Colorectal cancer

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BMJ 2007;335:715-8

doi:10.1136/bmj.39321.527384.BE

Colorectal cancer is common, the presenting symptoms are non-specific, and the stage of disease at diagnosis is closely related to survival. In this review we discuss disease presentation, criteria for urgent referral of patients to specialist care, and recent developments in the implementation of national screening programmes, which aim to reduce mortality from this common disease. Many general practitioners will also refer patients with suspected colorectal cancer “direct to test” and this review covers the various modalities for investigation of patients with colorectal symptoms.

Sources and selection criteria

We searched PubMed for recent papers using the keywords “colorectal cancer”, “screening”, “investigation”, and “incidence”. We also searched the Cochrane Database of Systematic Reviews using the search terms “colorectal cancer” and “inflammatory bowel disease”. In addition we used our personal reference archive.

How common is colorectal cancer?

In the Western world colorectal cancer is the second most common cancer in women after breast cancer and the third most common in men after lung and prostate cancer.^{1,2} Rates vary largely worldwide, being lowest in Africa and Asia and highest in Europe, North America, and Australasia. In the United Kingdom the lifetime incidence of colorectal cancer in people at average risk is 5% and the age standardised incidence rate is 44.3 per 100 000 population.³

How does colorectal cancer develop?

In most cases colorectal cancers arise from dysplastic adenomatous polyps. A multistep process involves the inactivation of a variety of genes that suppress tumours and repair DNA and the simultaneous activation of oncogenes. This confers a selective growth advantage to the colonic epithelial cell and drives the transformation from normal epithelium to adenomatous polyp to invasive colorectal cancer.⁴ Germline (hereditary) mutations underlie the well described inherited colon cancer syndromes whereas sporadic cancers arise from a stepwise accumulation of somatic genetic mutations. A single germline mutation in the APC tumour suppressor gene is responsible for the dominantly inherited syndrome, familial adenomatous polyposis coli. It is characterised by the development of hundreds to thousands of adenomatous polyps in the

colon and development of colorectal cancer and other cancers in the third and fourth decade of life. Clinical expression of the disease is seen when the inherited mutation of one APC allele is followed by a “second hit” mutation or deletion of the second allele.

Who is at greatest risk of colorectal cancer?

Increasing age is the greatest risk factor for sporadic colorectal cancer: 99% of cases occur in people aged more than 40 and 85% in those aged more than 60 (fig 1). In Europe the incidence of colorectal cancer is gradually increasing, in part due to the ageing of the population but also due to an increase in the age specific incidence, suggesting that lifestyle or environmental factors, or both, contribute. The much higher incidence of colorectal cancer in more affluent countries compared with less developed countries is also thought to be related to lifestyle factors such as obesity and consumption of processed meat, and an inverse relation with physical activity and consumption of fruit and vegetables.

Next to age, family history is the most common risk factor for colorectal cancer. Familial adenomatous polyposis and hereditary non-polyposis colorectal cancer are the most common of the familial cancer syndromes, but together these two syndromes account for fewer than 5% of cases. About 10-20% of patients describe a family history of colorectal cancer, but the pattern of inheritance and clinical features are not consistent with one of these well characterised syndromes (table 1).⁵

What are the symptoms of colorectal cancer?

Abdominal pain, change in bowel habit, and rectal bleeding or anaemia are the commonest presenting symptoms of colorectal cancer but these symptoms also commonly occur in other gastrointestinal conditions. A change in bowel habit is a more common presenting symptom for left sided cancers caused by a progressive narrowing of the bowel lumen, with diarrhoea, a change in stool form, and eventually intestinal obstruction. About 10% of patients with iron deficiency anaemia have colorectal cancer, most commonly on the right side, and thus iron deficiency in men, and women who are not menstruating, is an indication for urgent referral and investigation.^{7,8}

In 2005 the National Institute for Health and Clinical Excellence issued updated UK based guidelines that outlined signs and symptoms warranting

Table 1 | Lifetime risk of dying from colorectal cancer according to family history, and recommendations for colonic screening in United Kingdom^{5 6}

Risk group	Lifetime risk of colorectal cancer	Refer for colonic screening
Risk in general population	1:50	No
One first degree relative affected (any age)	2-3-fold increased	No
One first degree relative affected (age <45 years)*	3-4-fold increased	Yes
Two first degree relatives affected (any age)	3-4-fold increased	Yes

*Initial colonoscopy is recommended between the ages of 35 and 40 years, or 10 years before the age of cancer diagnosis in the family member if this is earlier. American guidelines use a cut-off value of <60 years.

urgent referral (within two weeks) for further specialist review or investigation of suspected colorectal cancer (table 2).

How should suspected colorectal cancer be investigated?

Colonic imaging

Table 3 summarises the advantages and disadvantages of the various investigations of the colon.⁹⁻¹⁴ All methods for examining the whole colon require full preparation of the bowel with oral laxatives, and the diagnostic yield of the examination depends on adequate preparation. Computed tomographic colonography (virtual colonoscopy) provides an endoluminal view of the colon similar to that of traditional colonoscopy. Technical improvements with this method (intravenous contrast material and oral faecal tagging agents) may allow stool and polyps to be differentiated and thus obviate the need for prior bowel preparation. The probability of colorectal cancer is low in patients with symptoms that suggest a lesion in the left colon (change in bowel habit or fresh rectal bleeding) but who do not have polyps or cancer visible at flexible sigmoidoscopy. Thus this may be an appropriate investigation in low risk patients—for example, fresh rectal bleeding only in patients aged less than 50 years—but otherwise the entire colon should be examined when colorectal cancer is suspected clinically.

Patient choice is an important factor in deciding on type of investigation. Prospective studies of patients who underwent two, or in some cases three, consecutive

Table 2 | Referral guidelines from the National Institute for Health and Clinical Excellence for suspected colorectal cancer, 2005

Symptoms and signs	Age threshold (years)
Rectal bleeding with change in bowel habit to looser stools or increased frequency of defecation, or both, persistent for six weeks	≥40
Definite palpable right sided lower abdominal mass consistent with involvement of large bowel	All
Definite palpable rectal (not pelvic) mass	All
Rectal bleeding persistently without anal symptoms*	≥60†
Change of bowel habit to looser stools or increased frequency of defecation, or both, without rectal bleeding, persistent for six weeks	≥60†
Iron deficiency anaemia without obvious causes (haemoglobin level <110 g/l in men or <100 g/l in women who are not menstruating)‡	Any

*Include soreness, discomfort, itching, lumps, prolapse, and pain.

†60 years is considered maximum age threshold. Local cancer networks may elect to set lower thresholds (for example, 55 or 50 years).

‡British Society of Gastroenterology recommends urgent referral and investigation for any level of iron deficiency anaemia.⁸

Fig 1 | Age specific incidence of colorectal cancer in men and women. Adapted from Cancer Research UK (<http://info.cancerresearchuk.org/cancerstats/types/bowel/incidence>)

imaging tests showed that computed tomographic colonography and standard colonoscopy were equally acceptable, and both were preferable to double contrast barium enema.^{15 16} Plain computed tomography of the abdomen is a useful investigation in patients with a large palpable abdominal mass of unclear colonic origin.

Frail and elderly patients

Conventional colonic imaging tests may be difficult to carry out in elderly or frail patients because of immobility and poor tolerance to bowel preparation. Prospective studies with clinical outcome at 12-30 months have shown that in patients with symptoms plain computed tomography of the abdomen with oral contrast (but without bowel preparation) has a sensitivity for detection of colon cancer of 88-94%.^{17 18} Equivocal tests may need further investigation.

Other tests

Testing for faecal occult blood and measurement of serum tumour markers such as carcinoembryonic antigen are not useful in the investigation of suspected colorectal cancer. Faecal occult blood testing is an effective means of population screening in asymptomatic people but it is too insensitive to guide the investigation of patients with colonic symptoms. Similarly, tumour markers lack sensitivity and specificity but may be useful in the follow-up of treated patients. Wireless capsule endoscopy for imaging the colon is currently under development.

How is colorectal cancer managed?

Staging of the disease and complete visualisation of the colon are required once colorectal cancer is diagnosed, other than in the emergency setting. Liver and chest imaging, usually with computed tomography, is necessary to detect metastases, and a complete colonic assessment can detect synchronous cancers, present in 3-5% of patients. Endorectal ultrasonography or magnetic resonance imaging is also necessary to stage rectal cancer. Surgical resection for localised colorectal cancer offers the only curative possibility. Postoperative chemotherapy offers a survival benefit for patients after

Table 3 | Comparison of current methods for examining the colon

Modality	Seda-tion	Perfora-tion rate (diagnostic)	Biopsy or polypectomy, or both	Sensitivity for detection (%)	
				Large polyps (>10 mm)	Cancer
Endoscopic:					
Standard (optical) colonoscopy	Usually	2:1000*	Yes	98	97
Flexible sigmoidoscopy	Rarely	1:10 000*	Yes	Examines left colon only	Examines left colon only
Radiological:					
Double contrast barium enema	No	1:10 000	No	48	83-94
Computed tomographic (virtual) colonography	No	5:10 000	No	59-85	97

*Highly operator dependent. Many expert endoscopists have lower rates than in quoted published series.

resection of stage II disease and selected patients with stage III disease. Preoperative chemoradiotherapy improves survival compared with surgery alone for rectal cancer. Palliative chemotherapy can alleviate symptoms, improve quality of life, and improve survival in patients with metastatic colorectal cancer.¹⁹ In some cases survival is improved by resection of liver and lung metastases.

What is the prognosis of colorectal cancer?

The outcome of colorectal cancer depends on the stage at diagnosis; about half of patients presenting with symptoms are at Dukes's stage C or D (table 4).^{20,21} Five year survival rates are lower in the United Kingdom, Denmark, and eastern European countries compared with the European average of about 50%.²² Analysis of the EURO-CARE data (European cancer registries study) suggests that lower survival in the United Kingdom results from later stage at presentation and diagnosis rather than inferior treatment for a similar stage.²³

Who should enter a screening programme?

Family history

Moderate risk

Healthy asymptomatic people with a family history of colorectal cancer should be considered for screening (table 1).^{5,6} Conventional colonoscopy remains the ideal investigation but computed tomographic colonography is used to examine the remaining colon when colonoscopy is incomplete—for example, as a result of technical difficulties preventing passage of the scope. The aim of colonic surveillance is to identify and remove adenomatous polyps thus preventing subsequent development into invasive cancer.

Table 4 | Approximate frequency and five year relative survival by Dukes's stage²⁰

Dukes's stage modified (equivalent TNM stage)	Description	5 yearly survival rate (%)
A (stage I)	Localised to mucosa and submucosa	93
B (stage IIA and IIB)	Extending into or through muscle layer without lymph node involvement	72-85
C (stage IIIA-C)	Lymph node involvement	44-83
D (stage IV)	Distant metastases	8

TNM=tumour, node, metastasis staging system.

High risk

People with one of the defined genetic family cancer syndromes—for example, familial adenomatous polyposis or hereditary non-polyposis colorectal cancer—have a high risk of colorectal cancer and should be referred to a local clinical genetics unit for possible formal counselling and mutation analysis of the respective gene. Hereditary non-polyposis colorectal cancer is the commonest of the family cancer syndromes and is caused by a DNA mismatch repair gene (that is, a gene that helps DNA to repair itself) mutation that predisposes patients to colorectal and also extra-colonic cancers (endometrial, ovarian, genitourinary, small bowel, and biliary tract).

Inflammatory bowel disease

Patients with longstanding total ulcerative colitis and Crohn's colitis are also at risk for colorectal cancer. National guidelines recommend that colonoscopic surveillance should begin after 8-10 years for pancolitis and 15-20 years for left sided disease. A recent Cochrane review did not find conclusive evidence that surveillance colonoscopy prolongs survival in these patients. Cancers are, however, likely to be detected at an earlier stage, with an associated better prognosis, and indirect evidence suggests that surveillance reduces death from colorectal cancer associated with irritable bowel disease.²⁴

What are the methods for screening populations for colorectal cancer?

Population screening for colorectal cancer has been the subject of several recent high quality controlled clinical trials. The most widely investigated screening modality has been faecal occult blood testing based on the knowledge that cancer and polyps may bleed. A positive result is followed by imaging of the whole colon, usually with colonoscopy. Cancers detected by such screening are at an earlier stage (mostly Dukes's A and B) than

Fig 2 | Expected outcomes in bowel cancer screening programme²⁶

Additional educational resources

National Institute for Health and Clinical Excellence (www.nice.org.uk/guidance/CSGCC)—Department of Health document for improving outcomes in colorectal cancer

British Society of Gastroenterology (www.bsg.org.uk)—Clinical practice guidelines for a variety of gastrointestinal conditions

Cochrane Library (www.cochrane.org)—Independent systematic reviews of healthcare interventions to guide clinical decision making

Information for patients

NHS cancer screening programmes (www.cancerscreening.nhs.uk/bowel/index.html)—Contains information leaflets about the NHS bowel cancer screening programme

BBC (www.bbc.co.uk/health/conditions/cancer/typescancer_bowel.shtml)—Information about bowel cancer, with a section on lifestyles that are associated with a reduced risk, and details of organisations that can provide medical and emotional help and support

Cancer Research UK (<http://info.cancerresearchuk.org>)—Colorectal cancer and other cancers covered in detail

symptomatic cancers (table 4).²⁰ Meta-analysis of four randomised controlled trials has shown that screening using faecal occult blood testing reduced the risk of death from colorectal cancer by 25% of those screened. It is estimated that screening using faecal occult blood testing will avoid about 1 in 6 of deaths from colorectal cancer.²⁵ Ongoing studies should prove if removal of polyps reduces the subsequent development of colorectal cancer. The National Health Service bowel cancer screening programme began in 2006 and will be phased in gradually over three years. Home testing kits for faecal occult blood testing are sent to people aged 60–69 years every two years and on request to those aged 70 or more. Patients with positive results are invited to undergo colonoscopy at their local designated screening centre (fig 2).

Other screening strategies include flexible sigmoidoscopy every five years with or without faecal occult blood testing, double contrast barium enema, or colonoscopy every 10 years. All of these methods, used in people from age 50 years, reduce mortality from colorectal cancer compared with no screening and the cost per life saved compares favourably with mammography for women aged more than 50 and treatment of moderate hypertension. No single strategy has, however, proved to be the most effective or cost effective for screening.²⁷ American guidelines recommend that people at average risk should be offered one of these screening strategies from age 50 and thus at a younger age than in the United Kingdom but at a higher cost per life saved.⁵

SUMMARY POINTS

The lifetime risk of developing colorectal cancer is about 5%

Increasing age and a family history of colorectal cancer are the greatest risk factors for the disease

Patients presenting with suspicious symptoms and signs should be referred and investigated urgently in a specialised unit

Colonoscopy and computed tomographic colonography are of equal sensitivity for detection of colorectal cancer

Colonoscopy allows biopsy of suspicious lesions and removal of polyps

Population screening by testing for faecal occult blood has begun in the United Kingdom

Contributors: ABB and CA participated in the literature search and writing of the article. ABB is the guarantor.

Competing interests: None declared.

Provenance and peer review: Commissioned and externally peer reviewed.

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