BMJ

BMJ 2013;346:f3172 doi: 10.1136/bmj.f3172 (Published 21 May 2013)

PRACTICE

EASILY MISSED?

Colorectal cancer

William Hamilton *professor of primary care diagnostics* [1], Mark G Coleman *director and consultant surgeon*[2], Greg Rubin *professor of general practice and primary care*[3]

[1]University of Exeter, Veysey Building, Exeter EX2 4SG, UK; [2]Lapco National Training Programme in Laparoscopic Colorectal Surgery, Derriford Hospital, Plymouth, UK; [3]Durham University, Wolfson Research Institute, Stockton on Tees, UK

This is one of a series of occasional articles highlighting conditions that may be more common than many doctors realise or may be missed at first presentation. The series advisers are Anthony Harnden, university lecturer in general practice, Department of Primary Health Care, University of Oxford, and Richard Lehman, general practitioner, Banbury. To suggest a topic for this series, please email us at easilymissed@bmj.com.

A 72 year old recently widowed man presents to his general practitioner with vague symptoms, including fatigue. Nothing is found on examination, but his haemoglobin concentration is 114 g/L (range 140-180 g/L) with a hypochromic, normocytic picture and serum ferritin 75 ng/mL (30-336 ng/mL). As his diet has been poor since his wife died, he was treated with ferrous sulphate, which was associated with a small improvement in his fatigue and haemoglobin level. Six months later he presented with intestinal obstruction, which was subsequently found to be due to a carcinoma of the colon.

Surgically, the colon and rectum are distinct, but for the purposes of this diagnostic article, they have been merged.

Why is colorectal cancer missed?

Many colorectal cancers are diagnosed easily and quickly and times to diagnosis (generally measured as the diagnostic interval from first presentation to primary care up to diagnosis) are less than three months—particularly for patients whose clinical features meet the referral guidelines of the National Institute for Health and Clinical Excellence for suspected cancer.[4] Symptoms include diarrhoea or rectal bleeding for six weeks in patients aged more than 60, or for patients older than 40 if both symptoms are present; rectal or abdominal masses or iron deficiency anaemia with haemoglobin concentrations less than 110 g/L in men and less than 100 g/L in women. However, about half of patients do not meet this guidance and have longer diagnostic intervals.[5] Mortality from colorectal cancer is strongly related to the first symptom, with mildly anaemic patients having the worst prognosis; adjusted proportional hazard ratio compared with all patients with colorectal cancer of 1.9 (95% confidence interval 1.1 to 2.7).[6] Audits from several countries suggest that about a third of patients experience diagnostic delays, with anaemia, rectal bleeding, and abdominal pain being the most usual missed opportunities.[7-9] These three symptoms are common in primary care, with alternative diagnoses to cancer more likely. Furthermore, NICE guidance recommends urgent investigation only for pronounced iron deficiency anaemia (haemoglobin <110 g/L in men, and <100 g/L in women) or for persistent rectal bleeding (six weeks, unless accompanied by diarrhoea).[4] Additionally, the possibility of cancer may be dismissed in patients with rectal bleeding and haemorrhoids.

Why does this matter?

A complex J-shaped relation exists between the diagnostic interval and mortality.[10] The best prognosis is for patients with an interval of around one month, probably reflecting the timely diagnosis of non-emergency patients. The high mortality with shorter intervals probably represents obviously ill patients with an inherently poor prognosis (including emergency admissions). The prognosis steadily worsens with increasing intervals thereafter. Expedited diagnosis may allow identification at an earlier stage, or may obviate emergency admission.

How is colorectal cancer diagnosed?

The rest of this article assumes patients who meet current NICE guidance are investigated, and concentrates on presentations that do not meet NICE guidelines.[4] It does not concern factors before presentation to medical care: there can be major delays from patients not recognising that their symptoms are important.[11] We found no literature suggesting that colorectal cancers in patients under 40 present differently from those in older patients. Similarly, we found no primary care study of colorectal cancer symptoms in patients with inflammatory bowel disease.

Correspondence to: W Hamilton w.hamilton@exeter.ac.uk

Search strategy

WH and colleagues recently performed a systematic review of primary care symptoms of colorectal cancer.[1] This was supplemented by specific searches on missed or delayed diagnoses, plus searches on young people, irritable bowel syndrome, and inflammatory bowel disease. No randomised controlled trials have been reported on the selection of patients for investigation, so most of the quoted studies are large cohort studies, often using national primary care databases. Cited studies can be assumed to be of this nature unless specifically stated otherwise.

How common is colorectal cancer?

- Colorectal cancer is the third most prevalent cancer in the United Kingdom, the incidence increasing with age, and it is slightly more common in men
- More than 41 000 new cases of colorectal cancer are diagnosed annually in the United Kingdom, with the median age at diagnosis 72 years, although 6% occur below the age of 40[2]
- Screening identifies a few patients with cancers; the remainder present with symptoms, with around a quarter presenting as an emergency[3]
- A full time general practitioner will have around one patient with a new diagnosis of colorectal cancer each year

Anaemia

Around a third of patients with colorectal cancer in a hospital case series had anaemia but of insufficient severity to meet current NICE guidance, as in our hypothetical case.[12] For those meeting the guidance, the estimated risk of cancer in a large UK case-control study was 13.3% for men and 7.7% for women.[13] The most common measure of iron stores is serum ferritin level, with values below 44.9-67.4 pmol/L (20-30 ng/mL) being regarded as abnormal (individual laboratories have differing ranges). However, in anaemic patients investigated by colonoscopy, those with ferritin levels below 112.4 pmol/L and 112.4-222.5 pmol/L had a similar risk of cancer.[14] Together, this suggests that current guidance is too restrictive. In men aged more than 60 with iron deficiency anaemia, the risk of cancer with a haemoglobin concentration of 110-119 g/L is over 4%; even haemoglobin values of 120-129 g/L represent risks of 3.9% in the 70-79 year age group.[13] The values for women reflect their lower normal haemoglobin range: even so, the risk of cancer in women with haemoglobin concentrations of 110-119 g/L is more than 2.4%. Raising the haemoglobin threshold to allow investigation at such levels would require more colonoscopies but would be in keeping with the threshold risk values used by NICE for other colorectal cancer symptom patterns.[4]

Abdominal pain

Abdominal pain is the most typical symptom of colorectal cancer (alongside rectal bleeding) but it has a low positive predictive value for colorectal cancer of 1.1%, although this increases to 3.0% if abdominal pain is reported again to primary care.[15] When other symptoms, such as diarrhoea or loss of weight, are present, the risk is higher, although rarely above 3%.[15] Few patients with abdominal pain are investigated for possible colorectal cancer at their first presentation. One classic misdiagnosis is irritable bowel syndrome. There is no causative association between irritable bowel syndrome and colorectal cancer; however, around 1% of patients with an initial diagnosis of irritable bowel syndrome prove to have colorectal cancer.[16] All patients with a new diagnosis of irritable bowel syndrome warrant clinical review to confirm that their symptoms are stable and responding to management (diagnostic safety netting). Some guidelines, although not those from NICE, recommend that patients over 50 with new onset irritable bowel syndrome should undergo colonoscopy.

Change in bowel habit and rectal bleeding

Change in bowel habit is a medical term, unused by patients. It is not the same as diarrhoea or constipation, and the risk of cancer is considerably higher when general practitioners' record "change of bowel habit" (3-4% in men aged >60) than when they record diarrhoea (0.9-1.3%) or constipation (0.8%), in the same age group.[17] The most plausible explanation is that when doctors record change in bowel habit they have included other factors in their assessment and deem the total risk to be higher. Arguably, all such patients warrant investigation.

Rectal bleeding is a classic symptom of colorectal cancer. In primary care the risk of cancer ranges from 0.5% in women aged less than 60 to 4.5% in men aged more than 80.[17] The risk is higher when diarrhoea is present or when local anal symptoms such as pain, soreness, and itch are absent.[18] A similar pattern of higher risk with increasing age, multiple symptoms, and absent perianal symptoms is seen in the referred population.[19] The Association of Coloproctologists of Great Britain and Ireland have developed a bowel symptom checker for the public and for primary care (www.haveigotbowelcancer.com).

How is colorectal cancer investigated?

Complete examination of the large bowel by colonoscopy after full bowel preparation remains the standard investigation for patients suspected of having bowel cancer. Where colonoscopy is incomplete (in around 11% of patients),[20] it may be repeated, or computed tomography colonography performed. Computed tomography colonography has a similar identification rate for cancer and polyps to that of colonoscopy, and both are superior to barium enema.[20 21] All the standard investigations have low false negative rates, although persistent symptoms may require reinvestigation.[22]

How is colorectal cancer managed?

National guidance on the management of colorectal cancer was published in November 2011.[23] Surgery, either open or laparoscopic, is the primary treatment. Adjuvant treatments include postoperative chemotherapy in patients with node positive (Dukes' stage C) results, and preoperative radiotherapy, which reduces the risk of local recurrence in rectal cancer. Metastases to the liver or lung may also be resected. Patients presenting with large bowel obstruction can sometimes be decompressed with an endoscopically placed stent, allowing resection later.

We thank Eustacia Hamilton for help with the initial searches.

Key points

- Patients with mild anaemia can still have colorectal cancer, even if their haemoglobin level is above the threshold recommended by NICE for urgent investigation
- In people aged over 60, women with a haemoglobin concentration ≤110 g/L and men ≤120 g/L and iron deficiency are worth investigating for cancer
- Patients with a new diagnosis of irritable bowel syndrome should have their response to treatment monitored in case of misdiagnosis
- Doctors who record "change in bowel habit" rather than diarrhoea or constipation are potentially thinking of colorectal cancer and further investigations should be considered

Contributors: WH performed the initial searches and drafted the first version of the article. All three authors revised the article, adding additional references. WH is the guarantor.

Competing interests. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: WH has received several research grants for studies on cancer diagnosis, including one from Colonix, a commercial firm. He is the clinical lead for the current revision of the NICE 2005 guidance. His contribution to this article is in a personal capacity and is not to be interpreted as representing the view of the Guideline Development Group or of NICE itself. He has received travel support to give lectures and attend conferences, plus occasional modest speaker's fees, from conference organisers in the charitable and educational sector, though none from commercial sources. MGC is the national lead clinician for the Lapco National Training Programme in Laparoscopic Colorectal Surgery. He is the chairman of external affairs for the Association of Coloproctologists of Great Britain and Ireland and a national peer review advisor for the hepatopancreaticobiliary cancer peer review group. His contribution to this article is in a personal capacity. He has received travel support to give lectures and attend conferences, plus fees, from conference organisers in the educational sector, and some from commercial sources to lecture abroad on laparoscopic colorectal surgery from Olympus, Johnson & Johnson and Covidien. GR is the Royal College of General Practitioners clinical lead for cancer, a post part funded by Cancer Research UK. He has received support for travel and conference attendance, and payment for advisory services from Lilly, Almirall, and Warner Chilcott. His contribution to this article is in a personal capacity. All authors are members of the Bowel Cancer UK Medical Advisory Board. No other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review: Commissioned; externally peer reviewed.

Patient consent not required (patient anonymised, dead, or hypothetical).

1 Astin M, Griffin T, Neal RD, Rose P, Hamilton W. The diagnostic value of symptoms for colorectal cancer in primary care: a systematic review. *Br J Gen Pract* 2011;61:e231-43.
2 Cancer Research UK. CancerStats key facts: bowel cancer. Cancer Research UK, 2012.
3 Elliss-Brookes L, McPhail S, Ives A, Greenslade M, Shelton J, Hiom S, et al. Routes to diagnosis for cancer—determining the patient journey using multiple routine data sets. *Br J Cancer* 201;107:1220-6.
4 National Institute for Health and Clinical Excellence. Referral guidelines for suspected cancer. NICE, 2005.
5 Hamilton W. Cancer diagnosis in primary care. *Br J Gen Pract* 2010;60:121-8.
6 Stapley S, Peters TJ, Sharp D, Hamilton W. The mortality of colorectal cancer in relation to the initial symptom and to the duration of symptoms: a cohort study in primary care. *Br J Cancer* 2006;95:1321-5.
7 Singh H, Daci K, Petersen LA, Collins C, Petersen NJ, Shethia A, et al. Missed opportunities to initiate endoscopic evaluation for colorectal cancer diagnosis. *Am J Gastroenterol* 2009;104:2543-54.
8 Domínguez-Ayala M, Díez-Vallejo J, Comas-Fuentes A. Missed opportunities in early diagnosis of symptomatic colorectal cancer. *Rev Esp Enfirm Dig* 2012;104:343-9.
9 Damery S, Ryan R, Wilson S, Ismail T, Hobbs R, On behalf of the Improving Colorectal Outcomes Group. Iron deficiency anaemia and delayed diagnosis of colorectal cancer: a retrospective cohort study. *Colorectal Dis* 2011;13:e53-60.
10 Torring M, Frydenberg M, Hansen R, Olesen F, Hamilton W, Vedsted P. Time to diagnosis and mortality in colorectal cancer: a cohort study in primary care. *Br J Cancer* 2011;104:934-40.
11 Thompson MR, Heath I, Swarbrick ET, Faulds Wood L, Ellis BG. Earlier diagnosis and treatment of symptomatic bowel cancer: can it be achieved and how much will it improve survival? *Colorectal Dis* 2011;13:6-16.
12 Masson S, Chinn DJ, Tabaqchali MA, Waddup G, Dwarakanath AD. Is anaemia relevant in the referral and diagnosis of colorectal cancer? *Colorectal Dis* 2007;9:736-9.
13 Hamilton W, Lancashire R, Sharp D, Peters TJ, Cheng K, Marshall T. The importance of anaemia in diagnosing colorectal cancer: a case-control study using electronic primary care records. *Br J Cancer* 2008;98:323-7.
14 Sawhney MS, Lipato T, Nelson DB, Lederle FA, Rector TS, Bond JH. Should patients with anemia and low normal or normal serum ferritin undergo colonoscopy? *Am J Gastroenterol* 2007;102:82-8.
15 Hamilton W, Round A, Sharp D, Peters T. Clinical features of colorectal cancer before diagnosis: a population-based case-control study. *Br J Cancer* 2005;93:399-405.
16 García Rodríguez L, Ruigómez A, Wallander M, Johansson S, Olbe L. Detection of colorectal tumor and inflammatory bowel disease during follow-up of patients with initial diagnosis of irritable bowel syndrome. *Scand J Gastroenterol* 2000:35:306-11.
17 Hamilton W, Lancashire R, Sharp D, Peters TJ, Cheng KK, Marshall T. The risk of colorectal cancer with symptoms at different ages and between the sexes: a case-control study. *BMC Med* 2009;7:17.
18 Ellis BG, Thompson M. Factors identifying higher risk rectal bleeding in general practice. *Br J Gen Pract* 2005;55:949-55.
19 Thompson MR, Perera R, Senapati A, Dodds S. Predictive value of common symptom combinations in diagnosing colorectal cancer. *Br J Surg* 2007;94:1260-5.
20 Atkin W, Dadswell E, Wooldrage K, Kralj-Hans I, von Wagner C, Edwards R, et al. Computed tomographic colonography versus colonoscopy for investigation of patients with symptoms suggestive of colorectal cancer (SIGGAR): a multicentre randomised trial. *Lancet* 2013; published online 14 Feb.
21 Halligan S, Wooldrage K, Dadswell E, Kralj-Hans I, von Wagner C, Edwards R, et al. Computed tomographic colonography versus barium enema for diagnosis of colorectal cancer or large polyps in symptomatic patients (SIGGAR): a multicentre randomised trial. *Lancet* 2013; published online 14 Feb.
22 Johnson CD, Chen M-H, Toledano AY, Heiken JP, Dachman A, Kuo MD, et al. Accuracy of CT colonography for detection of large adenomas and cancers. *N Engl J Med* 2008;359:1207-17.
23 National Institute for Health and Clinical Excellence. Colorectal cancer: the diagnosis and management of colorectal cancer: CG131. NICE, 2011.

Cite this as: *BMJ* 2013;346:f3172