Colorectal cancer: prevention and early diagnosis

Shivaram K Bhat

James E East

Abstract

Colorectal cancer (CRC) is one of the leading causes of cancer death worldwide. This article examines strategies for the prevention and early diagnosis of CRC, and reviews the aetiology and risk factors for CRC. Preventative strategies involve improving modifiable risk factors through public health awareness. Patients known to be at higher risk of CRC development, such as those with a genetic predisposition or long-standing inflammatory bowel disease, should undergo endoscopic surveillance in order to detect early cancer or polyps. Population screening for CRC is now strongly established as an effective method for the early detection of CRC and prevention through polypectomy. Screening has been shown to improve the stage of disease at diagnosis and CRC-specific mortality. This article will highlight recent developments in the understanding of the serrated pathway for CRC development and discuss the clinical relevance of this in terms of cancer prevention, as well as exploring future directions for research into the prevention and early diagnosis of CRC.

Keywords Colonoscopy; colorectal cancer; colorectal polyps; screening; surveillance

What's new?

- Improved understanding of the serrated pathway in the development of colorectal cancer
- The importance of high-quality endoscopic examination to detect and remove adenomas and sessile serrated polyps in the colon
- Research continues into the optimal population screening strategy between colonoscopy, flexible sigmoidoscopy, and stool blood and DNA testing
- A large, population-based, randomized UK trial has demonstrated that once-only flexible sigmoidoscopy between the ages of 55 and 64 years reduces colorectal cancer incidence and mortality

Introduction

Colorectal cancer (CRC) is the fourth most common cancer in the UK and the second most common cause of cancer death.[1] The incidence of CRC increases with age; the median age at diagnosis is 70 years.[2] The lifetime risk in the UK is approximately 6%. CRC is more common in men than in women with a male:female ratio of 13:10. When detected early CRC is highly treatable, with survival rates of over 90% at 5 years for patients with early stage (stage I) disease (localized to the bowel wall). Patients with regional spread (stage III) have a worse prognosis with approximately 65% surviving at 5 years. However, only a minority of symptomatic patients are detected with early stage disease, so strategies for the prevention and early detection of CRC are vitally important to improve survival from CRC. The prevention of CRC involves tackling modifiable risk factors through health promotion, surveillance of patients deemed at high risk, and screening of the population.

Shivaram K Bhat *PhD MRCP is a Specialty Registrar in Gastroenterology at Antrim Area Hospital, Antrim, UK. Research interest: Gastrointestinal endoscopy, cancer epidemiology. Competing interests: none declared.*

James E East *MD (Res) FRCP is Consultant Gastroenterologist and Endoscopist at Translational Gastroenterology Unit, Experimental Medicine Division, Nuffield Department of Clinical Medicine, University of Oxford, John Radcliffe Hospital, Oxford, UK. Research interest: Gastrointestinal endoscopy, early detection of colorectal cancer. Competing interests: Research Funding: Olympus, Cosmo technologies; Speaker: Olympus, Abbvie.*

Aetiology and risk factors

Colorectal cancer may develop over a number of years, with dysplastic adenomas the most common precursor lesion. CRC is thought to develop through the 'adenoma – carcinoma sequence', the term used to describe the stepwise progression from adenomatous polyp to cancer. A series of genetic mutations in oncogenes (e.g. KRAS and c-myc), tumour suppressor genes (e.g. APC and p53) and DNA repair genes occur over time resulting in neoplastic progression from polyp to cancer. Our understanding of the genetics of CRC has come about largely through studying familial cases of CRC. Hereditary non-polyposis colorectal cancer (HNPCC; Lynch syndrome) and familial adenomatous polyposis (FAP) are the most common familial CRC syndromes, but together account for less than 5% of all CRC cases.[3]

In recent years the 'serrated pathway' for development of CRC has become better understood. Colorectal polyps were previously broadly categorized into two groups, adenomatous polyps, which were thought to be the sole precursor to CRC, and hyperplastic polyps, which were thought to be benign. However, over time it has become clear that another pathway involving hyperplastic polyps and related lesions such as sessile serrated adenomas could result in progression to CRC.[4] It is now thought that 20–30% of CRC cases arise through this 'serrated pathway'.

A number of risk factors for the development of CRC have been established through epidemiological studies (Table 1). Increased age, male sex, family history of CRC, smoking, obesity and dietary factors are all known to play a role. Modifiable risk factors such as diet and smoking can be tackled through public health promotion campaigns. Non-modifiable risk factors allow categorization of patients at higher risk, who can then be selected for surveillance programmes.

Diet, lifestyle and colorectal cancer

The relationship between diet and development of CRC has been examined in a number of studies and is complex. The European

Factors associated with colorectal cancer

	Increased risk	Decreased risk
Modifiable	Smoking	Dietary fibre
	Excess alcohol	Large bowel endoscopy
	Obesity	Aspirin
	Red meat	Physical activity
Non-modifiable	Increased age	
	Male sex	
	Family history/known genetic risk	
	Inflammatory bowel disease	
	Acromegaly	

Table 1

prospective investigation into cancer and nutrition (EPIC) study is one of the largest cohort studies conducted worldwide. It reported a linear decrease in the risk of colorectal cancer with increasing fibre intake, a finding confirmed by meta-analyses.[5] Increased red meat consumption has previously been associated with an increased risk of CRC, but meta-analyses have suggested weak associations between red meat consumption and CRC risk.[6] Increased fish consumption (80 g or more) has been shown to be protective.

Obesity has been shown in epidemiological studies to be associated with increased risk of CRC. The mechanisms are poorly understood but the metabolic syndrome, insulin resistance and modifications in concentrations of adipocytokines are thought to play a role.[7] Conversely, increased physical activity has been shown to be protective against CRC. Proposed mechanisms include the increase in gut motility, decreasing insulin and insulin-like growth factor concentrations, decreasing obesity, and altered prostaglandin concentrations.[8]

As in other cancers, smoking has been shown to be a risk factor for the development of CRC. In the EPIC study the risk of CRC was increased in both 'ever smokers' and former smokers compared with 'never smokers'. The study also showed that smokers who had not smoked for at least 20 years had a similar risk of developing CRC to that of 'never smokers'.[9]

Research into diet, smoking and lifestyle has assisted in guiding public health messages for the primary prevention of CRC in the population.

Surveillance of high-risk groups

Colonoscopic surveillance is recommended in groups of patients known to be at higher risk of development of CRC.[10] Guidelines currently recommend surveillance in patients with a known inherited genetic predisposition, such as HNPCC or FAP, or a strong family history of CRC, and in patients with long-standing colitis.[11] Surveillance intervals vary according to risk, with patients deemed to be at higher risk of CRC development being surveyed more frequently. For example, in patients with long-standing colitis, surveillance colonoscopy is initially offered after 10 years, with subsequent surveillance between every 1–5 years dependent on the severity and extent of the colitis. Patients with previous colorectal cancer may be offered surveillance in an attempt to identify tumour recurrence or adenomas, but the evidence of clear clinical benefit from these strategies is weak.[11]

Surveillance following adenoma removal

Patients with previously detected adenomas are at risk of developing further adenomas, and are usually offered endoscopic surveillance between every 1 and 5 years based on the size and number of polyps detected (Figure 1). The practice of endoscopic removal of polyps in an effort to prevent future CRC is supported by evidence from several studies. In the US National Polyp Study polypectomy was shown to reduce both the incidence of subsequent CRC and CRC mortality.[12] More recent studies have shown that the quality of endoscopic examination is likely to be of importance, measured by adenoma detection rate. In a US study, increased adenoma detection rate was inversely associated with the risk of subsequent development of CRC.[13] Advanced polypectomy removal techniques such as endoscopic mucosal resection (EMR) now allow very large polyps several centimetres in size, which would otherwise have required surgical resection (with a high risk of operative mortality), to be safely removed endoscopically.[14]

Prevention of colorectal cancer through screening

Population-based screening for CRC has begun relatively recently in many countries worldwide with the UK Bowel Cancer screening programme beginning in England in 2006. The aim of screening is to identify CRC at an earlier, more treatable stage to improve clinical outcome. Screening can also identify and remove colorectal polyps, the precursors to cancer, thereby reducing the risk of CRC development in screened patients. The evidence supporting screening has accumulated over time, with several large trials showing a reduction in CRC mortality with initial screening using faecal occult blood (FOB) testing.[15] Patients with a positive FOB test are subsequently offered colonoscopy. A systematic review showed an approximate 25% relative risk reduction in colorectal cancer mortality in screened patients compared to unscreened.[15] In England, screening using FOB testing is offered to men and women in the general population every 2 years between the ages of 60 and 74 (Figure 2); other UK nations have variations in entry criteria. Research has shown that in the screened population CRC is detected at a significantly earlier stage than in a non-screened population.[16]

Methods of screening

Debate exists as to the optimal test to use for CRC screening. The advantages of initial FOB testing are its relatively low cost and the clinical trials supporting its use. However, FOB testing has lower sensitivity compared to other more expensive faecal tests such as the faecal immunochemical test (FIT). In addition, the principle behind FOB testing is the detection of blood in the stool and not all colonic lesions will bleed. There is an argument for the initial use of structural screening tests, such as colonoscopy or flexible sigmoidoscopy, which allow the detection and removal of polyps that may not always bleed.[17] A large multicentre study performed in the UK suggested that a once-only