845)	35 (12,913)	36 (13,358)	59 (21,978)	45 (16,823)	73 (27,130)	34 (12,776)
Gender							
Men	*43 (7070)	*34 (5573)	35 (5839)	*59 (9647)	48 (7787)	*69 (11,345)	*35 (5781)
Women	47 (9775)	35 (7340)	36 (7519)	58 (12,331)	43 (9036)	75 (15,785)	33 (6995)
Age group							
15–34	*49 (4723)	*31 (3042)	*33 (3191)	*58 (5669)	*47 (4574)	*73 (7087)	*35 (3377)
35–54	45 (6187)	37 (5067)	38 (5186)	59 (8118)	46 (6285)	75 (10,432)	35 (4826)
55–74	43 (5039)	35 (4119)	37 (4286)	60 (6982)	44 (5051)	71 (8279)	34 (3902)
75+	42 (896)	31 (685)	31 (695)	55 (1209)	42 (913)	61 (1332)	31 (671)
Quintile of area							
1 (most affluent)	*43 (1875)	*38 (1666)	*40 (1720)	*64 (2802)	*49 (2108)	*76 (3296)	*38 (1633)
2	44 (2290)	35 (1847)	37 (1952)	60 (3167)	47 (2447)	73 (3823)	34 (1811)
3	45 (3564)	36 (2815)	37 (2936)	60 (4702)	46 (3610)	73 (5776)	35 (2774)
4	46 (3668)	34 (2748)	37 (2932)	58 (4669)	46 (3651)	72 (5750)	33 (2670)
5 (most deprived)	46 (5448)	32 (3837)	32 (3818)	56 (6638)	42 (5007)	71 (8485)	33 (3888)
Education							
With degree	47 (3125)	*42 (2849)	*45 (3015)	*67 (4504)	*54 (3,625)	*78 (5262)	*41 (2751)
No degree	45 (10,120)	31 (7097)	32 (7165)	57 (12,851)	42 (9526)	71 (16,122)	31 (7107)
Missing	45 (3600)	37 (2967)	40 (3178)	58 (4623)	46 (3672)	72 (5746)	36 (2918)
Employment							
Employed	*45 (6701)	*34 (5214)	*36 (5364)	*60 (8992)	*46 (6870)	*75 (11,280)	*34 (5169)
Unemployed	47 (3276)	32 (2196)	32 (2199)	56 (3922)	45 (3117)	72 (4998)	32 (2214)
Retired	44 (3376)	34 (2613)	35 (2704)	60 (4589)	43 (3243)	68 (5232)	33 (2517)
Missing	45 (3492)	37 (2890)	40 (3091)	58 (4475)	46 (3593)	72 (5620)	37 (2876)
Marital status							
Married	*45 (7252)	*35 (5663)	*35 (5679)	*60 (9790)	*45 (7271)	*74 (11,927)	*34 (5487)
Single	47 (3457)	32 (2357)	35 (2526)	58 (4234)	47 (3397)	71 (5231)	34 (2492)
Separated	44 (2562)	33 (1917)	34 (1973)	56 (3279)	42 (2438)	71 (4152)	31 (1825)
Missing	45 (3574)	37 (2976)	40 (3180)	58 (4675)	46 (3717)	72 (5820)	37 (2972)

*Values were significant at 95% Confidence Interval ($p < 0.05$), using Kruskal-Wallis tests

In terms of prompted questions, 73% of participants were able to recognise that "drinking more than 1 unit of alcohol a day" might be a risk factor of colorectal cancer, and 59% of participants were able to recognise "being overweight" as a risk factor (Fig. 1.3). Participants were least likely to recognise that "eating red or processed meat each day", "eating less than 5 of fruit and vegetables a day" and "less than 30 minutes of moderate physical activity 5 times a week" were risk factors, which were reported by approximately a third of all participants (Fig. 1.3).

There were statistically significant differences between some socio-demographic groups in recognition of risk symptoms of colorectal cancer (Table 1.4). Women

slightly less frequently reported risk factors related to physical appearance, such as "being overweight" and "moderate physical activity"; while men less frequently reported risk factors related to consumption, such as "drinking more than 1 unit of alcohol a day" and "eating less than 5 of fruit and vegetables a day". The elderly (75+ year-olds), the underprivileged and participants without a degree least frequently recognised all risk factors. The only exception was observed for "drinking more than 1 unit of alcohol a day", which was least frequently recognised by participants from the most affluent SEP. There were no clear patterns in recognition of cancer risk factors in terms of employment and marital status.

1.4 Discussion

Knowledge about the most common types of cancer was very poor, as only about 10% of participants were aware that colorectal cancer is the third most common type of cancer in men and women. Only a third of participants knew that colorectal cancer was among the top three common cancers. Almost a half of participants could not recall any symptom (46%) or any risk factor (44%) of colorectal cancer. Overall, participants who least frequently recalled and recognised the four cancer symptoms were men, the youngest, participants with low SEP, currently unemployed and single. Over a third of participants reported that they would delay help-seeking for more than 2 weeks for "unexplained weight loss" (38%), but only 5% of them reported that they would do the same for "unexplained bleeding". Anticipated delay to help-seeking was more frequently reported among the youngest, the affluent and participants with a university degree. Recognition of cancer risk factors was better than recall. Approximately a third of our participants recognised that "eating red or processed meat each day", "eating less than 5 of fruit and vegetables a day" and "less than 30 minutes of moderate physical activity five times a day" were risk factors for cancer, and only about 10% was able to recall them. Less than every tenth recalled age being the most important risk factor. The elderly (75+ year-olds), the underprivileged and participants without a degree least frequently recognised all risk factors.

1.4.1 Strengths and Limitations

Strengths of this study include a large, population-based sample, which enabled us to do robust statistical analyses on a number of socio-demographic factors and to adjust for potential confounding factors. We are reasonably confident that our sample was representative of the English population. We also used a validated measure of public cancer awareness. The interviewers were trained to ensure they appear neutral during data collection and to reassure participants of confidentiality and anonymity. This may have reduced potential interviewer bias and a tendency of some participants to give socially desirable answers.

Possible limitations are that about a fifth of our study population refused to provide information of their marital status, educational attainment and employment status. It is possible that some participants felt that this information, which was optional in the CAM questionnaire, was too personal to share with an interviewer. However, we were not able to exclude participants with missing information on these three variables or to impute these missing values, because their data were not missing completely at random. It is possible that some participants were focusing on change in bladder habits, because an interviewer asked about a *"persistent change in bowel or bladder habits"*. We cannot identify the exact proportion of participants who focused on either of these sets of symptoms, or whether some participants considered them together. Some socio-demographic groups may have a propensity for acquiescence bias, i.e. to give more "yes" then "no" responses during interviews [26]. This might explain some of the differences observed between recall and recognition of cancer symptoms and risk factors. However, it is more likely to believe that participants were able to remember a range of different symptoms and risk factors once the interviewer read them from the list.

1.4.2 Comparison with Previous Studies

Our findings confirm results of previous studies that people in England are able to freely recall only one or less than one symptom of colorectal cancer [11, 12]. Unexplained bleeding was the most frequently recalled symptom—by 26% of participants in our sample, and 15% [11], or 36% [12] in other studies. A recent study evaluating the effects of the first national bower cancer awareness campaign, which was introduced in England in 2012, found little evidence of improvement in recall and recognition of colorectal cancer symptoms [27]. For example, recall of "change in bowel or bladder habits" increased from 31% in 2010 to 33% in 2012 ($p = 0.282$). Some symptoms participants were less able to recall following the campaign. For example, 27% of participants were able to recall "unexplained weight loss" in 2010, which dropped to 22% in 2012 ($p = 0.013$). This symptom was recalled by approximately a quarter of participants in our sample (24%), but by as little as 4% of participants in another study [11]. A systematic review concluded that weight loss is a complex symptom, which is not well understood or managed by cancer patients, family caregivers or health care professionals [28]. This might be because it may be easily explained by causes other than cancer, such as temporary lifestyle changes.

The first national bowel cancer awareness campaign had some positive effects, as recall of change in bowel habit doubled following the campaign (21–43% in 2 years, $p < 0.01$) [27]. The improvement was also statistically significant when recognition of this symptom was taken into account (87–91%, $p < 0.01$). In our sample, participants least frequently recalled change in bowel habit (14%), but the percentages were slightly higher in other studies, for example, 23% in Power et al. [11], or 17% in McCaffery et al. [12] study. Although awareness about early symptoms of colorectal cancer seems to be difficult to improve, it is possible to make progress using well-structured and targeted campaigns [27].

Findings from other countries are mixed, with high-income countries reporting better results than low-income countries. A study done in Ireland reported that only 27% of patients were aware of at least one symptom of colorectal cancer [29], while another Irish study reported that 55% of patients correctly recognised "rectal bleeding" and 35% recognised "change in bowel habit" [30]. Another study found that 56% of participants from Spain recognised at least one symptom of colorectal cancer; where 22% of participants recognised "rectal bleeding" and 20% recognised "change on bowel habit" [31]. In Netherlands 60% of study participants recognised "unusual bleeding" and 43% recognised "change in bowel habit" [32]. In middle-, and low-income countries awareness of colorectal cancer symptoms was rather poor. A study carried out in Lebanon reported that 59% of participants could not name any symptom of colorectal cancer [33], which was reduced to 38% in Malaysia [34], and 29% of participants from Saudi Arabia [35]. Therefore, it is necessary to improve recognition of early symptoms of colorectal cancer worldwide, and initiatives such as Colorectal Cancer Awareness Day do not seem to be sufficient to encourage early presentation.

Our findings are in line with previous studies in terms of socio-demographic factors associated with recall and recognition of early symptoms of colorectal cancer. The youngest, men, and the underprivileged had the lowest colorectal cancer awareness cancer [9, 11, 12]. Studies investigating general public cancer awareness reported similar results [14, 20]. This evidence should be used to develop targeted campaigns, which focus on specific needs of population groups which are most at risk of low colorectal cancer awareness. Although the first national bowel awareness campaign was targeted to people from lower socio-economic groups and those over 50 of age [27], men and younger age groups (below 50) were neglected. This might partially explain why this campaign did not improve awareness of all early symptoms of cancer. Although we found some evidence that the unemployed and single participants least frequently recalled and recognised the four cancer symptoms, this needs to be confirmed in future studies before it could be used to target campaigns.

Evidence suggests that being able to recognise early symptoms of cancer was associated with faster anticipating help-seeking [7, 14]. Over a third of our participants reported that they would delay help-seeking for more than 2 weeks for "unexplained weight loss" (38%), about a fifth of them (19%) would delay for "change in bowel habit", and 5% would delay for "unexplained bleeding". These percentages are generally lower than in another study which used the same questions [14], but similar to those in other studies [7, 12]. McCaffery et al. [12] reported that 17% of their participants would adopt a "wait-and-see" approach if they noticed a change in bowel habit for more than 2 weeks, while 5% of them said the same thing for "blood in stool". Quaife et al. [7] reported that 7% of participants from a representative sample of the English population anticipated waiting for 2 weeks or more for a symptom of rectal bleeding. In general, we confirmed previous findings that younger and more educated people were more likely to delay help-seeking [7], as well as those from the most affluent SEP [14]. Possible explanations for these findings include underreporting of delay among some population groups, likely differences between actual and hypothetical behaviour [36], and/or increased barriers to help-seeking, which were found to be associated with greater anticipated delay [14]. For

example, barriers such as being 'too busy' and 'worry about many other things' were most frequently reported by the youngest, more educated participants, and those from the most affluent SEP [20]. Finally, it is also possible that these groups have generally better health in comparison with their counterparts, and/or they might be less concerned about access to health care [37, 38].

Participants were least likely to recognise that "eating red or processed meat each day", "eating less than 5 of fruit and vegetables a day" and "less than 30 minutes of moderate physical activity 5 times a week" were risk factors. Approximately a third of our participants recognised these risk factors, but only every tenth was able to recall them. Even lower percentages were reported in other studies [11, 12]. In Power et al. [11] study, only 0.8% of participants were able to recall factors such as "eating red or processed meat each day" or "eating less than 5 of fruit and vegetables a day", and 3% recalled "being overweight" (vs. 12% in our study) and "being >70 years old" (vs. 9% in our study). It is interesting that less than every tenth of our participants recalled the strongest risk factor for colorectal or any other cancer—older age. This is alarming, because it shows very low awareness of colorectal cancer risk factors and because rising awareness about them is not included in the national bowel awareness campaign.

Awareness of risk factors was considerably better when respondents were asked to recognise rather than recall colorectal cancer risk factors. However, even with the aid of a list most risk factors were not recognised by more than a half of participants, which was comparable with other studies [11]. Keighley et al. [39] compared public awareness of colorectal cancer risk factors in 21 European countries. They concluded that the overall awareness was low. For example, only about 20% of participants in Great Britain were aware that older age was associated with higher risk of colorectal cancer, in comparison with 15% of participants from Sweden, and 7% of participants in Netherlands. Only about 20% of participants in Great Britain were aware that family history of cancer was associated with higher risk of colorectal cancer, in comparison with 10% of participants from Poland, and 5% of participants in Netherlands. Overall, the European average was that only 57% were aware of age-related risks and 54% of risks related to family history [39]. There is also evidence that some people consider protective factors to be risk factors of cancer. For example, a high-fibre diet was reported to be a bowel cancer risk factor by 24% of participants from England (Birmingham) and 11% of participants from Australia (Melbourne) [40]. It seems that it may be necessary to educate people about what risk factors are, before linking them to different types of cancer, especially since a fifth of our sample believed that "nothing" is a risk factor for cancer.

We did not confirm previous findings where men were less aware of risk factors [41], but we confirmed that higher educational attainment [12, 41] and higher SEP were associated with better recognition of risk factors [11]. Therefore, it is necessary to develop campaigns aimed at improving awareness of colorectal cancer risk factors, especially among the underprivileged people.

Future research should clarify the role of educational attainment, marital and employment status in cancer symptom awareness, anticipated time to help-seeking for these symptoms, and recognition of risk factors for colorectal cancer. We also need more prospective studies to assess help-seeking behaviour in relation to most

common symptoms of colorectal cancer. Future campaigns should be piloted in areas where groups with low cancer symptom awareness tend to gather, such as pubs and football/rugby matches for males, and local communities where people from lower socio-economic background live. Distributed materials with relevant information on early colorectal cancer symptoms, risk factors and incidence should be developed to address the needs of these population groups.

Conclusion

This study highlights the need for developing and improving targeted campaigns aimed at raising awareness of early symptoms of colorectal cancer, associated risk factors and general knowledge about how common this cancer is. These efforts will be in line with the English Department of Health's *Improving Outcomes: A Strategy for Cancer*, which aims to improve cancer care services and outcomes, by promoting early diagnosis [42]. The first national bowel cancer awareness campaign showed limited improvements in awareness about early symptoms of colorectal cancer, but awareness of risk factors was not addressed. Before implementing any changes to the existing campaigns, it is necessary to pilot them and ensure their effectiveness.

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Authors' contributions

M.N. conceived and designed the study, performed statistical analyses, interpreted the data, drafted the manuscript and participated in revisions of the manuscript. L.F. participated in revisions of the manuscript.

Competing interests

The authors declare that they have no competing interests.

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Bowel Symptoms in Relation to Colorectal Cancer

2

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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].

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Faecal Immunochemical Tests (FIT) for Haemoglobin for Timely Assessment of Patients with Symptoms of Colorectal Disease

3

Robert J.C. Steele and Callum G. Fraser

Abbreviations

AA	Advanced adenoma
ACRN	Advanced colorectal neoplasia
AUC	Area under the curve
BSG	British Society of Gastroenterology
CEA	Carcinoembryonic antigen
CRC	Colorectal cancer
EWG	Expert Working Group on FIT for Screening
f-C	Faecal calprotectin
f-Hb	Faecal haemoglobin concentration
FIT	Faecal immunochemical test for haemoglobin
GI	Gastrointestinal
Hb	Haemoglobin
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
iFOBT	Immunochemical faecal occult blood test

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M2-PK	The dimeric form of the pyruvate kinase isoenzyme type M2
MH	Mucosal healing
NAA	Non-advanced adenoma
NICE	National Institute for Health and Care Excellence
NPV	Negative predictive value
OBD	Organic bowel disease
POCT	Point-of-care test
PPV	Positive predictive value
ROC	Receiver operating characteristic
SIGN	Scottish Intercollegiate Guidelines Network
UC	Ulcerative colitis

Key Points

- Faecal immunochemical tests for haemoglobin (FIT) have many advantageous characteristics and are now proven to be very useful in the timely assessment of patients with symptoms of colorectal disease as well as in asymptomatic population screening.
- Quantitative faecal immunochemical tests for haemoglobin (FIT) provide numerical estimates of faecal haemoglobin concentration (f-Hb) and, at low f-Hb cut-off, FIT have high sensitivity for colorectal cancer (CRC) and could be used as a rule-in test and stimulate rapid referral for endoscopy.
- Undetectable f-Hb provides considerable reassurance that significant colorectal disease (CRC + advanced adenoma + inflammatory bowel disease) is absent and further investigation may not be required: however, no test is perfect so some cases will remain undetected and, in consequence, robust safety-netting is required.

3.1 Introduction

3.1.1 The Importance of Timely Detection of Colorectal Disease

Colorectal cancer (CRC) remains a major health issue, since it is the third most common cancer developed worldwide and the fourth cause of cancer-related death [1]. Outcomes for individuals are much improved if colorectal neoplasia and other significant colorectal diseases (SCD), such as inflammatory bowel disease (IBD), are detected at an early stage [2]. Asymptomatic population-based screening programmes for colorectal neoplasia have been widely introduced, in which early disease is detected and removal of adenomas, which are sometimes precursors of CRC, is facilitated. As well as improvement in lifestyles, screening is considered to be a major reason why the incidence and mortality of CRC is decreasing, at least in developed countries [3], although models suggest that the ageing population will lead to rises in incidence over the next decade [4]. However, in spite of much

emphasis on the value of screening, most colorectal disease is diagnosed after presentation with symptoms [5], For a variety of reasons, including many publicity campaigns on the benefits of early diagnosis and treatment of CRC in particular, the number of patients presenting with lower abdominal symptoms to both primary and secondary healthcare sectors continues to rise, putting significant stress on the availability of endoscopy, particularly colonoscopy, currently the most frequently applied investigation. However, colonoscopy exposes patients to an invasive and unpleasant procedure that carries a small, but ever present, risk of complications. Further, colonoscopy is a scarce resource in many countries.

3.1.2 Current Problems in the Diagnosis of Colorectal Disease

Symptoms, such as rectal bleeding, dark bowel motions, change in bowel habit (both constipation and especially diarrhoea), abdominal pain, cramping, anaemia and unintended weight loss are all associated with CRC and other SCD. However, these symptoms are also common in patients without SCD and have been shown, in three meta-analyses, to have poor clinical sensitivity for detection of CRC [6–8]. Indeed, the "rule of sixths" [9] should be remembered in this clinical context: one-sixth of patients presenting with lower abdominal symptoms have serious colorectal disease (CRC, advanced adenoma (AA) and IBD), two-sixths have less serious bowel disease (e.g., simple diverticular disease, haemorrhoids and hyperplastic and small polyps) and three-sixths have no detectable abnormality on colonoscopy. The challenge is to decide an appropriate strategy to dissect out those patients who would benefit most from colonoscopy. A number of approaches have been developed, but the use of faecal immunochemical tests (FIT) for haemoglobin (Hb) has considerable potential to contribute to reducing unnecessary colonoscopy for a significant number of symptomatic patients. This Chapter will present the evidence that this simple and inexpensive investigation, with easy to collect single faecal samples, has an important role in everyday clinical practice.

3.2 Faecal Immunochemical Tests (FIT) for Haemoglobin

The terminology "faecal immunochemical test for hemoglobin" and the abbreviation FIT were recommended by the Expert Working Group (EWG) on FIT for Screening of the Colorectal Cancer Screening Committee, World Endoscopy Organization, to ensure that these newer tests for the presence of blood in faeces were not seen as the same as, or even similar to, guaiac-based faecal occult blood tests, either traditional (gFOBT) or so-called high sensitivity (sFOBT) [10]. Use of the FIT terminology rather than other descriptors such as immunochemical faecal occult blood tests (iFOBT) highlights the significant analytical and clinical differences between these methods for detection of haemoglobin (Hb) in faeces. The older gFOBT, based upon the pseudo-peroxidase activity of the haem moiety of Hb, have significant disadvantages compared to FIT [11–13], in that:

- two samples from each of three faecal specimens are required,
- all samples must be taken directly onto the cards to ensure stability,
- the cards must be dried for some days before development to minimise interference from plant peroxidases,
- dietary constituents, especially meat, can cause false positive results and large intake of vitamin C can cause false negative results,
- the test is not specific for lower gastrointestinal (GI) tract bleeding,
- most importantly, the test has low clinical sensitivity and specificity
- the analytical sensitivity is set by the manufacturer and
- the performance of the test by users is very poor.

Moreover, many published guidelines on assessment of patients presenting with symptoms, such as those from the National Institute for Health and Care Excellence (NICE) [14], the Scottish Intercollegiate Guidelines Network (SIGN) [15] and the British Society of Gastroenterology (BSG) [16] did suggest that there was no role for gFOBT in assessment of patients with symptoms and those with iron deficiency anaemia. However, more recently, new guidelines from NICE [17] have suggested that faecal tests for occult blood should be used to investigate patients with a low risk of CRC, but these have led to much discussion and debate, generally deprecating the suggestion of using gFOBT for this purpose [18, 19].

However, since the promulgation of these contentious guidelines, there has been rapid realisation that FIT is a very appropriate investigations for use in this clinical setting [20], that is to triage patients presenting in primary healthcare with lower abdominal symptoms, particularly those at low risk of SCD, particularly CRC. The advantages are many [21], including:

- FIT have user-friendly hygienic specimen collection devices that are much simpler to use than the cards used for gFOBT,
- the collection devices ensure stability of Hb after collection for a number of days,
- only one faecal sample is generally required,
- there are no interferences from dietary constituents,
- use of aspirin and anti-coagulants by patients is actually beneficial in that any bleeding lesion will bleed more, probably leading to higher clinical sensitivity [22],
- FIT are more specific for lower GI lesions since the globin of Hb is unstable as it passes through the gut and
- FIT are generally more analytically sensitive than gFOBT and so more significant lesions are detected since faecal haemoglobin concentration (f-Hb) is related to colorectal disease severity [23].

Using labelled antibodies, the antibody-Hb complex formed if globin is present in the sample can be detected and measured by a variety of techniques. FIT are available in two formats, qualitative, in which the test result is dichotomous, that is, only positive or negative test results are reportable, or quantitative FIT in which a numerical estimate of the f-Hb is generated.

3.3 Qualitative FIT

3.3.1 Analytical Methodology

Qualitative FIT are generally based on lateral flow immunochromatographic analysis similar to most over-the-counter pregnancy tests and many point-of-care tests (POCT) for detection of misused drugs [24]. Using test cassettes or strips, these FIT involve separation of Hb in samples collected from faeces using a variety of devices using passive flow along a separation material for any Hb present to be captured by antibodies to the globin of human Hb and made visible using various chemical techniques. Often such qualitative immunochemical tests are said to be simple to perform. However, they present many real difficulties in practice [25]. Faecal specimen collection is problematic since Hb in faeces is unstable [26], and this requires the use of rapid collection of passed faeces into the FIT specimen collection devices rather than later analysis of samples collected in the traditional faecal pots widely used in laboratory medicine. Further, the colour development on the cassettes or strips of qualitative FIT is very dynamic and early and late reading will lead to false negative and false positive results, respectively: in consequence, accurate timing is required. In addition, the results are not easy to interpret, especially when very faint, borderline, positive test lines are present, unless performed following adequate training and in good light, preferably by those with good visual acuity. A very important disadvantage of qualitative FIT is that what is often called the analytical sensitivity or analytical detection limit, or C_{50}, the f-Hb at which 50% of the results are negative and 50% of the results are positive [27], varies considerably between available FIT [28, 29]. Part of the reason for this is that manufacturers, suppliers and users have documented results in units of ng Hb/ml buffer and, because different masses (or, more correctly, volumes) of faeces are collected and taken into different volumes of buffer in the devices, the results are not transferable over qualitative FIT systems. Even if the units of μg Hb/g faeces recommended by the EWG [30] are used to improve comparability, or even better μg Hb/ml faeces as recently recommended [31], the C_{50} of different FIT will not be the same. Consequently, the clinical outcomes obtained with different qualitative FIT will be different, the positivity rate and the clinical sensitivity decreasing as the C_{50} increases and the specificity decreasing. Further, the conclusions stated in publications using qualitative FIT may not be applicable to other POC FIT with varying C_{50}. In addition, even lots of one qualitative FIT from a single manufacture can show lot-to-lot variation [32]. Moreover, manufacturers of FIT continually evolve their products and thus, outcomes may not be comparable over time—an example of change over time is that two FIT systems have both had improvements made to the buffers in their specimen collection devices to increase the Hb stability [33, 34].

3.3.2 Use of Qualitative FIT at Home

Qualitative FIT could, at least in theory, be used by individuals in their own homes as well as in primary healthcare centres and outpatient clinics. The merits would be that POCTs bring the investigation close to the patient. This is alleged to increase

the likelihood that the results will be obtained more quickly and such timely results will be acted upon more rapidly. However, no studies evaluating the diagnostic accuracy of any of the "home bowel testing kits" available to the UK consumer were found in a diagnostic technology update on home-use of FIT [35]. This might be an interesting area for future research, comparing FIT done at home with other approaches to determining whether Hb is present in faeces.

3.3.3 Use of Qualitative FIT in Primary Care

In 2010, Jellema et al. summarised available evidence on diagnostic tests that might help to identify patients with an increased risk for CRC among those presenting with lower abdominal symptoms in primary care [8]. It was documented that the clinical sensitivity of the small number of studies using qualitative FIT reported ranged from 50% to 100% and specificity from 71% to 93%. However, it was concluded that, although combinations of symptoms and the results of FIT showed good diagnostic performance for CRC, evidence from primary care was lacking. It was suggested that high-quality studies on the role of FIT in primary care were urgently needed. Since that time, there have been a small number of studies using qualitative FIT with sanguine results, but further work is definitely warranted on whether and where qualitative FIT can be applied best, if at all, in the assessment of those with lower abdominal symptoms.

A study performed in The Netherlands investigated faecal biomarker tests that might differentiate between organic bowel diseases (OBD) and non-OBD in primary care patients with persistent lower abdominal complaints [36]; this use of the term OBD is unusual and deprecated by some but, in fact, OBD is similar to the SCD defined earlier in this Chapter except that all adenomas were included. The diagnostic accuracy of faecal calprotectin (f-C) and FIT, as POCT, as well as a quantitative f-C method, was assessed. Samples from 386 patients with lower abdominal complaints were obtained, with OBD found in 99 patients. Sensitivity for OBD was 64% for f-C and 56% for FIT. More importantly, negative predictive values (NPV) were 81% and 84% respectively. Combining both POCT improved sensitivity to 79% and NPV to 87%. Very interestingly, when adenomas $\leq$1 cm in diameter were considered non-OBD, the NPV of all tests improved to more than 90% with the combined f-C and FIT POCT rising to 97%. This exclusion of smaller adenoma, the vast majority of which will not progress to CRC, is very much in keeping with current ideas of what constitutes SCD (CRC plus AA plus IBD). The clear conclusion was that SCD could be ruled out to a reasonable extent, particularly with the combined POCT, but these were less useful for the inclusion of disease.

In what is essentially a follow-up study, recently published in 2016, Elias et al. generated data from a prospective study on patients with persistent lower abdominal symptoms referred from primary care practices to develop a multivariable diagnostic model for SCD with routine clinical information, which was extended with f-C and

FIT [37]. POCT were used for both tests, the basis for this being that POCT can be easily performed at the time and place of patient care. It was demonstrated that the diagnostic model with routine clinical data discriminated between patients with and without SCD with an area under the receiver operating characteristic (ROC) curve (AUC) of 0.741. This AUC increased to 0.763 when the f-C result was added, to 0.831 when the FIT result was included and to 0.837 with both POCT results. Approximately one-third of the patients tested negative based on this combined POCT extended model, with a NPV of 96.4%. This high NPV clearly indicated that this approach provided a good rule-out test for SCD. However, excluding the f-C from this model still yielded a NPV of 96.0%. It was concluded that a diagnostic strategy with routine clinical data and f-Hb alone might safely rule out SCD and prevent unnecessary referral for colonoscopy in approximately one-third of patients. As will be discussed later in this Chapter, there is much evidence that a single measurement of f-Hb, obtained by quantitative FIT, could well be sufficient to determine who should be referred for colonoscopy. Elias et al. [37] stated that their results confirm that a positive FIT result supports the value of referral and admitted that the clinical data did not add further information: however, the clinical information was stated to be informative when the FIT result was negative. Further, the argument put forward to support use of clinical information as well as the FIT result was that healthcare professionals in primary care would not immediately request tests in patients presenting with symptoms and signs of SCD without considering other pretest information from history taking and physical examination., Thus, this study evaluated the diagnostic value of history taking, physical examination, and simple blood testing and, subsequently, the added value of the POCT FIT, in that sequence. However, an accompanying commentary article [25] put forward the thesis that, as described earlier, although lower abdominal symptoms are very common presenting complaints, SCD is rarer and, because of the significant overlap of symptoms in those with and without SCD, clinical data are of limited value. Thus, since FIT provide such a good rule-out test for SCD, this should be the first investigation to be performed on all patients. This concept will be explored further later in this Chapter.

In a recent study from Sweden [38], FIT and a f-C test were compared for detecting CRC, AA and IBD in primary care, along with assessment of the value of combining these with anaemia and iron-deficiency tests; 373 consecutive patients that received a qualitative FIT or a f-C ordered by a primary healthcare physician were included. The FIT was regarded as positive when one or more of three samples showed a positive result. Symptoms, as found in many studies, showed low PPV. Patients diagnosed with CRC and IBD presented with largely the same symptom pattern. The only symptom significantly associated with CRC and IBD was rectal bleeding, but 52.2% of patients with a history of rectal bleeding had a negative FIT result and none of these patients was diagnosed with CRC or IBD during the study period. Although the authors proposed that the best approach for detecting CRC and IBD was the combination of FIT and blood Hb results since this had sensitivity, specificity, PPV and NPV of 100%, 61.7%, 11.7% and 100%, respectively; for the FIT alone, for CRC plus IBD, although the PPV was only 12.7%, the NPV

was 99.2%. It was concluded that a negative FIT, combined with a normal blood Hb, could largely rule out CRC and IBD and this diagnostic strategy could be useful in prioritising referrals from primary care.

3.3.4 Use of Qualitative FIT in Secondary Care

A small study done in secondary care evaluated the sensitivity and specificity of FIT in patients with colorectal symptoms without overt rectal bleeding. Consecutive patients referred for urgent colonic investigation were prospectively studied; a faecal sample was obtained from patients and a qualitative FIT performed [39]. Of 126 tested, 112 underwent colonoscopy: 30 patients gave FIT positive results. In the 82 patients with FIT negative results, no CRC were found: the FIT had 100% sensitivity and 86.3% specificity for CRC. The authors concluded that qualitative FIT was good at detection of CRC and might be useful in identifying those patients who warrant rapid investigation. It was also suggested that routine use of such FIT might be useful in the allocation of resources.

3.4 Quantitative FIT

3.4.1 Analytical Methodology

Quantitative FIT provide numerical estimates of the f-Hb. A number of small to medium size FIT analytical systems are now available [40]; these examine only f-Hb and can be described as *closed* because the calibration materials, reagents, specimen collection devices and other materials required are unique to the system and cannot be interchanged between systems. One manufacturer has calibrators and reagents that can be used on *open* analytical systems and protocols are available for a large number of clinical chemistry laboratory systems, but there appear to be no peer-reviewed published studies to date on use in assessment of patients with symptoms. All of these analytical approaches are based upon immunoturbidimetry and, like qualitative FIT, make use of antibodies raised against the globin moiety of human Hb [24]. These antibodies are either monoclonal and bound to one part of the globin protein, or polyclonal and bound to the intact globin and some of its breakdown products: the antibodies are bound to a carrier particle such as polysaccharide, latex or gold and, when faeces in buffer is added to the reaction mixture, if globin is present, this binds to the antibodies and small aggregates form. The change in absorbance of the reaction mixture on addition of the sample is measured and an estimate of the f-Hb derived. Although the spectrum of available FIT systems is ever increasing, to our knowledge, good data in the peer-reviewed literature concern only two analytical systems to date. In addition, there are methods based on enzyme-linked immunosorbent assay (ELISA), a plate-based assay technique, but again these do not seem to have been used specifically in investigating the role of FIT in timely assessment of patients with symptoms.

3.4.2 Data on Faecal Haemoglobin Concentrations Using Quantitative FIT

Most publications on the use of FIT are concerned with asymptomatic population-based screening. This clinical setting is not the subject matter of this Chapter, but it has to be recognised that much basic information on f-Hb in health and disease has been gained through studies involving screening. For example, in a study using three estimates of f-Hb in 1000 consecutively recruited ambulatory patients, unfortunately heterogeneous in that some were asymptomatic, but at increased risk for colorectal neoplasia, and others were symptomatic, who were undergoing elective colonoscopy and volunteered to collect samples for FIT, it was nicely demonstrated that f-Hb was directly related to the severity of the colorectal neoplastic lesions found [41]. Thus, it seems surprising that the idea that f-Hb might be considered as a useful diagnostic test in assessment of the symptomatic as well as in screening took so long to become the subject of research studies. Similarly, many studies investigating the f-Hb cut-off used to refer asymptomatic individuals for colonoscopy have shown, unsurprisingly, that, as the cut-off is increased, positivity rate, neoplasia detection rate and sensitivity decrease while specificity and positive predictive value increase [42, 43]; such findings might influence selection of the f-Hb cut-off to be used in triage of the symptomatic, as will be discussed later. Further, it has been shown that f-Hb rises with age and is higher in men than women [44, 45]; such variations differ from country to country [45–47] and vary with degree of socio-economic deprivation [45, 48]. Recently, it has been suggested that the estimates of f-Hb obtained by different analytical systems are not transferable [49] and a commentary on this comparison of FIT supported the concepts that FIT differed for two reasons [50]. Firstly, FIT generally sample wet faeces into buffer in the specimen collection devices and, although the assumption is that the volume of faecal material sampled is constant over devices, the amounts sampled can vary substantially in reality. Secondly, different FIT make use of antibodies against different globin epitopes and this could potentially influence positivity rate. It was stated that it was important to remember that, as for many other measurands examined in laboratory medicine, these systems are all said to measure "faecal Hb" but, in reality, they measure faecal Hb plus a range of early degradation products, which probably vary from system to system. All of these factors might again influence f-Hb cut-off applied as the criterion for referral for further investigation and might have to be taken into account in risk-scoring strategies, as will be discussed later in this Chapter.

3.4.3 Studies on Quantitative FIT in Patients with Lower Abdominal Symptoms

There have been seven peer-reviewed published studies to date to our knowledge which specifically address the role of quantitative FIT in assessment of patients with lower abdominal symptoms. These have been performed on two of the analytical systems available in the UK and Europe, the OC-Sensor (Eiken Chemical Co, Ltd., Tokyo, Japan) and the HM-JACKarc (Kyowa-Medex Co, Ltd., Tokyo, Japan), both

of which are widely used in CRC screening programmes. The study, analytical system used, strategy for recruitment populations studied, number with both f-Hb and endoscopy outcomes and healthcare source of referral are shown in Table 3.1. The heterogeneity of the studies is clear, but each gives unique information that impacts on use of quantitative FIT in assessment of the symptomatic. These studies will now be described, highlighting the most relevant points from each.

Table 3.1 Studies on FIT in assessment of the symptomatic, analytical system used, strategy for recruitment of populations studied, number with both faecal haemoglobin concentration and endoscopy outcomes and healthcare source of recruitment

Author, reference, country	Analytical system	Invitation strategy	Number with faecal haemoglobin concentration and endoscopy data	Recruitment from primary/ secondary care
McDonald et al., [51], Scotland	OC-Sensor	Phone call of invitation by research nurse after referral from primary care for endoscopy	280	0/100
Godber et al., [52], Scotland	HM-JACKarc	Request for FIT included with bowel preparation materials on invitation to, and appointment for, endoscopy.	484	0/100
Mowat et al., [53], Scotland	OC-Sensor	Request for FIT analysis made in primary care along with documentation of symptoms and referral for endoscopy	755	100/0
Cubiella et al., [54], Spain	OC-Sensor	Consecutive patients with gastrointestinal symptoms referred for colonoscopy from primary and secondary healthcare.	787	Both—but percentages not documented.
Auge et al., [55], Spain	HM-JACKarc	Consecutive patients who attended for colonoscopy for the investigation of symptoms or polyp surveillance.	208	Not documented. However, tests requested on attendance at secondary care clinic.
Rodriguez-Alonso et al., [56], Spain	OC-Sensor	Patients referred for diagnostic colonoscopy after consultation in which an exhaustive interview was performed by a gastroenterologist.	1003	66.3/33.7
Widlak et al., [57], England	HM-JACKarc	Patients recruited from “two week wait” clinics after primary healthcare referral.	430	0/100

3.4.3.1 The Study of McDonald et al.

This study seems to be the first aimed at determining whether f-Hb found by a quantitative FIT can assist in deciding which patients with lower abdominal symptoms would benefit from endoscopy [51]. Among 739 invited patients, FIT and endoscopy were completed by 280 (median age 63 years, 59.6% women). Six (2.1%) participants had CRC, 23 (8.2%) had AA, 31 (11.1%), non-advanced adenoma (NAA) and 26 (9.3%) IBD as the most serious diagnosis. As with findings in screening, f-Hb was clearly related to severity of colorectal disease since those with CRC had a median f-Hb of >200 μg Hb/g faeces and those with CRC + AA + IBD having a median f-Hb of 15 μg Hb/g faeces, which were both significantly higher than that of all remaining participants without SCD. The NPV using a cut-off f-Hb of 10 μg Hb/g faeces were 100%, 94.4% and 93.9% for CRC, AA and IBD respectively. The AUC for all four clinical groups examined, with the more important colorectal diseases classified as positive, ranged from 0.734 to 0.671; these AUC suggest only a "fair" to "poor" rule-in diagnostic test. However, the high NPV, particularly for the group that is considered of most clinical interest, that is SCD (CRC + AA + IBD), was 88.1%. In consequence, a negative FIT result with f-Hb <10 μg Hb/g faeces means that SCD is unlikely to be present and, when used as a rule-out test, could facilitate patient reassurance of patients and saving of colonoscopy resources.

3.4.3.2 The Study of Godber et al.

This study followed up that described above in a different part of Scotland and with a different FIT system [52]. Again designed to determine whether patients with lower abdominal symptoms can be investigated quickly using f-Hb, 909 consecutive patients referred from primary care for colonoscopy were invited: 507 submitted samples for f-Hb and a colonoscopy was completed in 484 patients. As with the study of McDonald et al. [51], those with CRC, AA or IBD had higher f-Hb than the group of 243 with normal colonoscopy plus the 196 patients with less significant clinical findings. Again, using a f-Hb cut-off of 10 μg Hb/g faeces, for the group with SCD, the test was a poor rule-in test with low sensitivity (68.9%) and PPV (26.3%,), but the NPV of 96.2% confirmed that FIT was a good rule-out test for SCD. The clinical characteristics at different f-Hb cut-offs were examined and, as expected, as the cut-off f-Hb was increased, sensitivity fell and specificity rose; while the PPV rose, the NPV remained very high at all f-Hb cut-offs. Interestingly, the 11 (2.2%) patients with CRC all had f-Hb >190 μg Hb/g faeces and sensitivity was therefore 100% for CRC, as found by McDonald et al. [51]. It was suggested that it might be that FIT could be of considerable value as either a rule-in for CRC on its own or a rule-out investigation for SCD.

3.4.3.3 The Study of Mowat et al.

This investigation studied the diagnostic accuracies of f-Hb and f-C in a group of symptomatic patients [53]; only the f-Hb component of this work will be addressed in this section of the Chapter. The PPV of referral symptoms for a diagnosis of CRC were not high and the values for specific symptoms were: palpable mass: 50.0%, weight loss: 14.3%, anaemia: 9.0%, rectal bleeding: 4.3%, abdominal pain: 3.6%, diarrhoea: 2.4%, and altered bowel habit: 2.2%. Rectal bleeding had a PPV of 21.0%

for any SCD, but only one-third of these had undetectable f-Hb. As expected from the known overlap of symptoms in those with and without SCD, the most common findings at colonoscopy were: normal in 241 (33.2%), diverticular disease in 190 (25.2%), haemorrhoids in 98 (13.0%), NAA in 65 (8.6%), AA in 41 (5.4%), IBD in 34 (4.5%) and CRC in 28 patients (3.7%). In total, 1043 patients returned samples and f-Hb was detectable, that is greater than 0 μg Hb/g faeces, in 57.6%; 755 patients (median age 64 years, 54.6% women) returned faecal samples and completed colonic investigations and 103 patients were found to have SCD. Using a cut-off of "detectable" f-Hb, NPV were 100%, 97.8% and 98.4% for CRC, AA and IBD, respectively. It was concluded that undetectable f-Hb is a good rule-out test for SCD and could guide who requires further investigation. However, in laboratory medicine, the requirement is to fully conform to ISO 15189—"medical laboratories—particular requirements for quality and competence"—means that only results greater than the lower limit of the analytical working range laid down by the manufacturer, best described as the "limit of quantitation", can be reported as concentrations [58]. Thus, while interesting for research studies, a cut-off of detectable f-Hb cannot be used in clinical practice, and only results for the OC-Sensor of <10 μg Hb/g faeces can be considered undetectable and only those ≥10 μg Hb/g faeces can be reported as numerical data. However, Mowat et al. also give comprehensive data using 10 μg Hb/g faeces as the cut-off. NPV for CRC, AA, IBD and SCD were 99.5%, 96.5%, 98.4% and 94.4%.: in contrast to previous studies in Scotland [51, 52], cases of CRC (3 of 28) would be missed using this cut-of as would 20 of 40 of AA and 9 of 34 of IBD, that is, 32 of 102 of those with SCD. Most interestingly, the three missed cases of CRC were all women (personal communication): this may reflect that fact that f-Hb is lower in women than in men [44, 45], possibly due to slower transit time of faeces passing through the colon [59].

3.4.3.4 The Study of Cubiella et al.

In this study [54], a f-Hb cut-off of 20 μg Hb/g faeces was used, rather higher than that in the three studies done in Scotland [51–53]; the rationale probably being that this is the most common f-Hb cut-off used in asymptomatic screening programmes. The novel aspect of this study is that FIT to detect CRC was compared with the then current NICE [14] and SIGN [15] referral guidelines. In 787 symptomatic patients referred for colonoscopy, patients were assessed to see if they met NICE and SIGN referral criteria and all patients collected one sample for an estimate of f-Hb. CRC was detected in 97 (12.3%) patients; 241 (30.6%) had f-Hb ≥20 μg Hb/g faeces and 300 (38.1%) and 473 (60.1%) met NICE and SIGN referral criteria. As shown in other studies discussed earlier, the median f-Hb was found to be statistically significantly higher in individuals with a CRC than the others. The important finding here is that f-Hb had a higher sensitivity for CRC (87.6%) than NICE (61.9%) and SIGN criteria (82.5%). The specificity of f-Hb was also higher than NICE and SIGN criteria (77.4%, 65.2% and 42.7%). It was concluded that f-Hb is more accurate for the detection of CRC than the then current NICE and SIGN referral criteria in symptomatic patients referred for colonoscopy. In view of the overlap of symptoms in patients with and without SCD, this is probably hardly surprising, since NICE and SIGN referral criteria are based on age and symptoms and other clinical information

rather than f-Hb. However, combinations of symptoms and f-Hb might have advantages and this will be discussed later in this Chapter. Finally, the authors of this study concentrated on the use of f-Hb as a rule-in test for CRC, but there are data on the NPV of f-Hb and NICE and SIGN referral criteria for both CRC and advanced neoplasia (AN), defined as CRC plus AA: these were 97.8%, 92.4% and 94.5% respectively for CRC and 90.8%, 82.1% and 83.6% for AN respectively. Thus, it was actually demonstrated that f-Hb is a good rule-out test for AN.

3.4.3.5 The Study of Auge et al.

Auge et al. [55] provided a unique perspective on use of FIT in assessment of the symptomatic since two samples were obtained on each patient for FIT. The aims of this study were to evaluate the diagnostic yield for what was termed advanced colorectal neoplasia (ACRN), equivalent to CRC plus AA, in symptomatic patients, assessing the f-Hb of the first of two samples (FIT/1) and the higher concentration of two FIT samples (FIT/max). Samples were collected from two consecutive bowel motions from 208 symptomatic patients who required colonoscopy. Patients were categorised into two groups: patients with any ACRN and those with other diagnoses or normal colonoscopy. Colonoscopy detected ACRN in 29 patients. FIT/1 and FIT/max were significantly higher than in patients with NAA, other findings and normal colonoscopy, confirming the now well-established relationship between f-Hb and colorectal disease severity, This study also showed that higher f-Hb are found in men with lower abdominal symptoms compared with women, consistent with other studies [44–47], Similarly, a higher clinical sensitivity and PPV for ACRN was observed in men than in women and the NPV was lower in men, which perhaps implies that different f-Hb cut-offs should be used for the different sexes. The AUC of FIT/1 and FIT/max were 0.71 and 0.69, respectively, again showing that FIT are less than good tests for detection of disease. However, undetectable FIT/1 gave NPV of 95.0%, but increasing the FIT/1 cut-off to 10 μg Hb/g faeces decreased the NPV to 89.2%. Similar results were obtained using FIT/max with a cut-off of 20 μg Hb/g faeces, providing NPV of 89.3% and 89.0%. The authors concluded that undetectable FIT is a good strategy to rule out ACRN in symptomatic patients, but the problems of using this and complying with ISO 15189 standards in routine practice have already been discussed. Considering which of one or two samples is better, it was shown that the diagnostic yield for a rule-in test of collecting two samples for FIT can be achieved with one sample, but a lower faecal f-Hb cut-off is required. Interestingly, the FIT/max result was not concordant with the FIT/1 result in 39.2% of patients: this might indicate that f-Hb has considerable within-subject variation and this would be very worthy of investigation as has been done recently for f-C [60].

3.4.3.6 The Study of Rodríguez-Alonso et al.

This was the second study done comparing quantitative FIT with NICE [14] and SIGN [15] guidelines for referral [56]. The authors prospectively studied 1054 symptomatic patients referred for colonoscopy from both primary and secondary healthcare. NICE and SIGN guidelines detected 46.7% and 43.3% of cases of CRC while f-Hb ≥15 μg Hb/g detected 96.7% of cases. Male sex, age and f-Hb ≥10 μg

Hb/g were independent predictive factors of advanced neoplasia. As found in all studies, symptoms often used as referral criteria were poor predictors of both CRC and AN. The performance characteristics of NICE, SIGN and f-Hb concentration ≥ 15 μg Hb/g for the detection of AN were: sensitivity: 38.3%, 36.1% and 57.1% and specificity: 71.8%, 69.5 and 86.6%, respectively. This study explored the known relationship between f-Hb and severity of disease in considerable detail. AUC for f-Hb in the detection of CRC and AN were 0.94 and 0.76 and the optimal f-Hb cut-off for CRC and AN detection were ≥15 μg Hb/g and ≥10 μg Hb/g, respectively. If f-Hb ≥ 15 μg Hb/g was used as the criterion for referral, only 19.2% of the patients would need urgent assessment for detection of 96.6% of CRC, one of 30 patients being missed. At a cut-off f-Hb of ≥10 μg Hb/g, 22.5% of the patients would need urgent assessment for detection of 61.6% of the AN. It was concluded that a FIT-based strategy performs better than the then current high-risk symptoms-based approaches for fast-tracking referrals for investigation of suspected cancer referrals. The authors also considered that, with NPV of 99.9% for CRC and 93.0% for AN at a f-Hb cut-off of 10 μg Hb/g faeces, f-Hb could also provide a single and excellent rule-out test, thus sparing those with lower abdominal symptoms who do not have SCD from undergoing a colonoscopy. This would save many referrals to colonoscopy and would allow fast-track referrals to be seen more quickly. For the first time, risk-scoring involving f-Hb in assessment of the symptomatic, along with sex and age, was investigated and it was shown that this could accurately estimate the risk of AN. Risk-scoring will be discussed later in this Chapter.

3.4.3.7 The Study of Widlak et al.

Similar to Mowat et al. [52], the aim was to investigate f-Hb and f-C to identify patients for referral for colonic investigation who are most likely to have CRC; here, only the data on f-Hb will be discussed. This study involved patients recruited via the "two-week wait" clinics rather than directly in primary healthcare. Of 430 study participants, median age 67 years, 176 (64.1%), had change in bowel habit, 185 (43.0%) rectal bleeding, 129 (30.0%) abdominal pain, 74 (17.2%) anaemia, 68 (15.8%) weight loss and 95 (22.1%) family history of CRC. Twenty-four patients with CRC and one patient with high grade dysplastic adenoma were grouped together as cancer. At a cut-off of 7 μg Hb/g faeces, f-Hb returned a sensitivity of 84% and specificity of 93% for CRC detection with an AUC of 0.94 and NPV of 99%. For adenoma detection, with no other pathology on colonoscopy or CT, f-Hb had a sensitivity of 69% and specificity of 56% with AUC of 0.70 and NPV of 94%. As found in all other studies described here, the evidence was that f-Hb alone has considerable potential for use in risk stratifying symptomatic patients.

3.4.4 Conclusions from Studies on Quantitative FIT

It would be of significant value for a meta-analysis to be performed on quantitative FIT in assessment of the symptomatic, but that is beyond the scope of this Chapter. However, the results of the seven published studies known to us to date provide evidence that unequivocally demonstrates the following:

- in patients with lower abdominal symptoms, f-Hb is higher in CRC than in those with AA and IBD, and f-Hb in these is higher than in those with less significant colorectal disease such as NAA, haemorrhoids and simple diverticular disease and those with no abnormalities found on colonoscopy,
- high f-Hb is not only found in patients with SCD but in some who have less significant pathology and no abnormality, and so the PPV is not optimal,
- the higher the f-Hb cut-off used for referral for colonoscopy, the lower is the sensitivity, positivity rate and the NPV, and the higher the specificity and PPV,
- f-Hb cut-off at the limit of quantitation documented by the manufacturers of the FIT system used should be applied to give highest sensitivity for detection of SCD and highest NPV, albeit at the expense of specificity and PPV,
- at such f-Hb cut-offs, few CRC and some AA and IBD will be missed and safety-netting, which will be discussed later in this Chapter, is mandatory,
- f-Hb provides a good rule-in test for CRC and a patient with a f-Hb above the lower limit of the analytical working range should be referred for urgent colonoscopy,
- f-Hb provides a good rule-out test for SCD: a result below the cut-off means that SCD is unlikely and the patient can be reassured regarding the absence of disease and not referred immediately for colonoscopy, although other strategies are options, as discussed later,
- f-Hb is better at detection of CRC than some guidelines based upon symptoms and age and other factors for referral from primary care when CRC is suspected,
- one sample is sufficient for detection of most SCD,
- men and women with symptoms have different clinical outcomes at a single f-Hb cut off,
- one study using two samples shows that there may be considerable within-subject variation of f-Hb from day to day and this is worthy of exploration as has been recently done for f-C [60] and
- ubiquitous use of f-Hb as the initial investigation in primary (and secondary) healthcare could undoubtedly help direct colonoscopy resources to those who would benefit most.

It might appear that use of central laboratory-based quantitative FIT would cause some, albeit small, delay in reporting of f-Hb results as compared to POCT qualitative FIT. This might delay diagnosis and, more importantly, might cause some drop out and loss of patients from pathways after presentation since they might not wish to undertake faecal collection, in spite that quantitative FIT have easy to use, hygienic collection devices and only one sample is needed. It would therefore be of interest to undertake further research comparing qualitative and quantitative FIT. Further, in view of the contentious issue of application of tests for occult blood in faeces in patients presenting in primary care, NICE established a Diagnostics Assessment Committee on quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care; the final guidance (DG30) has been published very recently [61]: The recommendations include the following:

1. Quantitative faecal immunochemical tests are recommended for adoption in primary care to guide referral for suspected colorectal cancer in people without rectal bleeding who have unexplained symptoms but do not meet the criteria for a suspected cancer pathway referral outlined in NICE's guideline on suspected cancer (NG12).
2. Results should be reported using a threshold of 10 μg of haemoglobin per gram of faeces. Companies should provide advice about the performance characteristics of the assays to laboratories, and ensure standardisation of results.

It is pleasing to see that, in general, the guidelines are in accord with the material in this Chapter.

3.5 Comparison of Faecal Haemoglobin, Faecal Calprotectin and M2-PK

3.5.1 Faecal Calprotectin

Calprotectin is one of the S100 family of proteins which occurs in large amounts in neutrophil granulocytes, where it accounts for 5% of total proteins and 60% of cytoplasm proteins: f-C is released into the gut lumen in the presence of inflammation. Thus, when f-C is detected, a patient might have IBD such as Crohn's disease or ulcerative colitis (UC). These diseases present symptoms similar to those seen in irritable bowel syndrome (IBS). But, in view of the major clinical differences, it is important to distinguish between IBD and IBS.

Testing using f-C is recommended by NICE as an option to help distinguish between IBD and IBS [62], the rationale being that many with IBS have unnecessary colonoscopy before the true nature of their problem is diagnosed. The guideline states that using f-C will mean that most people with IBS will be diagnosed without the need for these investigations. The NICE guideline is that: f-C testing is recommended as an option to support clinicians with the differential diagnosis of IBD and IBS in adults with recent onset lower gastrointestinal symptoms for whom specialist assessment is being considered, with the important caveat: only when cancer is not suspected, having considered the risk factors (for example, age) described in the then current NICE referral guidelines for suspected CRC [14].

Historically, f-C has often been suggested as a useful investigation for CRC asymptomatic screening [63], but here, only the use in assessment of SCD in the symptomatic will be discussed. It is a timely topic, since, in a very recent study [64], it was suggested that there would be a sufficient inflammatory component in patients with symptomatic CRC resulting in a raised f-C. In 654 patients (median age 69 years, female 56%), who completed f-C and evaluation of the colon using a variety of approaches, the NPV for CRC and AN were 98.6% and 97.2%. By altering the cut-off f-C to have an NPV of 97.0%, the PPV for CRC increased from 8.7% to 13.3%. It was concluded that f-C has a high NPV for CRC and AA in patients with suspected CRC and the 27.8% of patients who had a normal f-C could safely have

been spared a two-week wait referral. It was proposed that, in part since f-C was available and there was current confusion regarding the use of faecal tests for occult blood [17–20], the addition of f-C into current symptom-based assessment has potential to increase CRC detection and be both clinically and cost effective. However, studies on f-C as compared to f-Hb are more germane to this Chapter.

3.5.2 Comparison of Faecal Haemoglobin with Faecal Calprotectin

Two studies performed in The Netherlands described in detail earlier investigated POCT f-Hb and f-C to distinguish those with from those without SCD [36, 37]. It was concluded that a diagnostic strategy with routine clinical data and f-Hb alone might safely rule out SCD and prevent unnecessary referral for colonoscopy in approximately one-third of patients.

Mowat et al. [54] showed that using a cut-off f-C of 50 μg/g, as often used in differentiating possible IBD from IBS, the positivity rate was 62.0%, the PPV for SCD was 16.9% and the PPV for IBD was 6.4%. The NPV for IBD was 98.9%. However, 25 cases of SCD (5 CRC, 17 AA and 3 IBD) had f-C below this cut-off and would have been missed if f-C alone was used. This study examined combinations of f-C at cut-offs of 50 μg/g and 200 μg/g and undetectable f-Hb. The conclusion was that faecal tests requested in primary care can provide a reliable prediction of the absence of SCD and, importantly, that f-Hb is superior to f-C and enables, with a single faecal test, an objective assessment of the need for, and urgency of further investigation.

Similarly, Widlak et al. [57] investigated f-Hb and f-C alone or combined as a method to identify those patients for referral for colonic investigation who were most likely to have CRC. As discussed earlier, it was stated that the diagnostic accuracy of f-Hb indicated that undetectable f-Hb is a good rule-out test for CRC, with a NPV of 99%, and was also judged as being far more accurate than the current referral pathway based on symptoms alone. Both f-Hb and f-C also offered a good rule-out option for IBD and microscopic colitis with NPV of 100% and 99% respectively. It was said that this means that treatable (benign) symptomatic colonic pathology would not be missed either; however, adding f-C to f-Hb showed no additional benefit for the added cost of analysing two tests. The conclusion was that an undetectable f-Hb was sufficiently sensitive to exclude CRC, with higher concentrations in left-sided lesions, while f-C in combination did not appear to provide additional diagnostic information.

As discussed earlier, in a recent study from Sweden [38], a qualitative FIT and a f-C test were compared for detecting CRC, AA and IBD in primary care, along with assessment of the value of combining these with anaemia and iron-deficiency tests. The sensitivity of f-C for detection of CRC and IBD was stated to be too low, at the cut-off of 100 μg/g recommended, for use as a diagnostic aid on its own. With a cut-off f-C of 50 μg/g, the performance of f-C and FIT was similar, but four cases of AA were missed when compared to the FIT. It was concluded

that combining f-C and FIT showed no improvement over the FIT alone, which detected a significantly larger proportion of CRC, AA and IBD than f-C (0.92 versus 0.46).

There have now been studies on the use of f-Hb in assessment of UC. It has been suggested that consecutive measurements of f-Hb in quiescent UC patients who achieved mucosal healing (MH) with negative f-Hb results would help identify patients with clinical relapse whose symptoms had not yet presented [65]. It has also been shown in a study assessing the risk of relapse in UC patients in clinical remission using mucosal status and f-Hb, negative f-Hb results one year or more after remission induction correlate with complete MH and better prognosis; it was considered that performing FIT one year after remission induction might be useful for evaluating relapse risk [66]. Further, a comparison of the predictive ability of f-Hb and f-C for MH in UC showed that both f-Hb and f-C were significantly correlated with the Mayo endoscopic sub-score [67]; it was concluded that f-Hb and f-C can both efficiently predict MH in UC, but f-Hb appears to be more sensitive than f-C for predicting a Mayo endoscopic sub-score of 0.

These early data suggest that f-Hb is superior to f-C in detection of SCD and more useful in UC. Consequently, it has been suggested [25] that, perhaps in the near future, when quantitative f-Hb becomes more widely available for triage of symptomatic patients, f-C will be used mainly in the monitoring of patients with known IBD rather than in the diagnostic setting. Further research seems warranted to compare f-Hb and f-C and in a wide range of GI disorders.

3.5.3 M2-PK and Use with Faecal Haemoglobin

M2-PK is the abbreviation used for the dimeric form of the pyruvate kinase isoenzyme type M2, a key enzyme in metabolism of tumours. Although M2-PK can be raised in many tumour types, increased faecal M2-PK has been investigated as a method of screening for CRC [63].

There appears to be only one study on use of M2-PK in assessment of patients with symptoms. Parente et al. explored a combination of f-Hb, obtained using the HM-JACK system (Kyowa-Medex), M2-PK and f-C [68]. All tests were performed on a single faecal sample from 280 patients aged 50–80 years, without any dietary restriction, before colonoscopy; 47 had CRC and 85 patients had one or more AA. CRC was associated with a highly significant increase in M2-PK which correlated with Dukes' staging. For CRC detection, f-Hb was the test with the highest specificity and PPV (89% and 53%), whereas M2-PK had the highest sensitivity and NPV (87% and 96%); f-C showed performance similar to M2-PK in terms of sensitivity and NPV, but had lower specificity. It was suggested that the best combination to predict the risk of CRC was f-Hb plus M2-PK. Further studies comparing f-Hb with M2-PK, alone or in combination, would be useful.

3.6 Risk Prediction Models

As well described in a review by Vega et al. [69] on "CRC diagnosis: pitfalls and opportunities", many factors affect incidence and mortality of CRC, including sex, age, socio-economic status, diet, alcohol consumption and tobacco use. Since the same spectrum of symptoms occur in those with and without SCD, it is attractive to think that risk-scoring systems which include both factors affecting incidence and mortality and/or symptoms might be effective. Williams et al. recently reviewed risk prediction models which combine multiple risk factors and symptoms that have the potential to improve timely diagnosis [70]. The aim was to systematically identify and compare the performance of models that predict the risk of primary CRC among symptomatic individuals; 18 papers describing 15 risk models were included. Models with good discrimination had been developed in both primary and secondary care populations and most contained variables which are easily obtainable in a single consultation. It was suggested that further research was needed to assess clinical utility before incorporation into practice. Some include results of gFOBT but, in this Chapter, only the few models to date which include f-Hb are discussed.

The study from The Netherlands using POCT FIT that evaluated the diagnostic value of history taking, physical examination, and simple blood testing and, subsequently, the added value of the POCT FIT, in that order, has been discussed previously [37], but models using quantitative estimates of f-Hb are of more current interest.

A very simple model was developed by Rodríguez-Alonso et al. [56] to provide a risk score for AN. The model incorporates age in five groups, sex and f-Hb as <10 μg Hb/g faeces or ≥10 μg Hb/g faeces. The risk score has a range of 0–11 points based on the sum of the scores according to the presence or absence of risk factors (see Table 3.2). The AUC for the risk score was 0.79. The internal validity of the model was assessed by a split sample procedure with 680 individuals (67.8%) in

Table 3.2 Pocket chart for risk score calculation

Risk factor	Points
Age	
<40 years	0
41–50 years	1
51–60 years	2
61–70 years	3
>70 years	4
Sex	
Female	0
Male	2
Faecal haemoglobin (f-Hb)	
f-Hb <10 μg Hb/g faeces	0
f-Hb ≥10 μg Hb/g faeces	5
Final risk score	
Age + Sex + f-Hb	

Adapted from Rodríguez-Alonso et al. [55]

the training set, of whom 91 had AN, and 323 individuals (32.2%) in the validation set, of whom 42 had AN. Good agreement was found between the risk of AN predicted by the model and the observed prevalence of AN. The optimal cut-point for the score derived from the whole study population was ≥5, with 75.9% sensitivity and 72.0% specificity. Identical values were found for the score derived from the training set. The corresponding values in the validation set were 88.1% sensitivity and 63.3% specificity.

In the population studied, using a risk score ≥5 as the criterion for colonoscopy, only 36.4% of the population would be referred and no CRC and only 5% of AA would be undetected. The authors of this Chapter wonder if this approach would be improved by using more f-Hb classes, especially since f-Hb has been shown to be related to the risk of future CRC [71].

Cubiella et al. developed a risk prediction model, COLONPREDICT, for CRC detection in symptomatic patients based on clinical and laboratory variables, compared this with the then current NICE referral criteria [14] and externally validated the model [72]. Consecutive patients referred for colonoscopy were recruited and a derivation cohort created (1572, 13.6% with CRC) and then a validation cohort (1481, 9.1% with CRC). In the derivation cohort, symptoms were assessed and the NICE referral criteria applied: f-Hb, f-C, blood Hb and serum carcinoembryonic antigen (CEA) were determined before performing an anorectal examination and a colonoscopy. The final prediction model included 11 variables: age, male sex, f-Hb ≥20 μg Hb/g faeces, blood Hb <10 g/dl, blood Hb 10–12 g/dl, CEA ≥3 ng/ml, acetylsalicylic acid treatment, previous colonoscopy, rectal mass, benign anorectal lesion, rectal bleeding and change in bowel habit. The AUC was 0.92, higher than the NICE referral criteria of 0.59. The validation cohort had the same characteristics as the derivation cohort and it was concluded that COLONPREDICT provides a highly accurate prediction model for CRC detection.

The COLONPREDICT model is complex, requiring knowledge of 11 variables, including symptoms, examinations in laboratory medicine, knowledge of aspirin use and previous history of colonoscopy. In consequence, a simpler model, the FAST Score, the Faecal haemoglobin, Age and Sex Test Score, was developed through international cooperation, making use of data from the McDonald et al. [51], Godber et al. [52], Mowat et al. [53] and Rodríguez-Alonso et al. [56] studies, as well as the comprehensive data from the COLONPREDICT study [72]. This approach allowed comparison of results from different regions in different countries and with f-Hb obtained by the two most commonly used quantitative FIT systems [73]. Diagnostic accuracy in the derivation and validation cohorts was compared using ROC analysis and sensitivity and specificity at two example thresholds: 1572 and 3976 patients were examined in the derivation and validation cohorts. For CRC, the variables included in the model were simply f-Hb in three classes, namely, 0–<20, 20–<200 and ≥200 μg Hb/g faeces, age, and sex. The AUC of the FAST score was 0.88 in the derivation cohort and 0.91 in the validation cohort. At two example score thresholds with 90% (score: 4.50) and 99% (score: 2.12) sensitivity for CRC, the prediction model had equivalent sensitivity as the validation cohort. The results were generally independent of study, country and analytical system

used. The authors considered that the FAST Score provides an easy to calculate prediction tool highly accurate for CRC detection in symptomatic patients and also useful in those with SCD.

There are issues which might be worthy of future research. The authors of the FAST Score study considered that the diagnostic accuracy and applicability of the tool in a primary care setting must be addressed in a prospective study and compared with the COLONPREDICT score and current and developing referral guidelines. Moreover, further prediction tools based on laboratory findings other than f-Hb should be designed and evaluated in a primary care setting. In this respect, the evaluation of newer biomarkers that are developed or proposed for use alone or included in risk-scoring models would be a necessary prerequisite to their introduction as investigations to assist in assessment of symptomatic patients.

3.7 Potential Clinical Pathways Using Faecal Haemoglobin

Although there is much evidence that a single measurement of f-Hb, obtained by quantitative FIT could well be sufficient to decide whom to refer for colonoscopy, as discussed earlier, using POCT FIT, Elias et al. [37] stated that their results confirm that a positive FIT result supports the value of referral. However, they also stated that clinical information to be informative when the FIT result was negative. Further, the argument put forward to support this approach was that professionals in primary care would not immediately request tests in patients presenting with symptoms and signs of SCD without considering other pre-test information from history taking and physical examination. Thus, this study evaluated the diagnostic value of history taking, physical examination, and simple blood testing and, after these, the added value of the POCT FIT.

However, as documented earlier, although lower abdominal symptoms are very common presenting complaints, SCD is much rarer and, because of the significant overlap of symptoms in those with and without SCD, clinical data are of limited value and have low sensitivity and PPV. Thus, since FIT is such a good rule-out test for SCD, this should be the first investigation to be performed, immediately after presentation and recording of symptoms and decisions only made when the f-Hb is available.

Many clinical pathways are clearly possible and example options for the various stages involved follow.

- **Stage 1:** patient presents to primary healthcare professional with lower abdominal symptoms.
- **Stage 2:** symptoms are recorded, ideally using clinical information systems that allow data to be viewed by professionals in both primary and secondary healthcare, then:
  option 1; ask all patients, irrespective of their symptoms and whether these are "red-flag" or not, to collect one sample of faeces in a quantitative FIT specimen collection device and to return this to the practice as soon as possible for onward

transmission to the laboratory, or post directly to the laboratory before decisions are made regarding referral, or
option 2: refer patients directly for urgent endoscopy without the f-Hb result when "red-flag "symptoms, such as rectal bleeding or an abdominal mass are present, in spite of the fact that rectal bleeding, for example, has low PPV, and ask remaining "low-risk" patients to collect one sample for f-Hb

- **Stage 3:** for those patients with f-Hb now available (either all, or those with lower risk, respectively), then
  option 1: specialists in gastroenterology in secondary care take clinical information and f-Hb into account and then decide clinical pathway to be followed including: urgent appointment for colonoscopy, routine appointment for colonoscopy, referral to specialist clinic, or no action, particularly when the f-Hb is below the cut-off used for referral, or
  option 2: f-Hb result returned to primary health care for decisions on further clinical care to be made.
- **Stage 4:** for those with negative f-Hb results, decide on further care strategy:
  option 1: reassure patient in primary healthcare that SCD is unlikely, or
  option 2: since no test is perfect and some cases of CRC, AN and IBD will have f-Hb below the cut-off, institute safety-netting, especially if symptoms persist or get worse, through the following options: referral to secondary healthcare specialist clinics, further assessment of the patient in primary care and re-referral if suspicion remains high, or repetition of the f-Hb.
- **Stage 5:** undertake ongoing audit of outcomes performed and promulgate to all healthcare professionals involved in the pathway.
- **Stage 6:** develop and improve the pathway in the light of the results of the audit and feedback from healthcare professionals and patients and their relatives and carers.

Clearly, other approaches are possible and these may well depend on many factors including local, regional or national priorities, available colonoscopy resources and availability of funding to introduce f-Hb testing, Irrespective of the pathway adopted, it will be very valuable if those involved in introduction of f-Hb into routine clinical practice present and publish their results, positive or negative, so that lessons learned can be considered by others introducing use of f-Hb in routine clinical practice. Irrespective of the pathway adopted, education and training of all those involved will be a necessary prerequisite for success.

3.8 Conclusions and the Future

Many patients present in primary healthcare (and are referred for further evaluation in secondary care) with symptoms of SCD, but SCD is present in only a small proportion of these. Since colonoscopy is a scarce resource in many countries, strategies to direct these unpleasant and potentially risky invasive investigations to those who would benefit most would be very advantageous and would undoubtedly

enhance patient satisfaction with their clinical journey. Faecal tests for the presence of Hb provide a valuable approach, but it must be stressed that traditional gFOBT have no role to play in this context. However, there is now considerable evidence that FIT have many advantageous characteristics and are very useful in this clinical setting as well as in asymptomatic population screening, where they are now the non-invasive test of choice [74]. FIT come in qualitative and quantitative test formats. Qualitative FIT might have some merits when used at home, or in general practices, or in secondary referral clinics; evidence exists that these can be applied in both primary and healthcare settings to detect CRC and rule-out most SCD, but they have many disadvantages. Quantitative FIT provide numerical estimates of f-Hb. A number of well-designed studies in the peer-reviewed literature have shown that, at low f-Hb cut-off, ideally that claimed by the manufacture of the FIT system as the limit of quantitation, this investigation has high sensitivity for CRC and could be used as a rule-in test for this disease and prompt rapid referral for endoscopy. A recent Health Technology Assessment provides a systematic review supporting the NICE diagnostic guideline DG30, which recommends use of quantitative FIT, as described earlier [75]. Perhaps more importantly, f-Hb below the cut-off provides considerable reassurance that SCD is likely to be absent and further investigation many not be required. Using both POCT and quantitative methods, f-Hb seems to have advantages over f-C in assessment of symptomatic patients. Some risk-scoring models using f-Hb and other important variables associated with SCD, especially age and sex, have been advocated. Although FIT seem to have significant merits, it must be remembered that no test is perfect and some cases of CRC, AN and IBD will remain undetected. It follows that safety-netting, through referral to secondary healthcare specialist clinics, or further assessment of the patient and re-referral if suspicion remains high, or repeating the f-Hb, seem feasible options worthy of exploration.

It is clear that not all facets of the use of testing for the presence of Hb in faeces have been answered and, as discussed in each section of this Chapter, further research studies on the following might be of interest and might influence current practice:

- assessment of the benefits and harms of qualitative FIT being done by people in their own homes,
- further studies on the use of qualitative FIT in general practice and in secondary healthcare settings, particularly in gastroenterology and other clinics evaluating patients before colonoscopy,
- direct comparison of FIT analytical systems through patients collecting samples with more than one specimen collection device from a single bowel motion,
- assessment of whether age and sex stratified f-Hb cut-offs are of value,
- evaluation of the variation of f-Hb in individuals over time,
- further evaluation of the merits of other biomarkers, such as f-C and M2-PK either alone or in combination with f-Hb as tools to investigate the symptomatic,
- creation of further risk-scoring models, particularly that use f-Hb as a continuous variable, comparison with other models and with current referral guidelines

based on symptoms and exploration of reporting risk scores, perhaps with interpretative guidance, through laboratory information systems,
- comparison of approaches for safety-netting of those who have f-Hb below the analytical limit of quantitation, but continue to have symptoms and
- since about half of patients providing specimens for FIT have undetectable f-Hb, but the dogma is that everyone has some blood in their faeces, would the development of "high sensitivity" methods for estimation of f-Hb, that is methods with a lower limit of quantitation for f-Hb than current systems, be of any clinical value?

However, in spite of the potentially valuable new information that would be gained from such studies, f-Hb is considered to be a mature, evidence-based investigation, worthy of ubiquitous introduction as a routine test in clinical practice now.

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4 Enhancing Earlier Diagnosis of Colorectal Cancer by Algorithmic Analysis of Trends in Complete Blood Counts

Varda Shalev, Inbal Goldshtein, Gideon Koren, Pinchas Akiva, and Ran Goshen

Key Points

- We describe the evolution of a novel method for the detection of colorectal cancer, by analysis of changes, or trends in complete blood counts
- A novel algorithm calculates with high sensitivity and specificity the risk of colorectal cancer from routine complete blood counts measurements, long before anemia is apparent
- Due to low adherence with existing screening methods, or in countries with no screening programs, this method can become a meaningful clinical support system, potentially improving outcome in patients who have missed out on routine screening.

4.1 Introduction

With colorectal cancer (CRC) being the second most common malignancy among women and the third among men [1], early diagnosis is critical in reducing morbidity and mortality. Available screening methods, including sigmoidoscopy and fecal occult blood test (FOBT), have been shown to decrease CRC mortality by up to 30% [2, 3]. However, despite their established cost effectiveness, adherence of the target screening population (people older than 50 y/o) is low for both sigmoidoscopy and FOBT, with non-attendance rates ranging from

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21% to 86% in different studies, and hence the window of opportunity of early diagnosis is often missed [4, 5]. Algorithms based on typical symptoms of CRC have been constructed, showing different determinants to yield relatively low predictive values. For example, anemia, appetite loss, and weight loss are independent predictors of incident CRC [6]. However, these symptoms are typically appearing in advanced stages of the disease, thus often missing the opportunity to cure the cancer.

4.2 Index Case

A 70 y/o man who repeatedly missed his CRC screening visits, was diagnosed with advanced disease due to emerging gastrointestinal symptoms, and succumbed to his illness 2 years later. Careful review of his medical records revealed that in three subsequent complete blood counts (CBC) performed within the 5 years prior to his diagnosis, his hemoglobin and hematocrit levels steadily fell, before reaching the defined level of anemia (11.7 g/dl for men).

Intestinal blood loss typical of CRC is the basis for the worldwide use of FOBT as a screening method. Similarly, in the presence of iron deficient anemia, CRC is an important consideration in the differential diagnosis affecting up to 60% of CRC cases in some series [7].

However, till recently, the possibility of capturing changes in patterns of hemoglobin and hematocrit, as indicators of CRC-related blood loss, long before the anemia is apparent has not been systematically considered. In 2008 researchers at Maccabi Research Institute conceived the hypothesis that analysis of changes in CBC patterns in samples that were obtained clinically, long before anemia is apparent, may yield a sensitive and specific biomarker of CRC [7] and hence promote timely diagnosis. This is especially important for patients who have missed the routine clinical screening (e.g. FOBT or sigmoidoscopy), or in countries with no screening program operating.

In this chapter we describe the development of an algorithm which captures these changes and its retrospective and prospective validation processes. For ease of reading, we dubbed the new algorithm for the purpose of this review as ColonScore.

4.3 Variations in Hemoglobin Levels Within the Normal Range Before CRC Is Diagnosed

The concept that variations within the normal range of Hb levels can signify CRC was examined in a large scale retrospective study [8]. Similar to all other parts of this project, data were retrieved from the computerized database of Maccabi Health Services (MHS), which is the second largest health organization in Israel with two million under coverage, as well as from Israel's National Cancer Registry. The study included all MHS members between 45 and 75 years of age diagnosed with CRC between January 1, 2004 and January 14, 2009. To be included, their Hb levels had

to be within the normal range (not below 11.7 g/dl for women and 12.6 g/l for men) when recorded during the first year of the observation period. A total of 1074 CRC cases out of 3658 met these criteria. For each case, ten controls were selected randomly from MHS members with no evidence of cancer, and matched for age and sex. Results of Hb tests were grouped into 6 month intervals till the index date of applying the algorithm.

As per study definitions, Hb levels started within the normal range for all patients. Starting 10 years before the index date, the CRC cases and controls had similar and quite steady levels till 4 years before the index date, when visible and significant differences began to emerge between the CRC and control patients in both men and women, such that the slopes of Hb change over time in the last 3.5 years before the index date, expressed as logarithmic curves, were highly different in both sexes. As seen in Fig. 4.1, while still in the normal range, Hb levels among CRC cases trended down quite dramatically with little overlap when comparing it to the controls who showed very little age-dependent decrease in Hb over the 10-year period.

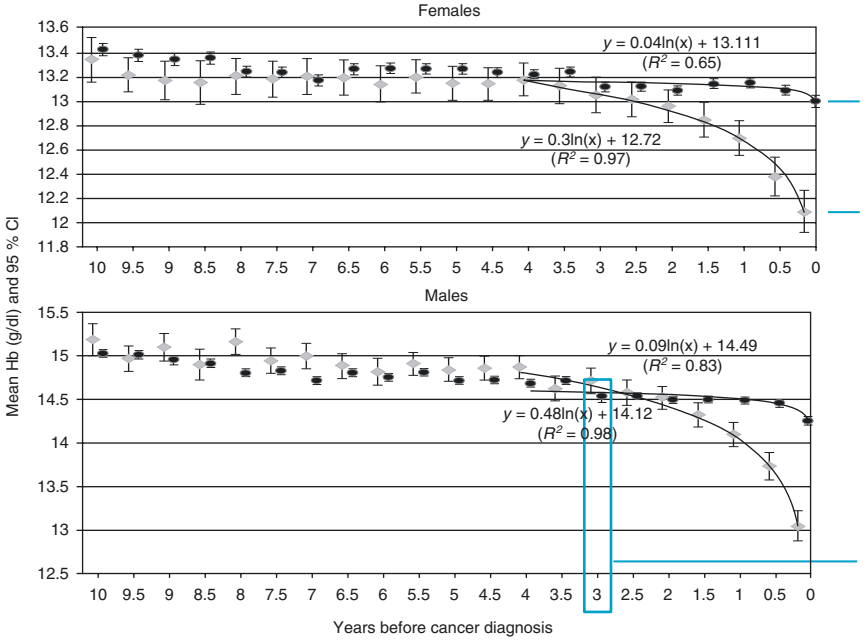

Fig. 4.1 Hb levels started within the normal range for all patients. Starting 10 years before the index date, the CRC cases and controls had similar and quite steady levels till 4 years before the index date, when visible and significant differences began to emerge between the CRC and control patients in both men and women, such that the slopes of Hb change over time in the last 3.5 years before the index date, expressed as logarithmic curves, were highly different in both sexes. As seen in Fig. 4.1, while still in the therapeutic range, Hb levels among CRC cases trended down quite dramatically with little overlap when comparing it to the controls who show very little age-dependent decrease in Hb over the 10-year period

4.4 Construction of the Model and Measures of Performance

Proving the notion that changes in Hb levels over time, long before anemia becomes apparent, can serve as an indicator for the flagging of CRC, has led to developing an algorithm, based on machine learning methodology, to generate a data-driven prediction model.

4.4.1 Machine Learning

Most traditional computer-based algorithms in medicine are sets of rules based on existing knowledge in a specific topic, which are applied to draw conclusions about specific clinical scenarios. These rules take general medical principles and apply them to new sets of patients. In contrast, machine learning algorithms [9] are a relatively new area of research in computer sciences and statistics, which aims to identify novel and valid patterns in data. Machine learning encompasses different modeling tools, which utilize computers to uncover "hidden insights" through learning from historical relationships and trends in the data. Similar to traditional regression models, there are generally outcomes, covariates, and a statistical function linking the two. Different from traditional statistics, machine learning considers large numbers of predictors by combining them in nonlinear and highly interactive computational methods.

As an example for the immense potential of machine learning one can consider radiology (e.g., mamographs) and anatomical pathology [10]. The interpretation of digitized images can be directly analyzed through algorithms, which will improve performance, and its accuracy is expected to exceed diagnosis by physicians [9].

In the model-construction phase of machine learning, the model automatically generates decision trees which aim at identifying the CRC cases. In the next phase, the decision trees are combined into a single unified model. These parameters are then optimized in a process of internal cross validation, which aims to reduce overfitting, whereby the researchers use 90% of the derivation data as a learning subset to construct a model, and examine its performance on the remaining 10%. This process is repeated ten times by dividing the derivation set into new and different learning and testing subsets. The model created through these steps could then be applied on a new and previously unused data of an individual, to quantify his/her risk stratification score of having CRC.

4.4.2 Performance of the Model

The performance of the model was measured by three different parameters:

1. The classical area under the receiver-operator curve (AUC), where the x axis demarks the false positive rate (1 minus specificity) and the y axis shows true positive rates (sensitivity). The closer the AUC is to 1.0, the better is the overall performance of the model.

2. Assessing the ability to identify individuals with the highest probability of having CRC, the model considered a threshold score corresponding to a very low false positive rate of 0.5% (a low proportion of CRC free individuals who are incorrectly identified), and evaluated the odds ratio of having CRC at that false positive level.
3. Examining the ability to identify a significant fraction of the CRC cases, the researchers evaluated the specificity of the model (the proportion of correctly identified CRC-free individuals) at a score threshold that corresponds to 50% sensitivity CRC detection rate.

4.5 Dataset for the Retrospective Derivation and Validation Study

Anonymized and de-identified patient records from Israeli and the UK cohorts as described below, were randomly divided into a derivation set that included 80% of cases, and a validation set containing the remaining 20% of the data. Included were all patients 40 year of age or older diagnosed with cancer in the years 2007–2012, and a random group of cancer-free patients of the same age range.

The Israeli derivation dataset consisted of 606,403 individuals, of whom 466,107 had CBCs. The Israeli validation dataset cohort consisted of 173,251 individuals, of whom 139,205 had CBCs. Overall, there were 2437 CRC cases with CBCs obtained before diagnosis in the derivation set, and 698 such cases in the Israeli validation set. Unlike the Israeli cohort, the UK external validation dataset was a case-control set that consisted of all available 5061 CRC cases and a randomly selected 20,552 cancer free individuals. Sex, birth year and all available CBC records were extracted for the period from January 2003 to June 2011 in Israel and from 1990 until May 2012 in the UK.

Colorectal and all other cancers were identified in Israel from the National Cancer Registry. In the UK, an ad hoc registry was created from all scanning records of malignancies and cancer treatments from January 2007. For every individual with CBC data, the input data consisted of age, gender and all available sets of CBC data parameters. In the data preparation phase, the CBC data of each individual were collected and changes in the values of the parameters over the last 18–36 months were recorded.

4.6 Accuracy of Prediction of CRC

The proposed model was applied to the Israeli validation dataset and included all CBC tests performed 3–6 months before CRC diagnosis. Measuring the overall performance of the model, the AUC was 0.826; the odds ratio at a false positive rate of 0.5% (measuring the model's ability to identify individuals with the highest probability of having CRC) was 26 ± 6 and the specificity at 50% sensitivity (i.e. a significant fraction of CRC cases detected) was high at 88.6%.

Subsequently, as an external independent validation, the model was applied to a new dataset extracted from the THIN database in the UK [11]. The population in this dataset was different in ethnicity, environmental backgrounds and health care practices from the original Israeli-based dataset used to develop the model. In the British population, fewer blood counts were performed, and some CBC parameters were not (e.g. Red blood cell Distribution Width (RDW)). Despite these different characteristics, the model achieved a similar performance in the British set as it did in the Israeli set (AUC 0.81, odds ratio 40, specificity 94%).

The potential clinical utility of this new model depends on its ability to detect CRC cases earlier than current practice. To evaluate this potential, the medical records available in the UK database were evaluated while focusing only on scores assigned to asymptomatic individuals. Considering CBCs in the 3–6 month time window prior to diagnosis, and the score threshold corresponding to 90% specificity, 67% of the CRC cases were asymptomatic. In addition, low hemoglobin levels (below 12 g/dl for men and 11 g/dl for women) were considered, even when there was no recorded clinical diagnosis of anemia by the physician caring for these individuals. Please note that these threshold values were set at a slightly lower levels than in the preliminary study described above which were 12.6 for men and 11.7 for women (under "Variations in hemoglobin levels within the normal range"). The specificity for detecting 50% of those cases was somewhat reduced (to 82%) but was still significantly better than age alone (74%) thus showing its potential clinical value.

One challenge in diagnosing CRC is the differential ability to identify tumors in different parts of the colon. During the validation of the ColonScore, there was an opportunity to examine the new method's performance on malignant tumors in different sites of the colon. In all cases, specificity at a sensitivity of 50% was high: rectum (85.9% specificity), left colon (87.4%), transverse colon (93.4%) and right colon (96.1%) [12].

4.6.1 CRC Detection Rate When Using ColonScore in Addition to FOBT

To evaluate the potential contribution of ColonScore to current CRC detection rate in the Israeli dataset, the ColonScore rates were compared to those of FOBT in the same cohort. The dataset for this comparison contained 75,822 FOBT tests for 63,847 individuals, compared to 210,923 individuals with CBCs. The overall FOBT positive rate was 5%, while ColonScore discovered 48% more CRC cases than FOBT (252 versus 170). Considering individuals who were identified either by ColonScore or by FOBT-ColonScore increased the number of CRC cases detected by 115% (from 170 to 365).

4.6.2 Comparison to Existing Anemia Guidelines

Guidelines of several health care organizations require further evaluation of individuals with unexplained iron deficiency anemia. Some guidelines specify hemoglobin levels below 12 g/dl for women and 13 g/dl for men which are slightly higher

Table 4.1 Estimated odds ratios of having CRC at 99% threshold for specificity

Time-window (months)	Age range (years)	Access to previous CBC	Odds ratios (95% CI)
30–180	50–75	Yes	29.3 [26.8, 32.1]
30–180	50–75	No, single CBC	21.2 [19.0, 23.3]

than the thresholds set during the validation of the model (12 for men and 11 for women). The specificity of such thresholds for predicting CRC for men and women of ages 50–75 is 97.3%. Considering this threshold with the same specificity for ColonScore (i.e. 97.3%), and comparing the sensitivities of blood counts taken 3–6 months before diagnosis, the anemia guideline sensitivity was 20%, while ColonScore's sensitivity was 30% ($P < 1e{-}5$).

4.6.3 Using a Single Set of CBC Values

Testing the ability of ColonScore to detect CRC at different times, revealed that using CBCs taken even 2 years prior to diagnosis was effective, based on AUC and specificity at 50% sensitivity. Moreover, in parallel the performance of the ColonScore was also tested using only **a single** set of values of CBC, without access to historical values over time.

As shown in the Table 4.1, the performance of the test using no history (i.e. only a single blood count over time at a 99% specificity threshold) yielded an OR of 21 not very far away from the OR achieved with analyzing two or more CBC measures (OR 29.3).

4.7 Contribution of Parameters to the Model

In addition to the 20 parameters derived from the CBC, age was found to be the single most important contributing parameter to the performance of the model. When comparing the final model to age alone, the model achieved significantly better performance in all three measures (AUC 0.81 vs. 0.72, odds ratio 34 vs. 2, and specificity of 90% vs. 79%). The predictive value of sex alone was lower for CRC—the odds ratio for males as compared to females was 1.15 in the Israeli dataset.

Estimating the importance of the blood-related parameters was complicated by the high correlation among various parameters. When evaluating the importance of a parameter, both its direct contribution to the performance measure, as well as the degree to which its contribution could be replaced by other parameters were considered. As an example: considering hemoglobin, there was a decrease of AUC between the full model and the model without hemoglobin. Subsequently the parameter that was most closely correlated to hemoglobin (hematocrit) was identified and removed it from the full model. Then the decrease in AUC between the partial model (without hematocrit) and partial model without hemoglobin was evaluated. The process was repeated until it was left with hemoglobin alone. The contribution of hemoglobin was defined as the maximal decrease in AUC, while the redundancy was defined by the number of other parameters that were removed until removing hemoglobin gave

a significant decrease (e.g. the point where other parameters could not compensate for its contribution). This process was repeated for all blood count parameters. This analysis revealed that age was followed in importance by various red blood cells-related parameters, consistent with previous findings in CRC patients [12]. For more details on this analysis, the reader is referred to the original paper [12].

4.8 Initial Results of a Prospective Validation Study

It was evident to the ColonScore project scientists that the very promising results of the retrospective analyses shown above, would have to prove themselves in a prospective study, where patients' CBC parameters are evaluated with the new ColonScore before having FOBT or colonoscopy performed, and this stage of the study will be described in details herein.

Using the algorithms created in the retrospective developmental phase of ColonScore, the prospective interventional phase commenced in October 2015 and included all MHS insured persons aged 50–75 years old who have not had an updated CRC screen with either colonoscopy (in the last 10 years) or FOBT (in the last 1.5 years). Using these members' routine CBC tests, ColonScore algorithm generates a personal risk score for each patient's sample. When a ColonScore risk is within the top 0.5% scores generated by the algorithm (equivalent to a 42-fold increased risk over population average) a real time pop-up alert is presented to the family physician, alongside the CBC results, with a recommendation to book the patient for colonoscopy.

Over the first few months of initiating this prospective pilot, each month around 50 patients have been detected as high risk ColonScore. Colonoscopy referral increased by 1% and the percentage of justified colonoscopies is slightly superior to that yielded by active FOBT testing, with over 5% cancerous and 30% pre-cancerous findings (Fig. 4.2).

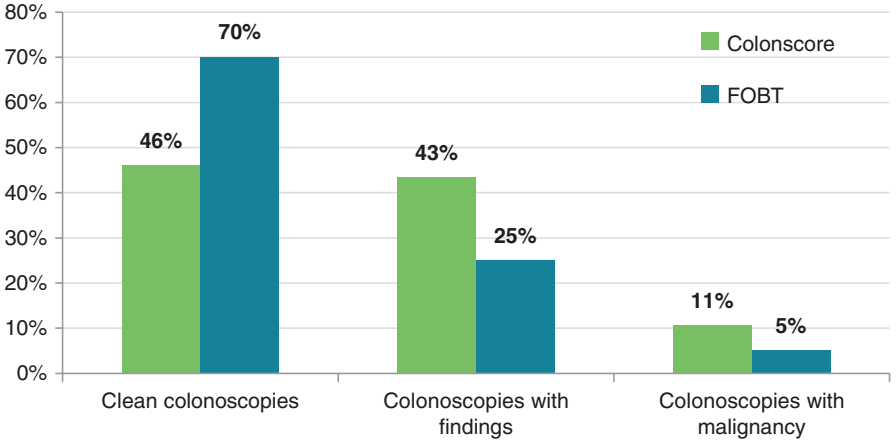

Fig. 4.2 Preliminary results of the first year of a prospective study, comparing the performance of FOBT and ColonScore. Presently over 200 cases have been collected

4.9 Limitations and Ethical Dilemmas

A potential limitation of ColonScore is the need to have access to repeated CBC values (at least two times) and their sub parameters. While these are commonly available in some countries, they are less used elsewhere; yet the fact that very similar results to the Israeli set were achieved in the UK, with significantly less CBC data, lends credibility to the new method.

Unlike the preplanned screening, where individuals 50–75 years of age are expected to be screened, the implementation of the ColonScore on individuals based on incidental findings of their CBC raise several important issues that need to be considered and addressed: Can such a test be performed at all on patients who did not consent to this secondary use of their data, based on existing series of CBC over time? Although this issue may be very country specific, it is clear that in most countries no such analysis can be performed without patient consent. A related question is whether such analysis can be done without consent by the physician caring for the patient, and what if the physician does not believe the results of the Colonscore are suitable for his/her patient? On the same vein, shall one encourage patients to perform routine CBCs in order to increase the chance of findings CRC?

These are some of the questions that will need to be addressed and accompany the implementation of the new test as a routine procedure. While it is beyond the scope of the present presentation, we are currently addressing them through the prospective implementation of the test.

Presently the cost-effectiveness of ColonScore has not been formally calculated. The fact that the method utilizes existing laboratory data suggests that incorporating it in clinical work may be highly cost effective, especially in cases where there is no general screening program in operation. The ongoing conduct of the prospective study supports these impressions, where ColonScore appears to support clinical work, although formal cost-effectiveness will have to be performed.

Conclusion

Utilizing a novel algorithm we describe the use of clinically available samples of CBC to calculate the risk of CRC. This has created a unique opportunity to improve timely diagnosis long before symptoms have emerged, and hence, when the disease is much more likely to be curable. Due to relatively low adherence with existing screening methods, or in countries with no screening program running, Colonscore can become a meaningful clinical support system, potentially improving outcome in patients who have missed out on routine screening.

More studies are needed to validate these findings in additional populations and settings.

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5 Investigating Symptoms Suggestive of Colorectal Cancer: Computed Tomographic Colonography or Colonoscopy?

A.A. Plumb and S. Halligan

Key Points

- Colonoscopy and CT colonography are the two most commonly employed tests for whole-colon evaluation in patients with colorectal symptoms.
- Both tests are highly sensitive for established colorectal cancer (CRC), each having >95% sensitivity in meta-analysis. Larger (1 cm+) polyps are also well depicted by both tests, but colonoscopy is superior for smaller polyps.
- CT colonography also evaluates structures outside the colon, which may be a benefit where symptoms are vague or may be unrelated to the colorectum; but can uncover incidental findings that are ultimately unimportant, adding to costs, patient inconvenience and worry.
- The two tests are likely to be best employed in complementary fashion, ensuring all patients have access to the most appropriate test for their presenting symptoms and degree of co-morbidity.

5.1 Introduction

Colorectal symptoms are common: Around 25% of individuals aged over 65 years will have one or more abdominal symptom [1], accounting for approximately 10% of attendances to primary care physicians [2]. Colorectal cancer (CRC) is also common, affecting approximately 1 in 20 individuals in the USA and Europe; over 600,000 new cases are diagnosed each year [3]. Unfortunately for both patients and clinicians, it is extremely difficult to determine upfront which of the vast number of patients with colorectal symptoms have CRC, and which do not. Neither individual

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symptoms and signs, nor combinations thereof, are sufficiently sensitive and specific to reliably diagnose or exclude CRC in the large majority of patients [4]. For example, change in bowel habit and/or abdominal pain are extremely common in the general population. Therefore, diagnostic testing must be employed. Furthermore, patients do not attend to their doctor with the goal of simply excluding CRC; they have one or more symptoms and will want an explanation for these (and, subsequently, effective treatment). In this scenario, the ideal diagnostic test would have several key characteristics; it would be both sensitive and specific for CRC (and, ideally, opportunistically detect pre-malignant adenomas as well), able to detect other diseases that cause colorectal symptoms, widely-available, safe, non-invasive, well-tolerated by patients, and cost-effective for healthcare systems to implement.

Although a perfect test may not exist, there are a wide variety of options available currently. It may not even be necessary to investigate the entire colon under all circumstances. Flexible sigmoidoscopy (FS) is extremely safe and relatively well-tolerated, as well as being much cheaper than colonoscopy, and it has excellent diagnostic performance for lesions within the reach of the instrument (i.e. the rectum, sigmoid, and much of the descending colon in many cases). It may therefore have a role in evaluation of symptoms that strongly suggest a distal left-sided colonic lesion (for example, bright red rectal bleeding). However, unselected use is problematic—it will inevitably miss proximal CRC if they are present. Where patients are selected carefully, a strategy based on FS alone can achieve high diagnostic yields at little risk of missing proximal cancer [5]. Conversely, high-risk symptoms, such as an abdominal mass or iron-deficiency anemia, mandate whole-colon investigation, as the chance of missing a right-sided CRC is substantial [5]. When this applies, the most widely-used options are colonoscopy and CTC. Further discussion of these two tests will form the remainder of this Chapter.

5.2 Historical Perspective

In the late 1980s and early 1990s, rapid helical and, subsequently, multiple detector row CT scanners were becoming increasingly available [6]. These machines capture inherently 3-dimensional data. This was accompanied by vast increases in computer processing power, meaning that CT image reconstruction was much more rapid. CT was already being used to stage CRC, and the concept of distending the colon with air to improve tumor visualization was known [7, 8], if not widely practiced. However, clinical and research interest was ignited by Dr. David Vining's realization that virtual reality computing, similar to that used in flight simulator games, could be applied to navigate helical CT datasets. After recruiting a healthy volunteer (a particularly amenable colleague, Dr. David Gelfand), a single-detector row helical CT acquisition was made through the cleansed, distended colon, and CTC as we know it today was born. The reconstructed images were presented at the 23rd Annual Meeting of the Society of Gastrointestinal Radiologists in Maui, Hawaii, as an endoluminal fly-through video, accompanied by Richard Wagner's "Flight of the Valkyries". This high-profile presentation [9] precipitated a flurry of research

interest, primarily in the USA. Early studies recruited patients at high risk of polyps or CRC who were scheduled for colonoscopy and performed same-day CTC prior to this, comparing results from both tests. These intra-individual studies suggested CTC was highly sensitive for both CRC and large polyps [10–13]. Larger prospective studies, in both symptomatic (or otherwise high-risk) [14, 15] and screening [16] cohorts confirmed these encouraging early results. The stage was set for large, multicenter, prospective evaluations of the technique in both screening and symptomatic populations—with the former being the primary focus in the USA and the latter being led by European groups. The remainder of this chapter will focus on the key characteristics of CTC and colonoscopy when employed to investigate symptomatic patients.

5.3 Test Characteristics

5.3.1 Diagnostic Accuracy: Sensitivity, Specificity and Referral Rate

When confronted with a patient presenting with colorectal symptoms, clinicians have a wealth of tests from which to choose. This may be influenced by their opinion of the most likely diagnosis following clinical history and physical examination (as well as by other initial tests, such as for iron-deficiency anaemia). However, whenever CRC is the major concern, diagnostic sensitivity and specificity are of prime importance.

A 2005 meta-analysis [17] of the diagnostic accuracy of CTC had made it clear that the vast majority of available data was derived from studies of symptomatic or otherwise high-risk patients; only 1 of 24 included primary studies recruited asymptomatic individuals with no personal history of colorectal adenomas (the famous Department of Defence study [16], led by Dr. Perry Pickhardt). Similarly, a separate meta-analysis from 2011 [18] (evaluating the sensitivity of CTC and colonoscopy for CRC specifically) found that only 6 of 49 studies targeted asymptomatic screenees. Therefore, the conclusions of these meta-analyses are most applicable to symptomatic populations. Both suggested that CTC had a sensitivity of 96% for colorectal cancer (Fig. 5.1). The 2011 study also analysed data from studies using the combination of CTC and colonoscopy as an enhanced reference standard for the presence or absence of CRC, via so-called "segmental unblinding". In this design, patients undergo CTC first, followed by same-day colonoscopy; the endoscopist interrogates the colon segment-by-segment, initially blinded to the CTC results. Having committed to their opinion using colonoscopy alone, the CTC result for the segment in question is then revealed by an independent research co-ordinator, and any discrepancies are resolved by re-examination of that segment if required. When employed in this fashion, the combination of CTC and colonoscopy becomes a superior "gold-standard" against which each individual test can be judged. This meta-analysis showed that initial (blinded) colonoscopy had a sensitivity for CRC of 95%, not significantly different from the figure for CTC. Importantly, between-study heterogeneity was far lower for CTC (0%) than for colonoscopy (50%),

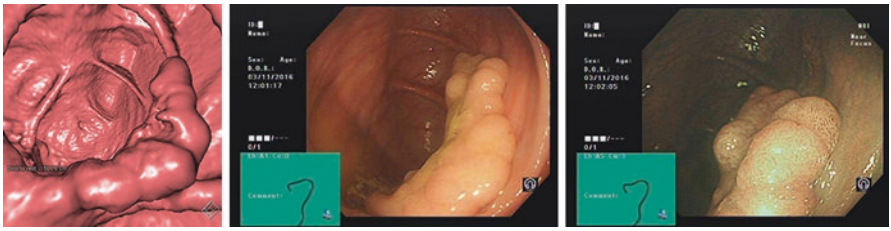

Fig. 5.1 Matched endoluminal CTC (*left panel*), white-light endoscopic (*middle panel*) and narrow-band imaging endoscopic (*right panel*) images of a tumour in the ascending colon, just above the ileocecal valve. This was macroscopically a laterally-spreading tumour, granular type (LST-G) and was removed by endoscopic mucosal resection (EMR). Histologically, the lesion was a tubulovillous adenoma with high-grade dysplasia and a small focus of invasive adenocarcinoma, which had been completely excised endoscopically

largely due to one study in which four of five CRCs were missed by unblinded colonoscopy (all of which were detected by CTC [19]). Therefore, not only is CTC highly sensitive for CRC, but the research literature is consistent across a wide variety of studies performed internationally.

Colorectal neoplasia occurs on a continuum, from benign, low-risk tubular adenomas that are destined to cause no harm (and indeed may even regress spontaneously [20]), via intermediate- and high-risk adenomas, through to frankly malignant invasive polyps and masses [21]. This, of course, is the rationale for CRC screening—removal of benign but potentially pre-malignant precursor lesions ultimately reduces subsequent CRC incidence [22–25] (and early detection and treatment of established cancer reduces disease mortality). However, polyps do not cause symptoms unless very large. Detection of small (6–9 mm) and diminutive (0–5 mm) polyps is therefore of considerably less importance for symptomatic patients than for screening populations, as these will undoubtedly be incidental to the index clinical presentation. It could be argued that each colonic examination has the potential to opportunistically detect and remove precursor lesions, and so their detection is an important facet of thorough testing. It must be remembered, however, that the large majority of polyps will never develop into CRC—over 40% of adults aged over 50 years have adenomas but only 5% will ever develop CRC [26]. Clearly, polyps with the highest risk of progressing to CRC are the most important to detect, and it has long been known that risk goes hand-in-hand with polyp size [21]. Since both meta-analysis [17] and more recent multicenter prospective cohort studies [27] show that CTC has sensitivity of approximately 90% for colorectal neoplasia of 10 mm or more, the technique seems well-suited to this role.

Our knowledge regarding the use of CTC for symptomatic patients, and in particular its relationship with colonoscopy, has been clarified significantly by the UK SIGGAR (Special Interest Group in Gastrointestinal and Abdominal Radiology) studies [28]. These parallel, multicenter, pragmatic randomized controlled trials were designed to compare CTC with the radiological alternative, barium enema [29]; and to compare CTC with colonoscopy [30]. It is important to note that the goals and primary outcomes of the two trials were different. The CTC vs. barium enema trial

was designed to achieve 90% power to detect a difference in detection rates between the two tests for CRC and large (≥1 cm) polyps, assuming that CTC detected roughly 30% more CRC and large polyps than barium enema. 3838 patients were randomized 2:1 in favor of barium enema [31]. A significant difference was indeed demonstrated—CTC had a significantly higher detection rate than barium enema (relative risk 1.31, 95%CI 1.01–1.68), and missed fewer cancers at 3 year follow-up (3 missed of 45 detected vs. 12 missed of 85 detected) [29]. The authors concluded that barium enema should be abandoned as a test for colorectal neoplasia in favor of CTC.

Conversely, the CTC vs. colonoscopy trial was not designed or powered to compare the detection rates of the two tests. As mentioned above, meta-analysis suggests that the two have near-equivalent sensitivity for established CRC [17, 18], and that CTC is 90% sensitive for large polyps when compared to colonoscopy or colonoscopy with segmental unblinding [17]. Accordingly, a trial powered to detect a difference in detection rates between colonoscopy and CTC would have required tens of thousands of patients.

Instead, the trial was designed to assess a different issue relevant to the clinical implementation of both CTC and colonoscopy—the need for further testing after the index procedure. Both CTC and colonoscopy can generate further tests; CTC cannot remove polyps or biopsy cancers, and colonoscopy may be incomplete (and detected cancers also require CT staging). If a significant proportion of patients having CTC to investigate colorectal symptoms require subsequent colonoscopy in any case, there is little point in them being subjected to CTC up-front, which would add inconvenience, risk and cost for no benefit. Therefore, the SIGGAR CTC vs. colonoscopy trial was designed to compare the referral rate for additional colonic investigation; the detection rate of CRC and large polyps was a key secondary outcome, as was the rate of subsequent (missed) colorectal cancer after 3 year follow-up. 1610 patients were randomized (1072 to colonoscopy and 538 to CTC), of whom 30 withdrew consent, leaving 1580 for analysis (colonoscopy: 1047; CTC: 533).

Overall, 160 (30.0%) of patients in the CTC arm had an additional colonic investigation compared with 86 (8.2%, $p < 0.0001$) in the colonoscopy arm. The majority of the referrals for an additional colonic test after CTC were to investigate a suspected cancer or large polyp (83 patients, 15.6%). Of these, 51 (61%) had CRC or a large polyp confirmed. A further 49 patients (9.2%) randomized to CTC were referred for an additional test to investigate smaller polyps (i.e. 9 mm or less)—only 3 (6.1% of the 49) of these ultimately had a large polyp, and none had cancer. Finally, 28 participants (5.3%) randomized to CTC were referred on as a result of diagnostic uncertainty; a single patient in this category had a ≥1 cm polyp, and, again, none had CRC. Therefore, of the 77 patients referred for a further test where CTC was either uncertain or showed small polyps only, none had cancer and only 4 (5.2%) had a polyp measuring ≥1 cm. The situation after colonoscopy was somewhat different; of the 86 patients requiring further testing, the majority (73; 7.0%) were referred because of clinical uncertainty after the (attempted) colonoscopy, primarily because of failure to intubate the caecum. Of these, three had CRC proven subsequently (4.1% CRC rate).

As noted above, a key secondary outcome of the study was the detection rate of CRC and large polyps (pooled). Here, no significant difference was detected

between the two tests; 119 (11.4%) for the 1047 patients randomized to colonoscopy versus 57 (10.7%) for the 533 randomised to CTC (p = 0.69). Detection rates of CRC were near-identical between the two tests; 58 (5.5%) in the colonoscopy arm and 30 (5.6%) in the CTC arm. After a minimum of 3 years follow-up via cancer registries, no additional CRC were reported in the colonoscopy group, and just 1 CRC was identified in the CTC arm (miss rate of 3.4%).

Taken together, the results of the SIGGAR CTC vs. colonoscopy trial showed that CTC had a higher referral rate for onward testing than colonoscopy, but that most of these referrals were to confirm the presence of a suspected polyp. Subsequent diagnosis of clinically-significant lesions (CRC or ≥1 cm polyps) was rare if index CTC found only small polyps or where the radiologist was uncertain. Missed cancer presenting within 3 years was rare for CTC (a single case in the CTC vs. colonoscopy trial and three cases in the CTC vs. barium enema trial, for an overall rate of 5.4% across both trials), and there was no significant difference in detection rates between CTC and colonoscopy. Although the study was not powered to detect a significant difference, this finding (and the point estimates of CRC and large polyp detection rates) does suggest that if there is a difference, it is likely to be small.

It may be somewhat surprising that only 51 of the 83 patients (61%) referred for onward colonic testing to investigate CRC or large polyp suspected at CTC were ultimately diagnosed with such a lesion; i.e. the positive predictive value (PPV) was moderate. This was primarily due to CTC false-positives, as size mismatching was rare (i.e. a polyp measured as over ≥1 cm at CTC, but found to be smaller at colonoscopy). The explanation for false-positives is likely twofold. Firstly, the study was conducted in an era when oral contrast faecal tagging was not yet mandatory. Oral contrast is used to "label" stool and liquid residue with dense iodine or barium-based compounds, which can then be distinguished from polyps by virtue of increased radiodensity at CTC. This prevents a common cause of false-positive diagnoses at CTC, namely residual stool, while simultaneously helping detect polyps that would otherwise be submerged and obscured (Fig. 5.2). Secondly, radiologists knew they were being studied, and that CTC was being evaluated. This may

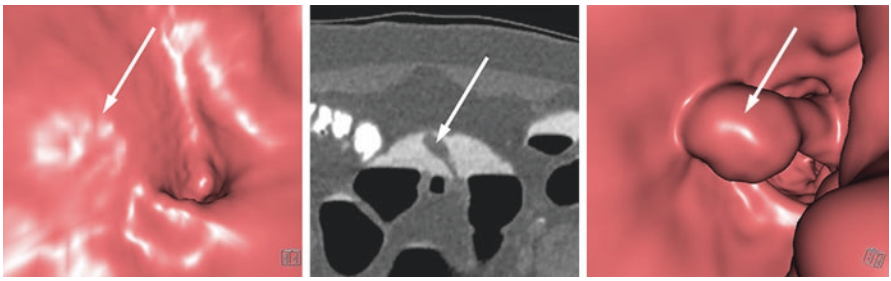

Fig. 5.2 Endoluminal image shows only a fluid level (*arrow* in *left panel*). The two dimensional image shows there is a pedunculated polyp (*arrow* in *middle panel*) which is submerged in oral contrast-tagged fluid. Tagged datasets can be interrogated endoluminally by using electronic stool subtraction ("electronic cleansing"), as in the *right panel* (*arrow* shows the head of the polyp), although these often cause digital artifacts that can impeded interpretation

have prompted them to "err on the side of caution" and to flag even equivocal findings as potentially positive, thereby reducing the chance of missed lesions (but potentially increasing false-positives). Irrespective of the reason, because the prevalence of CRC and large polyps was relatively low (11%), even high test sensitivity and specificity can result in moderate-to-low PPV, as was observed. For example, at a prevalence of 11%, and postulating a sensitivity and specificity both of 93%, PPV is only 62%, similar to that observed in the SIGGAR CTC vs. colonoscopy trial. Therefore, the findings were entirely consistent with existing literature and meta-analysis.

To summarize, the diagnostic accuracy of CTC for symptomatic patients is sufficiently high to advocate its use for the clinically-relevant target of CRC and ≥1 cm polyps. Meta-analysis of cohort studies, and now level 1 randomized trial data, confirm excellent sensitivity can be generalized across a wide range of sites. CTC detects important colorectal neoplasia at a similar rate to colonoscopy, although it is important to establish clear referral guidelines to avoid unnecessarily high rates of subsequent colonoscopy.

5.3.2 Extracolonic Detection

Abdominal symptoms are often vague and the organ of origin may be obscure, often beyond the colorectum. Therefore, the ability to interrogate structures outside the gastrointestinal tract at the same time as a high-quality examination of the colorectum may be advantageous for symptomatic patients. Furthermore, it may permit serendipitous discovery of unrelated (but clinically-important) pathology. Conversely, extracolonic detection may be a disadvantage if it precipitates further tests (with the associated costs, inconvenience and risks that these entail) for incidental findings that transpire to be of no clinical importance ultimately. CTC is readily able to depict extracolonic pathology in the torso from the lower chest to the bottom of the pelvis, since CT scanning of this region is a fundamental requirement of the technique (Fig. 5.3). Conversely, colonoscopy rarely detects extracolonic disease unless it spreads directly into the colon (for example, extrinsic involvement by serosal tumour, typically arising from the gynaecological tract; or by endometriosis) or involves it as part of a multiorgan process (e.g. vasculitis or amyloidosis), and rarely even then. In a symptomatic setting, where the colon is normal, the patient still has a problem that caused them to seek medical attention, and, at least in some cases, the next step would be to investigate the other abdominopelvic viscera, and CTC neatly combines these aspects in a single examination.

Although seemingly intuitive, this approach is not necessarily of clinical benefit. Not all symptoms or signs suggestive of CRC require extracolonic evaluation if colorectal investigation has been negative. Genuine bright red rectal bleeding is very rarely due to extracolonic pathology; iron-deficiency anaemia should initially provoke assessment of the upper gastrointestinal tract rather than the other abdominopelvic viscera; and so on. Although observational data provide some useful information confirming that CTC can and indeed does depict extracolonic pathology,

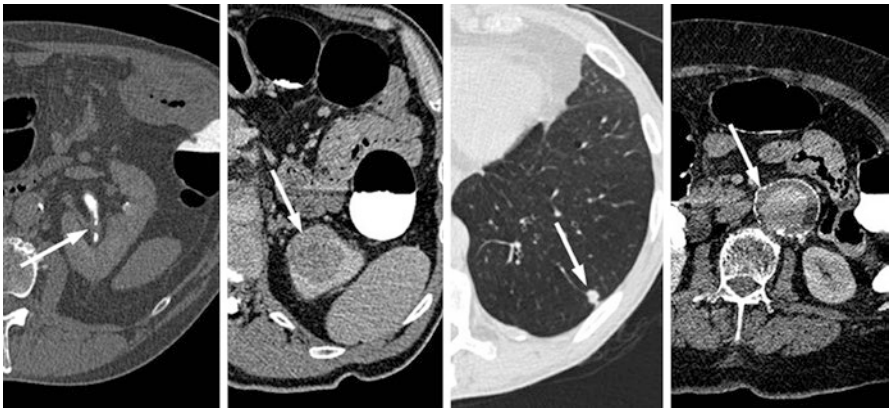

Fig. 5.3 Selected axial images from CTC examinations depicting incidental important extracolonic pathology; from *right* to *left*, left urothelial thickening (transitional cell carcinoma), a 3.5 cm left upper pole renal mass (renal cell carcinoma), a 1 cm left basal pulmonary nodule (non-small cell lung carcinoma) and a 4.8 cm infra-renal abdominal aortic aneurysm

including neoplasia [32], the clinical trajectory of such diagnoses in comparison to the default (colonoscopy) is largely unknown with such study designs, particularly for symptomatic patients. Randomized data from the paired SIGGAR trials [33] help address this issue, since this avoids the biases inherent to other designs.

Taken together, at least one previously unknown extracolonic finding was diagnosed by CTC in 959 (58.7%) of 1634 patients (excluding those patients with CRC). For the most part, extracolonic findings were unimportant, and did not merit further diagnostic investigation. However, 136 (8.3%) patients having CTC ultimately did have an extracolonic finding investigated (or treated); approximately half of these investigations were non-invasive imaging only, with the remaining half being an invasive procedure or surgery (with a roughly equal split between the two). Surgery was sometimes to combine treatment with diagnosis (for example, excision biopsy); the commonest surgical procedures were nephrectomy, oophorectomy (with or without hysterectomy) and aneurysm repair. Extracolonic diagnosis were judged to explain the patient's presenting symptoms in only 3–4% of patients overall. Ultimately, 25 patients (1.5%) having CTC were diagnosed with extracolonic malignancy. Conversely, no patients undergoing colonoscopy required evaluation for extracolonic pathology, and only 42 of 2223 patients (1.9%) having barium enema had one or more extracolonic finding reported. Five patients (0.2% of the total) ultimately received an extracolonic diagnosis, of which three were malignant. A further 14 patients having CTC had aortic aneurysms diagnosed, compared to none for barium enema or colonoscopy.

At first sight, therefore, this appears to be a clear benefit for CTC—1.5% of patients having CTC received a diagnosis of extracolonic malignancy, compared with 0.13% for barium enema and none for colonoscopy. However, this difference was short-lived; by 1 year, using cancer registry data, there was no difference in the diagnosis rates of extracolonic malignancy irrespective of the initial randomized

procedure. This is surprising—how are patients having barium enema or colonoscopy receiving a diagnosis of extracolonic malignancy? There are several possible explanations; firstly, not all malignancies can be diagnosed by CTC—early cross-sectional abdominopelvic imaging can only ever affect diagnosis rates for certain primary tumours (particularly renal, ovarian and pancreatic). Since the commonest malignancies are those of the lung, breast and prostate, none of which are readily diagnosed by CTC, it is implausible that CTC accelerates their diagnosis, diluting the effect of early CT. Indeed, in the SIGGAR trials, 58% of cancers diagnosed within 1 year of randomization to CTC had not been diagnosed by CTC itself; either because they were outside of the field of scanning or were occult (or overlooked) at that time. Secondly, and perhaps most pertinent, it is highly probable that patients randomized to barium enema or colonoscopy underwent cross-sectional imaging subsequently as the search for the cause of their symptoms continued. As noted above, even after normal colonic investigation, patients may still have symptoms, provoking their physician to investigate further. This is with good reason—incidence rates of extracolonic malignancy in the SIGGAR trials were double that of the general population (matched for age and sex)—abdominal symptoms are clearly an important flag and further investigation is warranted.

Therefore, although CTC permits rapid diagnosis of some extracolonic malignancies, there is no difference in the rate of such diagnoses by 1 year, when compared with colonoscopy. It is likely that this is partly because some cancers are not diagnosable by CTC, and partly because colonoscopy is often followed up by additional abdominopelvic cross-sectional imaging (namely CT). This has considerable implications for the cost-effectiveness of the two tests, and it is to this aspect that we turn next.

5.3.3 Cost Effectiveness

Most studies of the cost-effectiveness of CTC have described models rather than actual data observed in a trial. Furthermore, most models have compared the cost effectiveness of CTC versus alternatives in a screening context. The situation for symptomatic patients is different—prevalence of both colonic and extracolonic abnormality is much higher, implying that CTC is far more likely to be followed by confirmatory or therapeutic colonoscopy in a symptomatic setting versus screening. The goals of investigation are also rather different. Screening aims to (a) reduce CRC incidence (by prophylactic polypectomy, thereby interrupting the adenoma-carcinoma or serrated pathways to carcinogenesis) and (b) decrease CRC mortality by early detection, thereby increasing the likelihood of curative treatment. The cost-effectiveness of screening is largely contingent on improving these outcomes and may even be cost-saving because disease becomes less common, and is easier and cheaper to treat if it does occur. Conversely, investigation of symptomatic patients aims to explain symptoms and exclude serious causes. By the time CRC is symptomatic, it is on average more advanced than CRC detected by screening; and disease prevention is less effective because patients are typically older and have more

co-morbidity, meaning they may not have sufficient life expectancy to benefit from prophylactic polypectomy. Accordingly, symptomatic and screening scenarios require separate cost-effectiveness models.

Clearly, such models are highly dependent on the inputs, which include estimates for the frequency of tests (which depend on study setting and healthcare systems from which they are derived) and their unit costs. Unit costs of both CTC and colonoscopy vary widely internationally, as do the downstream trajectory and costs of future clinical activity (e.g. further tests, outpatient attendances, surgical procedures, hospitalization etc.). Most models have utilized estimates drawn from a wide range of primary research and so these estimates differ widely. However, it is well-recognised that the most accurate models use estimates drawn directly from observations obtained directly from a pragmatic clinical trial, since these best reflect what happens in "real life". Again, the most robust data to date are from the SIGGAR trials, which were pragmatic (i.e. designed to be representative of routine clinical practice), included a range of differing hospitals (21 in total), and health economic data were collected prospectively with the intention of a cost-effectiveness analysis. The results were surprising: Although the unit cost of CTC is considerably lower than that for colonoscopy (and subsequent testing was far higher for patients randomized to CTC), once downstream costs were considered, the difference between the two tests virtually disappears; total costs were £651 per patient for colonoscopy and £627 for CTC, a difference that was not statistically significant. Since referral rates for colonoscopy after CTC was a surprisingly high 30%, costs would move further in favor of CTC if referrals could be decreased. Additionally, for CTC specifically, roughly half of the overall per-patient costs were due to downstream costs (primarily, confirmatory colonoscopy or investigation of extracolonic findings). Since colonoscopy did not precipitate any immediate extracolonic investigation, downstream costs were much lower. However, the preceding section makes it clear that patients having colonoscopy are very likely having CT scanning or similar within 1 year of initial referral, representing costs that were not captured in the original trial data: costs beyond the immediate diagnostic episode were not captured. If true, this will increase the downstream costs of colonoscopy very considerably, and so reduce its cost-effectiveness relative to CTC.

Overall, the best available current data suggest that the cost-effectiveness of CTC and colonoscopy for investigation of symptomatic patients are similar. It is plausible, and indeed likely, that with modern CTC fecal tagging regimes (thereby reducing colonoscopy referrals without losing diagnostic sensitivity) and by factoring in more comprehensive assessment of downstream costs associated with colonoscopy, that CTC is the more cost-effective option.

5.3.4 Test Acceptability and Patient Preference

Patients may be anxious or confused about their colonic test; find it painful, embarrassing or undignified; and worry about its result. All of these facets are important aspects of how a test is perceived and used in clinical practice. Patient

experience of CTC and colonoscopy have been compared frequently in the research literature, with the majority of studies employing a tandem cohort design—patients undergo both tests, and are asked which they preferred. Both screening and symptomatic (or otherwise high-risk) patient cohorts have been studied, by both gastroenterologists and radiologists. Meta-analysis of such observational data, conducted in 2012 [34], showed no significant preference for either test when studies were conducted by gastroenterologists, but a significant preference for CTC in studies conducted by radiologists! The explanation for this difference is not absolutely clear but certainly, discrepant data suggests there is some bias. Investigators, consciously or otherwise, may have a vested interest in the success of one or other techniques.

Cohort studies have other limitations—since many patient preference studies of CTC were embedded into assessment of its diagnostic accuracy. Patients usually undergo CTC first, followed by same-day colonoscopy. This study design facilitates segmental unblinding as an enhanced reference standard (see prior sections), but may also bias patients' experience of the two tests—particularly for colonoscopy since it inevitably occurs second in such designs. Patients who have already experienced one relatively demanding and potentially uncomfortable test may find a second test, on the same day, less tolerable than if it had occurred in isolation. Perhaps most importantly, such studies do not capture the reality of how the two tests are employed—most patients do not have both CTC and colonoscopy—in real-life they have one test or the other. Accordingly, acceptability in day-to-day practice is rarely judged by direct comparison, but instead in the context of a patient's healthcare as a whole. Patients may consider CTC simply as a particular variety of "a scan", and therefore view it unfavorably because it is more invasive than they anticipate. Conversely, they may harbor preconceptions that colonoscopy is painful and embarrassing, and find the reality much less unpleasant than expected.

Randomization to one test or the other aims to eliminate bias, and perceptions of each test are measured in a setting most representative of normal daily practice. Using exactly this design, 547 patients recruited to the CTC vs. colonoscopy SIGGAR trial were asked to complete questionnaires regarding their randomized procedure. Patients undergoing colonoscopy were significantly less satisfied, more worried, and suffered more physical discomfort than those having CTC [35]. Conversely, patients having colonoscopy were more satisfied with how they received their results (i.e. often face-to-face on the same day, with histological results generally delivered in person). By 3 months, the overall psychologic consequences of the two tests were very similar, and both tests were viewed very positively.

In summary, meta-analysis of observational studies suggests small benefits in favor of CTC for overall test tolerability, which has since been confirmed by randomized data. However, colonoscopy has other benefits that only become apparent later, such as more satisfactory communication of the test result. Dogmatic assertions that one test provides superior patient experience over the other are unjustified—the most acceptable test will likely vary considerably between patients.

5.3.5 Safety

Both CTC and colonoscopy are extremely safe procedures; particularly in a screening setting. For symptomatic patients, risks are generally higher—the combination of increasing age, greater co-morbidities and higher prevalence of abnormality (entailing greater requirement for polypectomy) escalates the chance of perforation [36, 37]. Comparing relative risks of CTC and colonoscopy is complicated by the fact that the most sensitive means of detecting perforation is CT scanning; CTC therefore is able to depict minuscule quantities of extraluminal gas that are entirely asymptomatic and which would go unnoticed at colonoscopy. The frequency with which asymptomatic perforation occurs after colonoscopy is unknown because such patients are never investigated. The approximate rate of perforation at CTC has been estimated by systematic review and meta-analysis [38] at 1 in 2500 cases, falling to 1 in 5000 for asymptomatic screenees. As noted above, most of these perforations were incidental and asymptomatic—a need for surgery was estimated at 1 in 12,500. In comparison, systematic review of post-colonoscopy complications suggests perforation rates are similar, at around 1 in 2000 [39]. However, the risk of perforation at colonoscopy increases with age, even for relatively young patients; in one large Canadian series, perforation risk was greater for patients aged 60–74 years compared to those aged 50–59 [37], which may be more applicable to the older, frailer patients often being investigated for colorectal symptoms (as opposed to screening populations). In one large observational series, CTC was reserved for patients unfit for colonoscopy (or in whom it was incomplete) after a positive fecal occult blood test. Despite being employed in such a high-risk population, the overall adverse event rate for CTC was lower than for colonoscopy, and included fewer serious complications (e.g. perforation or major bleeding).

Although CTC itself is extremely safe, it must be considered in the context of the patient's trajectory as a whole—downstream complications from polypectomies precipitated by CTC are part of the same diagnostic episode and so must be factored into any consideration of its overall safety (unless the clinician choses to ignore findings from CTC). When doing this, randomized data from a Dutch screening trial [40] and the observational data from a national bowel cancer screening programme suggest that the two tests have very similar complication rates overall [41].

Radiation has been mentioned as a concern for CTC; however, for both screening and symptomatic patients, the doses involved carries very low risk, and the benefits of timely diagnosis likely outweigh these risks considerably. For example, as long ago as 2005 (when CTC doses were considerably greater than is now typical), the absolute risk of malignancy induction from a single CTC examination, for a 70 year old patient, was estimated to be approximately 0.07% [42]. Clearly, this is very considerably less than the background lifetime risk of malignancy, which is of the order of 33–50%. Furthermore, radiation-induced malignancy takes many years or even decades to develop (and therefore largely irrelevant at the age of 70), whereas risks of perforation or bleeding (whether from CTC or colonoscopy) are immediate. Patients with colorectal symptoms need rapid diagnosis, so a small, deferred risk becomes even less clinically important.

Overall, CTC and colonoscopy are both very safe techniques. The risk of colonic perforation is low with both tests, although CTC may be preferable in older, frailer patients with significant co-morbidities.

5.4 Infrastructure and Clinical Deployment

To be a viable option, a test must be widely available so that all patients are able to benefit. Fortunately for CTC, the underlying technology (i.e. CT scanning) is already disseminated widely. Virtually all acute hospitals already have a CT scanning suite, and the incremental costs of staff training and capital expenditure (e.g. to acquire CTC reporting software and a colonic gas insufflator) are relatively minor. Accordingly, CTC is widely available in most developed countries, and its availability has increased rapidly over the past decade. For example, in the United Kingdom (where several national surveys have occurred), availability of CTC has increased from little over a third of radiology departments offering the service in 2004 [43] to near-universal coverage by 2013 [44]. The number of CTC examinations in England has increased from 66,000 in 2013 to 86,000 in 2015 [45] (a 30% increase) and is forecast to reach 150,000 per year by 2020, thereby accounting for nearly 20% of all whole-colon testing.

Part of the reason for such successful deployment has been collaborative use of CTC and colonoscopy. Increasingly, services are configured with a single common referral pathway followed by early triage to appropriate diagnostic testing. Policies requiring a hospital visit and consultation ahead of testing are increasingly uncommon. Instead, patients follow a "straight-to-test" model, in which a rapid telephone triage assessment (often conducted by a trained nurse) establishes which test is most suitable. This scheme recognizes the fact that the vast majority of patients referred for exclusion of CRC ultimately require a whole-colon diagnostic test, meaning that little is gained from prior face-to-face outpatient assessment that cannot be done by telephone, and simply introduces delay unnecessarily. Individual services may configure their triage pathways according to local expertise and availability, but many will divert older, frailer patients for CTC and employ colonoscopy for younger patients who are otherwise fit. In all cases, close collaboration between gastroenterology, coloproctology and radiology services is critical to ensure that patients have rapid access to the most suitable test for them and their diagnostic target.

5.5 Summary and Conclusions

CTC has matured rapidly and disseminated widely, and is now a routine part of our diagnostic armamentarium. Diagnostic sensitivity for colorectal cancer and large polyps is similar to colonoscopy, and CTC is well-tolerated and extremely safe. Extracolonic detection, potentially problematic in screening practice, is likely beneficial for symptomatic patients because it improves the efficiency and cost-effectiveness of CTC when compared to tests that only image the colon. The choice

of test depends on the most relevant clinical target (i.e. established cancer or smaller polyps) and the presence of co-morbidities. Effective deployment of CTC requires close collaboration between radiologists, gastroenterologists and coloproctologists. Where this can be achieved, patients, clinicians and healthcare services can all benefit from the technique.

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Standardised Investigation and Referral of Alarm Symptoms for Colorectal Cancer

6

Jane Young and Michael Solomon

Key Points

- More timely diagnosis of symptomatic cancer could identify tumours at an earlier stage when treatment is more likely to be effective, thereby improving cancer outcomes
- Standardised referral pathways and 'fast track' programs aim to reduce the time interval between a patient's presentation to the health care system with a suspicious symptom and cancer diagnosis (the 'diagnostic interval')
- Suspicious colorectal symptoms are not strongly associated with colorectal cancer.
- Standardised referral pathways and 'fast track' programs are complex to evaluate; to date there is no clear evidence of effectiveness to reduce cancer burden in the population.

In recent years, several countries have introduced standardised investigation and referral pathways for people who present in primary care with symptoms that are suspicious for cancer. This chapter provides an overview of standardised approaches in terms of the underlying rationale, the international experience and the complexity that is inherent in evaluating the impact on cancer outcomes in the population.

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6.1 Impetus for Standardized Referral and Investigation Pathways

One of the major driving forces behind national cancer policies to standardise the assessment of people with suspicious symptoms for cancer is the marked disparities in cancer outcomes between countries that have been apparent over the past 20 years. In the mid-1990s, the EUROCARE Study was established within the European Union as a large, collaborative research project to analyse survival data obtained from cancer registries using standardized protocols. The purpose was to investigate trends in cancer survival over time as well as regional variations [1]. EUROCARE investigators reported marked differences in 5-year relative survival between countries for most cancers, including colorectal cancer. For example, during the period 1978–1985, for patients aged 60–69 who had colon cancer, the mean relative survival among the 21 populations studied was 40% but this varied from over 50% in Switzerland and the Netherlands, to 22% in Poland. Some countries, namely the United Kingdom (29–39%) and Denmark (42%), had considerably lower survival rates than comparable neighbours [2].

Subsequently there have been a number of iterations of EUROCARE to include more comprehensive and complete information about cancer cases across Europe, and several in-depth analyses have been undertaken to try to better understand these disparities. Differences in the stage of cancer at diagnosis have been consistently identified as one of the main drivers for the differences in outcome [3]. Over the ensuing years, further iterations of EUROCARE have demonstrated gradual improvements in 5-year relative survival across most regions and for most cancers, although the rate of improvement has been highly variable. For colorectal cancer, by 2007, the mean 5-year relative survival for Europe had improved to 57% for colon cancer and nearly 56% for rectal cancer, but with the UK and Ireland continuing to have among the lowest rates for colon cancer (51.8%) while ranking towards the middle (53.7%) for rectal cancer [4].

Extending the international comparisons beyond Europe, the International Cancer Benchmarking Partnership (ICBP) similarly reported substantial geographic differences in 1- and 5-year relative survival across a number of cancer types, with rates consistently higher in Canada, Australia and Sweden, intermediate in Norway and lowest in Denmark, the United Kingdom and Ireland [5].

These and other studies stimulated much debate about the possible reasons for the apparent disparities. While differences between countries in the proportion of patients diagnosed with more advanced disease is an important explanation and has been the focus of policy responses, other factors could include methodological differences between different cancer registries, regional differences in tumour biology, the comorbidity burden in the different populations, differences in access to treatment services and variations in the quality of cancer care provided [6].

Despite these international differences in cancer survival, in all populations there is a strong association between earlier stage of colorectal cancer at diagnosis and improved survival. In many regions, the 5-year relative survival for Stage 1 disease is over 90% compared with 40–60% for those with nodal involvement and around 10% or less for those with metastatic disease at diagnosis [7]. The self-evident

desirability of diagnosing colorectal cancer at an earlier stage has focused attention on the timeliness of cancer diagnostic pathways and whether there are any causes of delay that could be rectified so as to improve patient outcomes.

While there is consensus that earlier diagnosis of colorectal cancer is paramount, the impact of the timeliness of cancer diagnosis on cancer outcomes has been the subject of some debate [8, 9]. If the development, growth and spread of a tumour follows a linear path, then earlier diagnosis should identify earlier-stage cancers. However, tumour biology may be more complex. For example, it is possible that some tumours develop and spread as a result of previous irreversible genetic mutations that may not follow a predictable timeline [10]. Furthermore, even if the linear path were the predominant natural history, the timelines and likely duration of a 'window of opportunity' for curative treatment are far from clear. It is likely that efforts to improve the timeliness of diagnosis by days or weeks would be inconsequential if the time for development of the tumour took months or years.

For patients with symptoms that are suspicious for cancer, the pathway to diagnosis is complex, comprising a number of varying time intervals including the time from first becoming aware of a symptom to seeking medical advice and the time from first clinical presentation to definitive diagnostic testing. In order to standardize the measurement of diagnostic intervals between different studies of early cancer diagnosis, the Aarhus statement [11] has been developed by an international team to provide consistent definitions and methods. The 'diagnostic interval' has been defined as the time interval between the date of first presentation to the health care system to the date of cancer diagnosis.

A standardized approach to defining and measuring cancer diagnosis pathways is particularly important as much of the evidence informing the debate around early cancer diagnosis is derived from observational studies rather than randomised trials [10]. In a 2010 national survey of patients with cancer in England, 32% of those with colon cancer and 23% of those with rectal cancer had had three or more consultations with their general practitioner for cancer symptoms before they were referred to a hospital for investigation, suggesting there may be opportunities for earlier intervention in a substantial proportion of patients [12]. Other studies have investigated the time from presentation with suspicious symptoms to colorectal cancer diagnosis, with highly variable findings. For example, a Danish prospective, population-based study (n = 268) reported a median diagnostic interval of 40 days, but this varied between patients with alarm symptoms (37 days) and those with vague symptoms (74 days) [8]. In the UK, an analysis of 6557 general practice records for people with colorectal cancer found the mean diagnostic interval was 120 days (median 80 days), with significantly longer intervals for those with vague symptoms, older people and women [13].

There have been conflicting findings from studies investigating the relationship between the length of the diagnostic interval and two important outcomes, namely stage at diagnosis (often used as a proxy for cancer survival) and survival from colorectal cancer. In two systematic reviews, Ramos and colleagues found no association between the diagnostic interval and stage at diagnosis or cancer survival, although there were some suggestions of differences between colon and rectal cancer for cancer stage [14, 15]. However a more recent systematic review found that

for colorectal cancer, the weight of evidence tended towards earlier stage at diagnosis and improved survival for shorter diagnostic and therapeutic intervals [16].

Furthermore, the relationship between the diagnostic interval and survival for people with symptomatic cancer may not be unidirectional or linear. Some studies have demonstrated that for people with highly suspicious or 'alarm' symptoms, a shorter diagnostic interval paradoxically is associated with poorer survival whereas the reverse is apparent for those with vaguer symptoms. This could be explained the different presentation and behaviour of aggressive and more insidious tumours. People with highly aggressive disease could develop more 'high risk' or severe symptoms, thereby triggering faster diagnosis but this would have little impact on subsequent survival due to the underlying biology of the cancer [10].

Indirect evidence of the relationship between more timely cancer diagnosis and improved outcomes at a regional level is also apparent in an ecological analysis conducted as part of the International Cancer Benchmarking Partnership. Case scenarios were used to investigate general practitioners' readiness to refer a patient with suspicious symptoms for definitive diagnostic investigation. This study found a positive correlation between earlier referral and 1-year relative survival for the 11 participating regions in Scandinavia, Australia, Canada and the United Kingdom [17].

For it to be possible to reduce the diagnostic interval for symptomatic colorectal cancer, there must be suspicious symptoms or other clinical 'alarm' features that are good predictors of cancer and therefore flag that a patient is in a higher risk category. Common 'alarm' features for colorectal cancer include rectal bleeding, a change in bowel habit, iron deficiency anaemia and abdominal or pelvic mass. However, it is well recognised that several of these factors are not unique to colorectal cancer. General practitioners have the difficult task of urgently triaging patients who have serious disease whilst not over-investigating those with benign causes, often on the basis of vague symptoms. Furthermore, in many health care systems, general practitioners act as the gatekeepers to diagnostic services and specialist care, thereby taking responsibility for appropriate and efficient use of limited health resources.

Unfortunately, most studies of specific symptoms have found relatively poor associations with colorectal cancer. One systematic review of 15 primary studies concluded that that most alarm features had poor sensitivity but moderate to good specificity [18, 19]. The development of more sophisticated risk stratification models based on a combination of symptoms, clinical signs and other factors, such as patients' age and sex are likely to improve sensitivity and specificity and thereby better identify individuals who should be referred urgently.

6.2 Introduction of Standardised Approaches to Investigation of Suspicious Symptoms

In the early 2000s, several countries, notably the UK and Denmark, responded to the emerging international data on marked disparities in cancer outcome to introduce policies to accelerate and streamline patient pathways for cancer diagnosis and treatment. While there are differences in approach in different countries, consistent

components include identifying an agreed set of 'alarm' symptoms and the development of policy or guidelines about the nature and timeliness of subsequent referral for further investigation.

6.2.1 The Danish Approach

In response to growing concern about long waiting times, in 2001 the Danish government passed legislation mandating that the waiting period between a diagnosis of cancer and commencement of treatment was to be no longer than 2 weeks [20]. However, this did not address waiting times in the pathway to diagnosis. In 2005, a national cancer plan identified the development and introduction of standardised cancer patient pathways as a key strategy to reduce delays in the diagnosis as well as the treatment of cancer [21].

By 2007, it was apparent that pathways to diagnosis were still highly variable and often prolonged, the Danish Cancer Society argued that cancer should be treated as an acute disease. A new approach was developed in which the diagnostic and treatment intervals were defined on the basis of clinical appropriateness for an acute disease, and targets were set that patients with suspected cancer should be seen in secondary care within 2 days following GP referral [20]. A highly collaborative approach was taken to develop the clinical pathways, with input from policy makers, health administrators and politicians as well as health professionals. The rationale for this broad collaboration was to ensure that the pathways would actually be implemented into routine clinical practice [22]. Waiting times were to be measured and reported by the National Board of Health and there was a commitment to provide resources in equipment and staff and to increase general practitioners' access to diagnostic services.

The standardised cancer patient pathways described the clinical pathway that most patients who were suspected of having cancer would be expected to follow, and included referral pathways, medical procedures and specific information that should be provided to patients to help them navigate and understand their care. The clinical components of the pathway were based on current evidence-based clinical practice guidelines, or expert opinion for aspects of care where evidence was lacking. The multidisciplinary working groups identified relevant timelines for progression through the pathways from the perspective of an 'ideal' patient in an 'ideal' health system, ie not taking into account the need to treat comorbid disease or delays due to lack of resources [21]. Patients who should be fast-tracked on the basis of suspicious symptoms were identified for each of the common cancers. Organisational aspects of the new strategy included the quarantining of pre-booked time slots for fast track outpatient assessment and diagnostic testing. Thus the cancer patient pathways were operationalized within a 'package solution' or 'national integrated cancer pathway'. The pathways were first implemented in 2007 and 2008 and were supported by continuing medical education about cancer for general practitioners [20, 22].

In the absence of a randomised trial, the evaluation of the Danish standardised cancer patient pathways has relied on observational before-after studies or

non-randomised comparisons. Early assessment of the median waiting time for people with colorectal cancer decreased from 36 to 29 days after the introduction of the standardised pathways [22]. However, the study design is unable to distinguish the effects of the pathways from other concomitant changes, for example changes in the community in awareness of, or health seeking behaviour for, cancer symptoms.

More recently, a population-based study that compared tumour stage in patients diagnosed before and after the implementation of the Danish cancer patient pathways found no significant difference in cancer stage at diagnosis between the two time periods across a range of cancers, including colorectal cancer [23]. Furthermore, after the implementation of the pathways, the proportion of patients who were diagnosed with early stage disease was actually lower in the pathway patients than in the non-pathway patients. For colorectal cancer, 31.7% of pathway patients and 32.1% of non-pathway patients had local disease—a small and not significantly significant difference but consistent with the trend seen in other cancer types. A plausible explanation is that general practitioners were more likely to use the urgent referral pathway for patients presenting with severe or highly suspicious symptoms and these patients were more likely to have higher-stage cancer at diagnosis.

6.2.2 The UK Approach

In 2000, the UK national cancer plan for the National Health Service (NHS) introduced mandatory targets for referral and management of patients with cancer, including colorectal cancer [24]. With respect to timeliness of diagnosis and treatment for cancer, the stated goal of this plan was to ensure that no patient waited longer than 1 month from urgent referral for suspected cancer to the commencement of treatment unless there were good clinical reasons or patient preferences for this. With substantial additional resource of 570 million pounds sterling per year, the ambition was to achieve the goal within 8 years.

One of the main strategies to reduce waiting times was to impose a maximum wait of 2 weeks for an urgent hospital outpatient appointment for people with suspected cancer, the so-called ‘2-week wait rule’. The National Institute for Health and Care Excellence (NICE) has developed guidance about which patients are eligible for urgent referral, based on symptoms and clinical presentation. Since 2000, this guidance has become increasingly more focused on quantitative risk stratification and has considered the positive predictive value (PPV) of specific symptoms. The PPV is the probability that a patient with the specific symptom or clinical feature of interest will actually have cancer. The higher the PPV threshold that is set for urgent referral, the more likely it becomes that true cases could be overlooked. However, the corollary is that the lower the PPV threshold, the more people will be urgently referred, potentially overwhelming the health care system. The NICE guidance on urgent referral for cancer was most recently updated in 2015 with an explicit 3% positive predictive value threshold for urgent assessment within the 2-week referral pathway, substantially lower than the previous threshold of 5% [25].

Early evaluations of this strategy suggested high compliance with the target with 99% of urgent referrals being seen within 2 weeks in 2003, falling slightly to 95.5% by 2010/2011 [26]. However, there appears to be considerable variation between practices in which patients were considered urgent referrals. Among all cancer patients, only about a quarter were diagnosed via a fast track referral process in 2007 [26], so the impact of this pathway on access to care for other patients remains paramount.

Some evaluations of the 2-week referral pathway have been based on highly-selected samples of patients attending specific hospitals. For example, one hospital-based study of colorectal cancer patients in Bristol found that, compared with fast tracked patients, non-fast tracked patients waited a median of 38 days longer to be seen by a specialist and a median of 15 days longer to start cancer treatment, but 5-year overall survival and cancer-specific survival were no different between these groups [27]. Similarly, among patients presenting to a hospital in Cambridge, the median wait for fast track referrals (n = 462) was 12 days, half as long as for patients diagnosed through other routes during the same period (n = 131) [28]. However, only 64 (11.8%) of the fast tracked patients had colorectal cancer. More detailed analysis found that about a quarter of the fast tracked patients did not actually meet the fast track criteria, consistent with other studies that have reported high proportions of inappropriate fast track referrals [28–30].

A systematic review conducted in 2006 found that the colorectal cancer detection rate among fast track referred patients was only 10.3%, based on data from 12 studies and there was no evidence that these patients were identified at an earlier or more treatable stage of their disease [31].

6.3 Complexity in Assessing the Effectiveness of Standardised and Expedited Approaches

Theoretically, the best way to assess whether standardised and urgent referral pathways improve cancer survival would be to conduct a randomised trial. In the absence of such robust evidence, it is challenging to determine whether standardised cancer pathways for urgent referrals are effective to improve patient survival.

Lead time bias is a major concern in non-randomised studies of cancer survival. Survival time will be increased by diagnosing cancer earlier as well as by delaying death. Therefore, even if there is no change in the course of disease, diagnosing cancer earlier will improve survival. There are enormous challenges in defining comparable ‘starting points’ for the assessment of survival between patients who have colorectal cancer diagnosed through urgent referral, standard, emergency, screening or other routes. Population-based age-standardised cancer mortality rates are not affected by this bias, but these data reflect outcomes for patients who were diagnosed a varying number of years previously and so are less useful to assess the effectiveness of policy changes or interventions, particularly in the short-term.

Another major bias that makes it difficult to interpret non-randomised comparisons is confounding by the severity or aggressiveness of the cancer, as mentioned

earlier. Patients who are referred for fast track investigation are likely to be systematically different from those who are not deemed by general practitioners to need urgent referral. It is likely that the patients who already have more advanced or aggressive disease, and so perhaps have the least to gain from early referral, are selectively fast-tracked for investigation and specialist assessment.

Another consideration is whether the commonly used measures, namely lengths of the diagnostic and treatment intervals, cancer stage at diagnosis and cancer survival are the most appropriate metrics to evaluate the effectiveness of standardised approaches to the investigation and referral of patients with suspected cancer. The suspicion of cancer is a cause of much anxiety for patients and their families. Reducing the diagnostic interval minimises the length of time that people must live with uncertainty, and likely reduces distress particularly among the majority who will turn out not to have cancer.

In addition to setting targets for the timeliness of events along a patient pathway, the standardised approaches also provide clear guidance about the nature of investigations, referrals and treatments that patients should expect. The benefits of this in terms of improving patients' knowledge and confidence in the health care system, ability to navigate health services and their satisfaction with the care they have received warrant further investigation. Patient reported outcomes and experience have not, to date, been a major focus of the evaluation of standardised cancer pathways. Other important issues that should be assessed include any unintended negative consequences for patients, including those who meet the urgent referral criteria as well as those who are diagnosed through other routes, as well as the cost and resource consequences and cost effectiveness. A broad approach to evaluation will be needed to investigate the true impact in a population of standardised pathways for the diagnosis of colorectal cancer.

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The Psychological Implications of Diagnostic Delay in Colorectal Cancer Patients

7

Anne Miles

Key Points

- A third of patients undergoing investigations for suspected cancer have clinically significant levels of distress, and both distress and quality of life during the diagnostic phase are similar to people with a confirmed diagnosis of cancer.
- Distress and quality of life improve among people found to have benign disease and a speedier diagnosis will reduce the duration of adverse effects in this patient group. However, there is insufficient evidence at present about whether cancer patients may also benefit from a more rapid diagnosis.
- Patients who experience diagnostic delay have a higher number of consultations and medical tests and are more likely to experience substandard quality care, but the effect of these experiences on psychological outcomes among both patients and family members remains underexplored.
- Population subgroups that may be particularly vulnerable to distress during the diagnostic phase include women, younger adults, and people with lower social support, low optimism, and high intolerance of uncertainty.
- Further research is needed into the effect of rapid diagnostic pathways on psychological outcomes, but research also needs to explore the role of particular experiences during the diagnostic phase, such as number of consultations and diagnostic errors, and not just time to diagnosis, on patient wellbeing.

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7.1 Introduction

Cancer patients rate rapid diagnosis as one of the most important aspects of their hospital-based care [1], but while a great deal of research has examined the prognostic implications of diagnostic delay, very little has examined its psychological consequences. Diagnostic delay, which can include patient delay in seeking help as well as time from first contact with a healthcare professional until a diagnosis is established, can have both short and long-term effects on a patient's psychological wellbeing, quality of life, and satisfaction with care, as a result of what happens during the pre-diagnostic period, and the consequences any delay may have on the patient's prognosis and treatment.

7.2 The Pre-diagnostic Phase

During the pre-diagnostic phase, people with symptoms suspicious of cancer face the threat of serious illness while having to undergo invasive medical tests, which may be uncomfortable or frightening, and attend numerous appointments. Some may also experience substandard care that directly contributes to a delay in their diagnosis.

7.2.1 Distress and Quality of Life

Receiving the diagnosis has been rated as the most stressful aspect of having cancer among breast cancer patients, but periods of waiting were also high on the list [2]. In a review of research into distress in the diagnostic phase, Brocken et al. [3] found between 33% and 60% of patients undergoing investigations for cancer (breast, malignant melanoma, ovarian, prostate, and lung) reported clinical-levels of anxiety prior to diagnosis (i.e. high enough to be classified as an anxiety disorder using psychiatric assessment tools). While most studies found anxiety reduced in people with benign outcomes, anxiety levels were sustained or increased in people diagnosed with cancer. Although a couple of studies showed a *reduction* in anxiety following a cancer diagnosis (in patients with melanoma [4] and ovarian cancer [5]), both samples were small, and in the latter study baseline anxiety was measured prior to surgery probably inflating baseline scores.

Suspected cancer patients also reported poorer quality of life than members of the general population, with some studies showing poorer quality of life in the pre-diagnostic phase compared with post-diagnosis, while other studies showed no change post-diagnosis, regardless of whether the outcome was benign or malignant [3]. On the basis of their review, Brocken et al. [3] conclude that patients with suspected cancer have similar or worse levels of anxiety and quality of life than patients with a confirmed diagnosis of cancer.

The majority of the studies included in Brocken et al.'s review were on patients with suspected breast cancer, with none on people under investigation for colorectal

cancer. Similar rates of post-diagnostic distress have been reported in breast and colon cancer patients (32.8% for breast and 31.6% for colon) [6], suggesting similar pre-diagnostic rates might also be expected. A more recent study in Denmark of consecutively recruited patients onto a cancer patient pathway (which would have included people with suspected colorectal cancer) reported similar rates of distress as Brocken et al. [3], with one third of patients reporting clinical levels of anxiety during the pre-diagnostic phase. Consistent with previous findings, they also observed reductions in anxiety and improvements in quality of life and symptomatology among those receiving a non-cancer diagnosis, with no change in these variables among patients diagnosed with cancer [7].

A study conducted in Canada on patients with a confirmed diagnosis of colorectal cancer attending clinics for follow-up care, asked patients about their specific needs during the pre-diagnostic phase. The study found that patients reported high anxiety levels during this time, and the most frequently identified needs were informational and emotional, reported by 31.6% and 20.3% respectively [8]. Although the majority (84%) said their needs had been met, a high proportion of patients (77.9%) also reported that they had not been directed to any sources of help in coping with their anxiety during the pre-diagnostic phase, suggesting patients require more emotional support during this time. In addition patients were most likely to report needing more information after receiving test results.

7.2.2 Rapid Diagnosis and Feedback

Research has also examined whether speeding up the diagnostic process improves psychological outcomes. Prompt feedback of test results is clearly important to patients. Patients with symptoms of suspected colorectal cancer report higher levels of satisfaction with the way test results are conveyed when results are given following colonoscopy, where results are often given immediately and face to face, rather than CT colonography, where there is a delay due to the need for radiological reporting of results [9]. However, the majority of this sample did not have cancer and rapid feedback may be valued differently by people with benign versus malignant outcomes. Among people ultimately diagnosed with cancer, a more rapid diagnosis means a speedier transition from healthy person to patient. As a result, people have less time to prepare for bad news which may adversely affect their psychological wellbeing. On the other hand, it reduces the period of uncertainty which may be beneficial, particularly for people who find uncertainty difficult to manage.

There is limited evidence that rapid diagnostic pathways, e.g. one or two-stop shops, can improve psychological outcomes. In their review, Brocken et al. [3] found rapid pathways reduced the period of distress among those found to have benign disease, with no evidence of benefit, or harm among those diagnosed with cancer [3]. Although one study, comparing women diagnosed with breast cancer at a one-stop shop vs. a two-stop system, found higher levels of depression among women attending the one-stop shop 8 weeks later, differences were small [10] and not considered clinically significant [3]. In addition, depression was measured from

the date of the biopsy, and not from the date at which women were told of their diagnosis, so women in the one-stop shop had known about their diagnosis for 1 week longer which might account for the differences between the two groups. A more recent study, albeit among lung cancer patients, did find evidence of short-term benefit, with lower distress associated with a more rapid diagnosis among both patients with benign and malignant outcomes, although this benefit was no longer apparent 3 months later [11].

The review by Brocken et al. [3] excluded studies on cancer screening, but research in this area suggests that rapid diagnosis is beneficial to patients. Qualitative research into the experience of having colorectal cancer (CRC) detected at flexible sigmoidoscopy screening found that many people described the diagnosis as relatively untraumatic, due to the absence of a period of symptoms and associated worry about a potential cancer diagnosis, and the need for simpler treatment which often comprised surgery alone [12]. In addition, a cross-sectional study on colorectal cancer survivors in Scotland, between 3.5 and 12 years post-diagnosis, showed people with screen-detected disease reported lower levels of perceived diagnostic delay and better quality of life than people diagnosed symptomatically (either following a negative screening result or because screening was not offered), even when demographic, and prognostic factors were controlled for, although actual delay was not measured [13]. Although people with interval cancers are more likely to have right-sided disease [14], there were no differences in perceived diagnostic delay or quality of life among people with interval cancers compared with people whose cancers had been diagnosed in a geographical area not offering screening at that time. The same data showed that higher levels of perceived diagnostic delay were associated with greater cancer-related distress and more suspected cases of post-traumatic stress disorder (PTSD). Part of the relationship between perceived delay and cancer-related distress was explained by quality of life, but not by disease stage at diagnosis, or treatment received [15]. The exact reasons for the relationship between perceived diagnostic delay and cancer-related distress were unclear, and could be due to the traumatic experiences associated with delay. When it comes to experiencing cancer as a traumatic stressor, criteria for PTSD (in DSM-5) specify that "Medical incidents that qualify as traumatic events involve sudden, catastrophic events". The need for emergency admission to hospital, or the discovery that their cancer has been misdiagnosed by their primary healthcare provider or missed by previous investigations, could contribute to the development of distress or trauma.

7.2.3 Consultations, Investigations and Diagnostic Delay

Diagnostic delay does not just mean a longer period of waiting for a diagnosis, it is also associated with a greater number of medical consultations and investigations. A UK-based study showed diagnostic delay was associated with a higher number of consultations with a primary care provider prior to referral to a specialist, with 20% of patients ultimately diagnosed with colorectal cancer having three or more visits

before being referred [16]. The main predictor of number of consultations was cancer type, attributed to the non-specific nature of symptoms associated with some cancers more than others, making them harder to diagnose, with colorectal cancer classified as being of intermediate diagnostic difficulty [17].

People who experience a delay in their diagnosis also undergo a greater number of diagnostic tests than those who are dealt with promptly [16]. Undergoing additional tests may contribute to patients' psychological burden, over and above extending the waiting time for a diagnosis. Concern over test results has been cited as the most common cause of anxiety in patients waiting for diagnostic procedures in an oncology clinic [18], but undergoing procedures involves a number of additional challenges. Diagnostic tests and further investigations for colorectal cancer such as colonoscopy, computed tomographic (CT) colonography and MRI can be uncomfortable as well as anxiety-inducing (e.g. [9, 19]). Patients may need to undergo bowel preparations; injections, some involving radioactive ligand (e.g. PET-CT) which may promote fears about radiation risk; as well as scans, such as MRI which are noisy and require full body immersion into a relatively narrow tube, causing anxiety and claustrophobia in a substantial proportion of patients [19, 20].

Diagnostic delay can also impact patient satisfaction with their care, particularly if the patient believes the delay was due to lack of action by a physician or felt the wait for tests or referrals had been too long [21]. A greater number of visits prior to diagnosis is associated with lower patient satisfaction with care [21]. In addition, patients who reported that the time between seeking help and confirmation of a cancer diagnosis was "about right" vs. "a bit long" were more likely to report that they were satisfied with the communication around cancer diagnosis, prognosis and treatment (75% vs. 41% reporting high-mid levels of satisfaction) [22]. In a study on patients with anal cancer, Chui et al. found that any delay was associated with reduced satisfaction but this was much greater if the patients believed the cause of that delay was the fault of the medical profession rather than the patient failing to seeking medical help promptly [21].

Although there are a number of factors influencing diagnostic delay, in some cases patients may have good reason to believe any delay in diagnosis is the result of substandard medical care. Initial misdiagnosis (treating the symptoms, or attributing symptoms to a disease other than colorectal cancer), failure to examine the patient, and negative or false negative results have all been associated with increased diagnostic delay [23]. A retrospective review of colorectal cancer miss rate in a district general hospital in the UK found an 8% false negative rate across three investigative modalities (double contrast barium enema, colonoscopy and computed tomographic colonography) with lowest rates for colonoscopy and highest for barium enema [24]. The psychological consequences of misdiagnoses and false negatives are under-explored. One study on the consequences of a false negative in FOBt colorectal cancer screening in Scotland found no evidence of poorer psychological outcomes following a 'missed' cancer compared to people who had been diagnosed in the absence of an invitation to undergo screening [10], with no significant differences between the two groups on measures of perceived diagnostic delay, quality of

life or depression, however the study was conducted during the pilot phase of FOBt screening and patient expectations about test performance may have been lower than for an established screening service.

Research into GP and patient perspectives on so-called "quality deviations" (QD) (defined as an event "that should not have happened and that you don't want to happen again"), showed GPs in Denmark rated one third of cancer patients as having a QD, with longer diagnostic delay associated with GP report of a QD [25]. Although both GPs and patients reported a similar proportion of QDs, they showed poor levels of agreement about what counted as a deviation. Reports of a QD by GPs were more strongly associated with diagnostic delay (time elapsed) than patient reports of QD [26], suggesting that for patients, quality of care is more strongly associated with factors other than length of time to diagnosis.

7.2.3.1 Emergency Presentation

Emergency presentation of colorectal cancer is associated with more advanced disease at diagnosis and lower survival rates [27], and a quarter of colorectal cancers in England are diagnosed via this route [28]. Even after adjusting for disease stage, emergency presentation is associated with higher mortality and shorter disease-free survival, suggesting such patients have more aggressive tumour biology (e.g. extramural vascular invasion) [29]. Although conclusive data supporting the role of diagnostic delay in emergency presentations is lacking [28], rates of emergency presentation vary across primary health care providers suggesting some variability is attributable to patient and provider factors [27]. Patients who present via an emergency route in England are significantly less positive about their care than those who present through a planned cancer pathway [30]. This is perhaps unsurprising given that such patients are also more likely to present with pain and obstruction [28] have longer surgeries, longer admissions and more readmissions [29]. However the psychological consequences of emergency presentation among cancer patients has not been explored.

7.2.3.2 Vulnerability and Resilience

Few studies have examined predictors of emotional wellbeing during the pre-diagnostic phase. However studies on predictors of anxiety or depression after a cancer diagnosis show certain sectors of the population are more vulnerable, for example, people with a family or personal history of psychiatric disorder, people with low socio-economic status, women, and those of a younger age [7, 31–33]. Intolerance of uncertainty, defined as a tendency to react negatively to uncertain situations [34], is associated with higher levels of negative affect such as fear and worry in the short-term and is also a risk factor for the development of pathological anxiety [35]. In addition it has been shown to correlate with higher anxiety among men with low risk prostate cancer undergoing active surveillance of their condition [36], as well as higher depression and poorer emotional wellbeing among lung cancer patients [37]. This research suggests that diagnostic delay, and the associated period of uncertainty, may be particularly detrimental to people who find

uncertainty difficult to manage and further research should be directed at understanding subgroups who may be particularly vulnerable to distress in the pre-diagnostic phase.

Research on resilience, defined as "healthy adaptation in the context of adversity", has also been limited to the study of how people cope with cancer [38–40] rather than coping in the pre-diagnostic phase, although diagnostic workup of symptoms has been identified as one of the many events people with cancer have to deal with [41]. In their model of resilience in cancer, Deshields et al. [41] propose that personal attributes and environmental circumstances influence how individuals respond initially along the distress-resilience continuum, but that this initial response can be "recalibrated", either as a result of the individual's coping responses or through psychological interventions. Factors such as older age, male gender [42], optimism and social support [43] are associated with greater resilience. While the absence of other stressors is also beneficial [44], there is evidence for "stress-induced resilience": a study on breast cancer survivors showed moderate acute stress was associated with greater resilience, while either low or high levels of acute stress prior to a cancer diagnosis was associated with lower resilience [45]. Interventions that can be used to foster resilience include promoting emotional expression, reminding people of their previous successful coping efforts in the face of difficulties, and cognitive-behavioural therapy focused on reducing worry [41] (also see [43]).

7.2.4 Summary

Research to date shows a substantial proportion of people undergoing investigations for cancer have higher levels of distress and poorer quality of life than the general population, with rates similar to people with a confirmed diagnosis of cancer. Patients who experience diagnostic delay have a higher number of consultations and medical tests and are more likely to experience substandard quality care. Further research is needed into patient experiences during the pre-diagnostic phase that may affect psychological wellbeing and quality of life, including what procedures and diagnostic routes people take, as well as their perceptions of what counts as efficient and good quality care, and identify and provide support for areas of unmet need. More research needs to be done to identify vulnerable subgroups of the population and offer support where necessary. For example, cognitive-behavioural treatments can help reduce intolerance of uncertainty, through techniques aimed at getting people to recognise, accept and deal with uncertainty [46] and greater psychological support for people undergoing investigations for cancer could help patients cope better with the difficulties they face during the pre-diagnostic phase. In addition, although research has examined the psychological impact of cancer on family caregivers across the cancer trajectory, this has typically focused on the point of diagnosis onwards [47], with little work examining the impact of the diagnostic phase on family members. Although a recent study has examined patient and carer perspectives on a lung cancer

Table 7.1 Summary of the psychological implications of different aspects of diagnostic delay

Prediagnostic variables	Psychological effect
Length of time	Prolongs period of anxiety and poor quality of life among both people found to have cancer and those with benign disease.
Increased number of consultations and diagnostic tests	May increase anxiety. Reduces patient satisfaction with care.
Malpractice	Little research on psychological impact.
More advanced disease at diagnosis	Associated with increased anxiety, depression, greater likelihood of post-traumatic stress disorder and poorer quality of life.
Premorbid factors	Little research on factors specifically associated with poorer psychological outcomes in the diagnostic phase.
Emergency presentation	Reduces patient satisfaction with care but little research on psychological impact.
Information	Limited evidence suggests patients need additional information particularly after they have received test results.

diagnosis following emergency admission [48], the research focussed on lay understanding of symptoms and help-seeking behaviours before hospital admission, rather than the psychological impact of a delayed diagnosis.

A summary of prediagnostic variables, and psychological effects is in Table 7.1.

7.3 The Post-diagnostic Phase

Colorectal cancer survivorship can be affected by emotional difficulties; bowel, urinary and sexual problems; negative body image; and fear of recurrence, with such problems impacting on the patient's social life and ability to work [49]. Such problems can be exacerbated by later disease stage at diagnosis or the receipt of adjuvant therapies. Detection of colorectal cancer via screening in asymptomatic patients picks up cancers at an earlier stage and leads to a reduction in mortality [50] showing that earlier detection can improve prognosis. However the relationship between diagnostic delay and stage at diagnosis in patients with symptomatic colorectal cancer is complex, with both short and long delay associated with higher mortality [51]. While some studies have found no association between delay and mortality, the possibility that longer diagnostic delay did not impact on mortality could not be excluded (e.g. [52]).

7.3.1 Stage, Treatment and Emotional Difficulties

Emotional difficulties following a cancer diagnosis include depression, anxiety, and stress-related responses including post-traumatic stress disorder (PTSD). Such difficulties are often comorbid among cancer survivors [53]. A recent meta-analysis of

the prevalence of anxiety and depression among people 2 or more years post-diagnosis found anxiety rates of 17.9% (95% CIs: 12.8–23.0) and depression rates of 11.6% (95% CIs: 7.7–16.2) [54]. A large study of patients with colorectal cancer attending cancer clinics in Scotland found marginally lower rates of depression at 7% (95% CI: 6.1–8), with higher rates among women, younger patients, and people with higher levels of deprivation [32]. Rates of anxiety were not examined. Although symptoms of full-PTSD are typically less frequent than those of depression and anxiety, they are found in a significant minority of cancer survivors (e.g. 6.4% point prevalence, with a lifetime risk of 12.6% [55]).

Rates of emotional disorders such as depression and post-traumatic stress disorder are higher among cancer survivors than people with no history of the disease [56, 57], and patients with more advanced disease are more likely to report high distress [58] and the presence of PTSD [55, 59] than patients with earlier disease stage at diagnosis. Although distress tends to be higher shortly after patients learn the diagnosis than at later stages in their disease trajectory [22, 60], patients display different emotional trajectories over time. A longitudinal, prospective study in Australia examined distress in colorectal cancer patients from 5 months to 5 years post-diagnosis. The authors used the Brief Symptom Inventory-18 (a measure combining anxiety, depression and somatisation) and identified four different patterns of distress over time: consistently low distress (experienced by 19.4% of the sample), medium level distress (going from case to non-case, experienced by 29.4%), medium increase distress (going from non-case to case, experienced by 38.5%), and high distress (remaining at case level across time, experienced by 12.5%) [58]. The odds of being in a distress trajectory other than the consistently low one was higher for patients with later stage disease—stages III or IV compared with stages 0, I or II (controlling for age, gender, educational level and social support). Although treatment type was a significant predictor of distress group in unadjusted analysis, it was not significant when other variables were added into the model. Examination of the different subscales found disease stage also predicted poorer trajectories of anxiety and somatisation although not depression.

Patients with more advanced disease are more likely to receive chemotherapy and radiotherapy, and higher anxiety, depression and symptoms of traumatic stress have been observed in patients who have chemotherapy or radiotherapy in addition to surgery compared with those having surgery alone [61], although this study did not examine the effect of disease stage independently of treatment received.

Qualitative research on the concerns of Stage II and stage III colorectal cancer survivors who had completed active treatment, found higher distress was associated with treatment-related toxicities such as peripheral neuropathy (numbness/tingling in the hands and feet), a side-effect of the chemotherapy drug oxaliplatin, and major challenges in daily activities particularly around caring for their colostomy [62]. Oxaliplatin causes neuropathy in the majority of patients during the therapy itself, with 12% of patients experiencing persistent neuropathy 4 years after treatment [63]. Severe peripheral neuropathy during treatment has been associated with higher rates of depression and anxiety, and poorer sleep quality [64], impacting on people's ability to carry out everyday activities as well as work [65].

A study on symptoms among colorectal cancer patients undergoing chemotherapy, found they reported an average of ten symptoms, with the most common being peripheral neuropathy (64%), lack of energy (62%), feeling drowsy (49%), and nausea (45%), with lack of energy being one of the symptoms patients found most distressing [66]. In a large sample study of outpatient cancer patients with different types of cancer attending a regional centre in Scotland, clinically relevant fatigue (defined as fatigue worthy of further clinical attention) was reported by 33% of colorectal cancer patients. Across the sample of mixed cancer sites as a whole, both presence of local and distal disease, and receipt of radiotherapy or chemotherapy in the previous 2 months, were independently associated with a higher likelihood of fatigue, with the majority of respondents not in active treatment [67]. Such symptoms can impact patient distress, with this research also showing the presence of fatigue was associated with higher levels of distress (measured by the HADS) [67].

7.3.2 Stage, Treatment and Quality of Life

Quality of life typically comprises the patient's subjective assessment of their physical, functional, psychological, and social wellbeing, and as such overlaps with emotional outcomes and symptoms. Poorer quality of life is often reported among patients with more advanced disease (e.g. [68, 69]). While Foster et al. [70] found no relationship between disease stage at diagnosis and quality of life, people with advanced disease (stage IV) were excluded from the study.

As with emotional outcomes, trajectories of quality of life in colorectal cancer survivors have been shown to vary across individuals. In a related study to the one reported earlier on trajectories of distress, Dunn et al. [69] looked at quality of life over time from 5 months to 5 years post-diagnosis (assessed using the FACT-C, which contains physical, functional, social/family, emotional wellbeing and colorectal cancer specific symptom subscales), and found four different trajectories: constant high quality of life (26.2%), constant medium (47.1%), medium decrease showing dramatic decrease in quality of life 2 years post-diagnosis (7.4%), and constant low quality of life (19.2%). Again, disease stage, but not treatment received, predicted membership of the quality of life trajectories "medium decrease" and "constant low" compared with reference category of "consistently high" quality of life. Neither disease stage nor treatment received predicted membership of the trajectory 'constant medium' compared with the trajectory of "constant high" quality of life [69]. However other studies show links between specific treatments and their associated sequelae and quality of life.

Treatments such as radiotherapy can increase the risk of bowel and urinary incontinence [71]. Patients with diarrhoea have reported poorer quality of life 6 weeks after potential curative surgery for colorectal cancer [72] and in the longer term [56]. In a systematic review of quality of life in long-term colorectal cancer survivors (5 or more years post diagnosis) Jansen et al. [56] found overall quality of life was comparable with the general population with some evidence of slightly

lower physical quality of life in colorectal cancer survivors. However quality of life was lower among patients with bowel problems such as diarrhea (e.g. [73]). Pollack et al. [71] looked at patients who had previously taken part in a randomised controlled trial (an average of 15 years ago, to establish whether preoperative radiotherapy reduced local recurrence in rectal cancer patients). They found higher levels of faecal and urinary incontinence and diarrhoea in patients receiving radiation compared to those having surgery alone, although only among patients who had not had a stoma.

One risk factor for non-reversal of temporary stomas is more advanced disease [74]. Stoma-related complications, such as leakage, have been reported in over 40% of patients [74, 75]; and stomata can have adverse effects on quality of life [56, 70, 76] and impact on the patient's body image and sexual function [77].

Research consistently shows an adverse effect of radiotherapy on long-term bowel and sexual functioning, but evidence concerning the long-term adverse effects of chemotherapy is mixed. For example, Arndt et al. [78] found chemotherapy recipients reported poorer role and social functioning 1–3 years post-diagnosis, while others found no association between receipt of chemotherapy and quality of life (e.g. [79]). These differences may be due to the age group being studied as more pronounced deficits are typically observed among younger age groups (e.g. under 70 [80]).

Perceived quality of care at the time of cancer treatment (i.e. treatment information problems, problems with the control of nausea and vomiting, and pain and discomfort) has also been shown to predict subsequent quality of life in colorectal cancer patients, controlling for demographic and clinical variables [81] highlighting the importance of patient-centred care during treatment for cancer.

7.3.3 Fear of Recurrence, Social Distress and Ability to Work

Among colorectal cancer survivors, 5 or more years post-diagnosis, between one quarter and one third of patients reported concerns about recurrence (27–33%), and worry about developing another type of cancer (26–30%); with a higher proportion reporting concerns about symptoms indicating a recurrence (34–41%) and worry about future diagnostic tests (41–44%) [82]. In a study conducted in the Netherlands, fear of recurrence in colorectal cancer survivors was not associated with disease stage or treatment [83]. However it was associated with distress and quality of life, and indirect relationships between disease stage and treatment on fear of recurrence via distress and quality of life are a possibility, and remain to be explored.

Some procedure-related concerns, such as the effects of cancer risk caused by ionising radiation associated with medical imaging, become more apparent in the post-treatment phase, while patients earlier on in the treatment process are more concerned with surviving the initial disease [84]. This raises the possibility that an increased number of diagnostic tests may add to the worries patients experience after treatment has ended.

Disease stage at diagnosis and the type of treatment patients receive can also have wider impact. Social distress (indexed by concerns about everyday living, money worries, and concerns about oneself and other people) 12–36 months after a colorectal cancer diagnosis was higher among people with more advanced disease, those with recurrent or non-treatable disease, patients with a stoma, and among patients who had had radiotherapy [85]. Gastrointestinal cancer survivors are more likely to be unemployed than people with no history of the disease (48.8% vs. 33.4%). Reasons given by cancer survivors for unemployment included physical limitations, and/or cancer-related symptoms [86]. In addition, the treatment the patient receives also impacts on the psychological wellbeing of family care-givers, for example Graca-Pereira et al. [61] found higher anxiety and traumatic stress among partners of patients who had chemotherapy or radiotherapy in addition to survey vs. surgery alone.

7.3.4 Summary

Later disease stage at diagnosis adversely affects emotional and quality of life outcomes in colorectal cancer survivors. Adjuvant treatments, such as radiotherapy and chemotherapy can cause long-term symptoms such as diarrhoea or peripheral neuropathy that can also impact on patients' quality of life and distress. In addition, having a stoma can adversely affect body image, although may reduce rectal symptoms, leaving the overall effect of having on stoma on quality of life unclear. Although associations between diagnostic delay and disease stage at diagnosis remain unclear, with more convincing associations for rectal compared with colon cancer [87], it remains a possibility that a delay in diagnosis of colorectal cancer may result in more advanced disease and the need for adjuvant treatments, both of which adversely affect people's emotional and physical wellbeing for years after the initial diagnosis.

Conclusion

Undergoing investigations for cancer can be stressful, and rates of distress and poor quality of life among patients with suspected cancer are the same as those with a confirmed diagnosis. Rapid diagnostic pathways will reduce the period of distress for people eventually diagnosed with benign disease, and may also benefit people ultimately diagnosed with cancer, although further research is needed to confirm this. However, patients who experience diagnostic delay do not simply wait longer for a diagnosis, they also have a higher number of consultations and medical tests and are more likely to experience substandard quality care, which impacts on patient satisfaction. The psychological consequences of these experiences have been underexplored, and research into which sectors of the population are most vulnerable to adverse outcomes arising from delay is also lacking.

Priority areas for future research are summarised in Table 7.2.

Table 7.2 Priority areas for future research

Suggested priority of further research on psychological aspects of diagnostic delay in CRC
The impact of rapid diagnostic pathways on psychological wellbeing among people diagnosed with colorectal cancer.
Better understanding of patients' views about the relative importance of time to diagnosis versus quality of care.
Effect of particular experiences associated with diagnostic delay, such as number of investigations and consultations, as well as medical errors, and not just time to diagnosis, on psychological wellbeing and quality of life.
The role of demographic and psychological factors in vulnerability to distress in the diagnostic phase, such as age, gender, socio-economic status, history of mental illness and intolerance of uncertainty.
The impact of diagnostic delay on friends and family.

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