Colorectal cancer: prevention and early diagnosis

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Abstract

Colorectal cancer (CRC) is a curable disease; over 90% of patients who have surgical resection of a Dukes' A tumour will still be alive after 5 years. This is direct evidence that an early diagnosis will reduce mortality from CRC. Despite this, CRC is the second most important cause of cancer-related deaths in the UK. The discrepancy suggests that outcomes can be improved by a better understanding of the causes of the disease and its early detection and treatment. In this article, prevention and early diagnosis are discussed. The important associations of CRC with diet, obesity and exercise are considered, as well as the benefits of patient education and continued academic research into these areas. Screening for CRC using faecal occult blood test (FOBT) is examined in detail and surveillance programmes for hereditary non-polyposis colorectal cancer, familial adenomatous polyposis and other high-risk patients are reviewed. Finally, the impact of the 'two-week wait' rule introduced by the 'NHS Cancer Plan 2000' is analysed, and proposals made on how to maximize its purpose to detect CRC as early as possible.

Keywords colorectal cancer; EPIC; familial adenomatous polyposis; hereditary non-polyposis colorectal cancer; patient education; screening; surveillance

Colorectal cancer (CRC) is a major cause of cancer morbidity in the UK, and in 2002 there were 34,889 new cases and 16,000 deaths from the disease.[1] After lung cancer, it is the second most important cause of cancer-related deaths.[1]

Pathogenesis

The pathogenesis of CRC is well understood in terms of the 'adenoma–carcinoma sequence'. This describes the progression of CRC as an accumulation of mutations in key genes, for example, tumour suppressor genes such as the adenomatous polyposis coli (APC) and TP53 genes, and in proto-oncogenes such as K-ras. In macroscopic terms, these molecular changes contribute to the development of polypoid lesions and, later, invasive carcinoma. In polyps, the normal architecture of colonic crypts is disrupted by disturbances in the sequence of basal proliferation, migration and differentiation. Many individuals have polyps, but it is estimated that only 5% will develop invasive cancer. Prevention of colorectal cancer, therefore, depends on early elimination of these polyps and/or the factors that predispose the colonic epithelium to become transformed.

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Aetiology

Eighty-five per cent of CRC cases fall into the category of 'sporadic' disease, where the primary cause of polyp formation is unknown. The remaining 15% of cases are accounted for by less common causes of CRC, for example familial CRC (i.e. where one first-degree relative aged <45 years old is affected by CRC or there are two affected first-degree relatives), dominantly inherited CRC syndromes and inflammatory bowel disease (IBD). In the latter two groups, the molecular events of polyp formation are understood. The hereditary CRC syndromes (e.g. hereditary non-polyposis colorectal cancer (HNPCC), familial adenomatous polyposis (FAP), Peutz-Jegher syndrome, and juvenile polyposis) have germline mutations that predispose the epithelium to develop multiple polyps. A germline mutation of APC is responsible for the colorectal polyps that develop in FAP, whereas mutations in mismatch repair genes which usually detect, excise and replace any inadvertent nucleotide mismatches during DNA replication, result in HNPCC. Compared with the large number of polyps in FAP, there are markedly fewer polyps in HNPCC. The HNPCC polyps are predominantly located in the right colon but their rate of transformation is high compared with FAP (see Figure 1). In IBD such as ulcerative colitis and colonic Crohn's, the predisposition to CRC arises from the increased proliferation of colonic epithelium during inflammatory episodes.

Polyp formation in sporadic disease is not well understood, consequently, numerous studies on external factors such as diet, obesity and other lifestyle parameters have been, and are being, undertaken to identify causal relationships with CRC. Some of these studies are discussed below and are an important source of evidence-based preventative measures.

Prevention

Diet

In the 1960s, Burkitt proposed that 'the relationship between diet and bowel disease' should be investigated. His hypothesis was

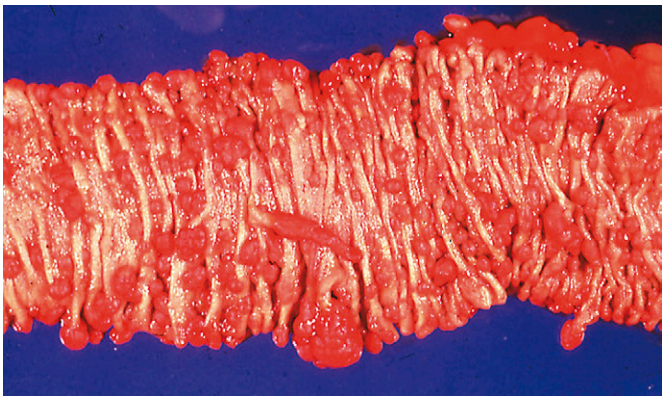

Figure 1 Macroscopic view of a polyposis seen in familial adenomatous polyposis. Reprinted with kind permission from Dr Mark Arends, Consultant Histopathologist, Addenbrooke's Hospital, Cambridge, UK.

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that low-fibre diets slowed colonic transit and thereby increased the opportunity of carcinogens, generated by bacterial activity on faecal constituents, to exert their effect on the colonic epithelium. The effect of diet (as well as metabolic, genetic and environmental factors) on the development of cancer is now being explored in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. EPIC is the world's largest prospective study and involves over half a million people recruited from 23 different regions of 10 European countries. The advantage of obtaining data from multiple regions is that a clearer relationship between different dietary habits and the development of cancer may be seen.[2]

The first completed data sets have now been analysed from the ongoing EPIC study; these show that dietary patterns are regional and that diet does have an impact on the development of CRC. For example, it has been demonstrated that dietary fibre is likely to be protective against colorectal cancer; comparison between the lowest daily fibre intake of 12 g and the highest intake of 30 g, showed a 40% reduction in the risk for CRC after calibration.[3] The source of fibre was not significant.[3] As a result, it has been suggested that about eight portions of fruit and vegetables and the equivalent of five slices of wholemeal bread should be eaten if the benefits of dietary fibre are to be realized.[2] Linked studies have also shown that a high intake of red or processed meat is associated with a 35% increase in colorectal cancer if more than 160 g are consumed per day (2 or more portions) when compared to less than one portion per week.[4] In contrast, a high fish consumption of 80 g or more is protective.[4] The increased risk of CRC with a high consumption of red and processed meat may be related to the association of these foodstuffs with increased amounts of N-nitrosocompounds in the faeces. These compounds bind to the epithelial DNA and may act as mutagens to initiate the adenoma–carcinoma sequence.

Some studies have not demonstrated that a high fibre diet reduces the risk of CRC,[5] therefore, continuing investigations are still necessary to confirm the findings and to identify any other dietary factors that might contribute to the risk of developing CRC.

Obesity and exercise

There is accumulating epidemiological evidence that central obesity is a risk factor for CRC. The biological mechanisms still need to be elucidated, but hyperinsulinaemia appears to play a role. With further research, it may emerge that weight loss is an important preventative measure against CRC as it is against endometrial cancer, heart disease and type II diabetes.

Regular exercise also protects against CRC. Furthermore, there is evidence that CRC patients have an absolute improvement of 14% in their five-year survival if they had active lifestyles before presenting with symptoms of CRC.[6] An active patient is defined as someone who exercises vigorously for 20 minutes at least once a week or participates in weekly general health and fitness.[6]

Alcohol and smoking

The link between alcohol and CRC remains equivocal. Some evidence suggests that there is a dose–risk relationship which is particularly pertinent to rectal cancer. However, the evidence for tobacco is slightly stronger; rectal cancer, rather than colon cancer, is related to smoking even after adjustment for alcohol.[7] This epidemiological evidence is also supported by other studies which have shown that smokers have a higher incidence of colorectal polyps.

Chemoprevention

Non-steroidal anti-inflammatory drugs (NSAIDs) may inhibit progression and development of CRC. A recent Cochrane meta-analysis analysed four randomized controlled trials which compared aspirin with a placebo in 'average'-risk populations.[8] No significant reduction in the incidence of adenomas was noted in the primary prevention trial, but data from the three secondary prevention trials showed a statistically significant reduction in the recurrence of sporadic adenomas in the 'treatment' groups. The overall results (which included trials treating FAP patients with aspirin) showed a trend in favour of treating with aspirin to prevent colorectal adenomas.[8] However, the largest trials preselected patients for aspirin tolerance, and therefore the risks of gastrointestinal bleeding and haemorrhagic stroke must be weighed against the benefit of treatment.

Patient education

Symptoms of CRC include a change in bowel habit (particularly loose stools for more than six weeks) and rectal bleeding (characteristically, dark blood which may or may not be mixed with stool). Bright red rectal blood in the absence of other anal disease (e.g. haemorrhoids, tags and fissures) is also a high-risk symptom. Efforts to educate patients about the importance of these symptoms, together with information about screening programmes, are likely to lead to earlier patient presentation, particularly as there is evidence that patients do ignore symptoms (for years in some cases), and express fears about unpleasant examinations and not wanting 'to waste the doctor's time'.

Early diagnosis through screening

There is evidence that polypectomy reduces the incidence of CRC.[9,10] Population screening for premalignant or early disease in the form of polypoid lesions is, therefore, likely to reduce the incidence of sporadic CRC in the longer term. For an average-risk individual (e.g. no family or personal history of CRC), the lifetime cumulative incidence of CRC is 6%,[11] but the risk of developing sporadic CRC doubles every 10 years after 40 years of age.[11] To achieve the maximum benefits of a screening test, it should be undertaken when the patient is most likely to have pre-invasive or very early invasive disease. Since the average age of patients who receive a diagnosis of adenomatous polyps is around 60 years old, the Department of Health guidelines in the UK advise that biennial screening should be offered to everyone between 60 and 69 years old (http://www.cancerscreening.nhs.uk/bowel/index.html). Initial screening will be performed using the faecal occult blood test (FOBT). Patients with positive tests will be offered colonoscopy in quality-assured centres.

Faecal occult blood test

The principle behind FOBT is that polyps and malignant lesions bleed, and blood from these lesions is shed into the faecal stream and the peroxidase activity of haem is detected by the guaiac impregnated test cards. However, not all colonic lesions bleed, and the principal criticism of FOBT is its low sensitivity and inadequate specificity which can translate into high levels of false-negative and false-positive rates respectively (see Table 1 for definitions). Estimates of the sensitivity for CRC range from 12.9%[12] to 50%,[13] and for large adenomas,

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Definitions of sensitivity and specificity

Sensitivity

- Definition: probability of a positive test when the disease is present
- Application: if the test has a high sensitivity, it will identify patients with the disease, and therefore a negative result indicates that the patient does not have the disease

Specificity

- Definition: probability of a negative test when the disease is absent
- Application: if the test has a high specificity, a negative result identifies people who do not have the disease, and therefore a positive result indicates that the patient has the disease

Table 1

sensitivity estimates are as low as 12%.[12] The specificity of FOBT is usually around 95%, which results in a 5% false-positive rate. In some clinical settings this may be acceptable, but in a national screening programme this means unnecessary colonoscopies for 1 in 20 of the people screened by FOBT. If, as expected, thousands of individuals take up the FOBT screening, the 1 in 20 unnecessary colonoscopies may lead to significant patient risk and financial burdens for patients and health services.

Despite the criticisms, FOBT is still a viable screening test; it is non-invasive and cheap, but more importantly it reduces mortality from CRC. Several trials have independently shown a significant reduction in mortality from CRC in the individuals randomized to receive FOBT.[13–15] In the FOB-tested groups, the reduction in mortality was 15–18%[13,15] for biennial screening and 33% for annual screening.[14] Furthermore, 18 years of follow-up from the Minnesota trial has demonstrated a significant reduction in the incidence of CRC in patients randomized to FOBT.

CRC prevention through the surveillance of screened patients with early disease

The number of patients diagnosed with adenomas and early CRC will inevitably increase as a screening programme becomes established. These patients need regular follow-up or surveillance because of their increased risk of recurrent adenomas. The interval between surveillance colonoscopies is timed to balance the risk of repeat colonoscopies against the need to diagnose and treat any further neoplasia and/or CRC before it causes significant morbidity. Initially a 3-year interval was proposed based on the data from the US National Polyp Study, but further studies have modified this recommendation. It has been shown that if adenomas are found, the number and size of the adenomas often predict the polyp findings at subsequent follow-up colonoscopies. As a result, patients can be risk-stratified according to the number and size of the adenomas that are found at initial colonoscopy.[16] At the next follow-up, the patient is re-stratified according to the new colonoscopic findings.[16] A summary of the stratification process is illustrated in Figure 2.

Surveillance following adenoma removal

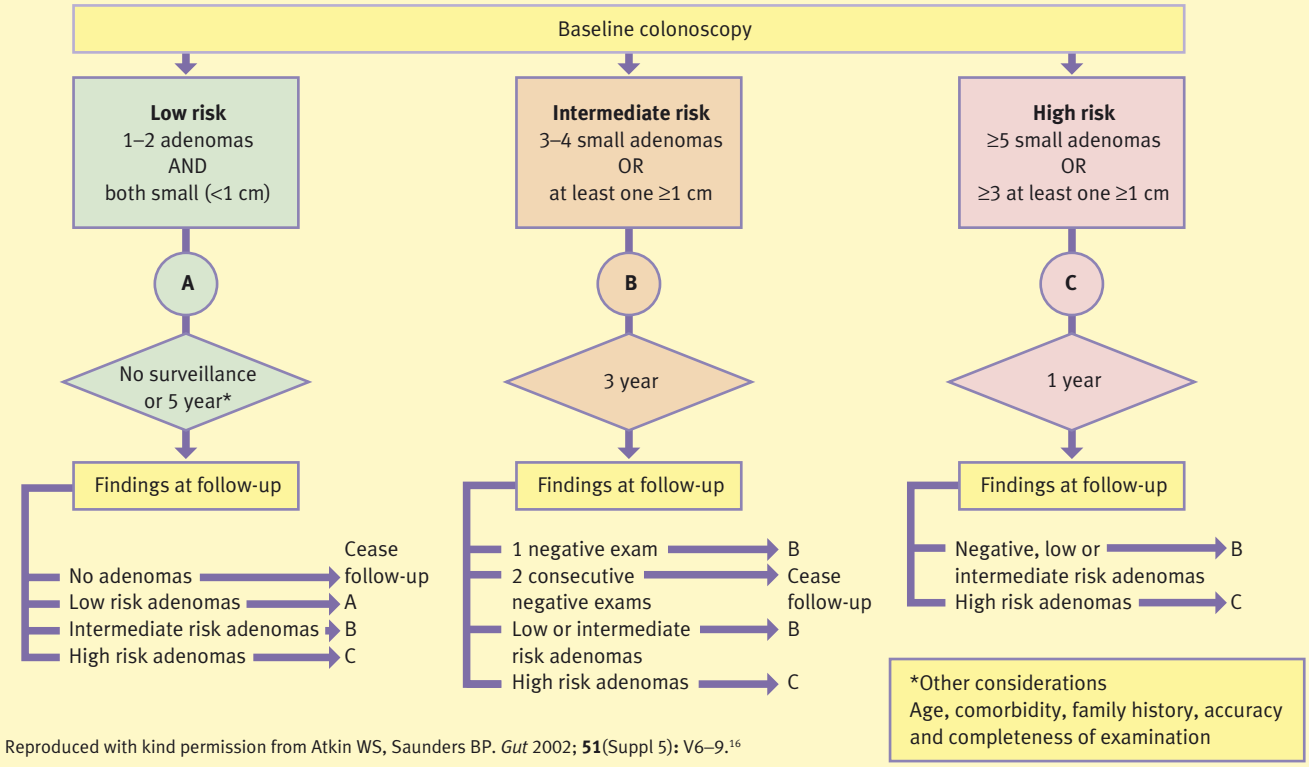

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Figure 2

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Prevention through surveillance of patients at above-average risk of CRC

For patients with a higher risk of CRC compared to the general population (e.g. inherited CRC syndromes and IBD), early detection of CRC depends on appropriate surveillance programmes. Strong evidence (Level II) has shown that surveillance of HNPCC patients reduces both the incidence of CRC and the risk of mortality from CRC[17] associated with this syndrome. Furthermore, surveillance frequency for HNPCC is based on the early age of presentation with the disease (median age 40–45 years) and the likelihood that progression from adenoma to invasive carcinoma is more rapid than sporadic CRC – sometimes within three years of a clear colonoscopy. In contrast to HNPCC, the disease profiles and risks for FAP, IBD and familial CRC are all different, and therefore different surveillance guidelines are required.[18–20] These guidelines are summarized in Table 2, but they remain flexible and practice standards will evolve as new data are published.

Prevention and early diagnosis through UK Government initiatives

The 'NHS Cancer Plan', introduced to reform cancer services, directed that, by 2005, the time from GP referral to treatment for all cancers should be a maximum of 62 days. The initiative introduced the two-week wait rule (TWR) and the 'two-week wait clinics'. An implicit benefit of the rule is the earlier diagnosis and treatment of CRC and, therefore, better survival rates for patients. However, although 99.5% of patients referred via the TWR are seen within the specified time, a recent study has shown that less than 25% of CRC cases were diagnosed through these clinics.[21] Most CRC patients still present through the emergency services and other routes (e.g. general medical or surgical outpatients). This suggests that for most CRC patients the TWR has had little impact. To optimize the benefits of the TWR, factors that inhibit its efficiency need to be explored. The reasons for delays are multiple and include patient, primary and secondary care factors. In the primary care setting, early referral via the TWR is available for patients with 'at risk' symptoms/signs, but delays still exist where, for example, the doctor gets 'locked' into the wrong diagnosis or makes a routine referral because TWR criteria are either not met or not included.[22] In practice, therefore, it may be necessary for all patients with suspicious symptoms, not just those who meet TWR criteria, to have rapid investigation. This could be via GP direct access colonoscopy or the 'direct to test' approach where a consultant receives a referral and arranges investigation prior to a clinic visit. Clearly this would require a significant improvement in colonoscopy services, especially since hospital waiting times, particularly for

Summary of the guidelines on colonic surveillance programmes for patients at increased risk of CRC

Disease	Risk	Colonic surveillance/surgery (guidelines)
HNPCC[18]	80% for CRC (13–20% for gastric cancer and ≥40% for endometrial cancer)	(i) Biennial colonosopy from 20–25 years old, or 5 years before the age of diagnosis of the youngest affected relative. Continue until 75 years old. If CRC diagnosed: surgical resection and prophylactic surgery (high risk of metachronous CRC) (ii) If documented mismatch repair gene mutation: consider prophylactic surgery with endoscopic surveillance if the rectum is retained because the risk of rectal cancer is 3% every 3 years for the first 12 years
FAP[18]	CRC almost certain without prophylactic surgery	(i) If patient is from a FAP family, but there is no documented mutation: annual flexible sigmoidoscopy (F/S) from puberty until 30 years old. Attenuated forms of the disease exist, therefore F/S every 3–5 years from 30–60 years of age (ii) If documented APC mutation or ≥100 adenomatous polyps: prophylactic surgery. If the rectum is retained, annual endoscopic review (risk of cancer in the retained rectal stump is 12–29%)
Familial CRC[20]	1:6 if two affected first-degree relatives, 1:10 if one <45 years old	Total colonic evaluation either after first consultation on family history or between 35–40 years old (whichever is later) to identify patients with adenomas/CRC. If no adenoma/CRC at first colonoscopy, repeat surveillance at 55 years old If no adenomas at 55 years of age, patients' degree of risk is probably equivalent to that of the general population
IBD[19]	5–8% after 20 years 18% after 30 years	(i) First surveillance colonoscopy 8–10 years after the onset of disease; surveillance every three years for next 10 years (ii) biennial colonoscopy for patients with a 20–30-year history, and annual colonoscopy if >30 years' history
CRC[24]	50% recurrence	80% of recurrences within 2 years, therefore close follow-up in this period. CT, CEA and patient symptoms are the principal means of detecting recurrence. Current guidelines suggest liver imaging for asymptomatic patients at least once within 2 years of resection. CRC patients are predisposed to further adenomas and metachronous cancers, therefore surveillance colonoscopy, repeated every 3 to 5 years depending on local guidelines, is recommended.

For HNPCC and FAP, families are advised also to register with the Regional Clinical Genetics Centre.
HNPCC, hereditary non-polyposis colorectal cancer; FAP, familial adenomatous polyposis; APC, adenomatous polyposis coli; CRC, colorectal cancer; IBD, inflammatory bowel disease; CEA, carcinoembryonic antigen.

Table 2

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colonoscopy and CT scans, are significant in many units. The common factor to improve the efficiency of the TWR is rapid access to high-quality colonoscopy, the current gold-standard investigation.

Prevention and early diagnosis – the future

Screening promises to improve the detection of early CRC and ultimately contribute to its prevention. However, FOBT as a single test is currently limited because of its low sensitivity and inadequate specificity, but if complemented by another non-invasive test, sensitivity could be significantly improved. Various potential 'complementary' non-invasive tests are currently being developed, such as faecal DNA tests and molecular tests on isolated colonocytes.[23] However, the availability of these tests for clinical investigation is still in the future. Consequently, continuing patient education about lifestyle, symptoms of CRC and screening, as well as promoting and funding initiatives to expedite diagnosis, staging and treatment of CRC, are vital to help prevent the mortality and morbidity associated with the disease. ◆

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