Colorectal cancer: prevention and early diagnosis

Krista Stockenhuber

James E East

Abstract

Colorectal cancer (CRC) is one of the leading causes of cancer deaths worldwide. This article reviews the aetiology and risk factors for CRC and focuses on strategies for prevention and early diagnosis. Prevention involves identifying and optimizing modifiable risk factors through public health awareness as well as population screening, for example using detection of occult blood in stool. Endoscopic surveillance in the UK is currently performed on a population basis with the bowel scope programme and faecal immunochemical testing, with colonoscopy reserved for patients known to be at higher risk of developing CRC. These include individuals with genetic predisposition or long-standing inflammatory bowel disease. Population screening for CRC is well established in clinical practice as an effective method for early cancer detection and prevention through polypectomy. It is effective at improving disease stage at diagnosis and thus reducing CRC-specific mortality. Recent changes to the NHS screening programmes and advances in the understanding of the serrated pathway for CRC development are highlighted and their respective roles for cancer prevention discussed. Finally, future directions in technology and research for prevention and early diagnosis of CRC, including computer-aided diagnosis (deep learning), are explored.

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

Introduction

Colorectal cancer (CRC) is the fourth most common cancer in the UK and accounts for 10% of all cancer deaths, making it the second most common cause of cancer death. The incidence of CRC increases with age, with the median age at diagnosis being 70 years;[1] the lifetime risk in the UK is approximately 6–7%.

Krista Stockenhuber MD DPhil MRCP *is a Core Medical Trainee at the Translational Gastroenterology Unit, Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Oxford, UK. Her research interests are gastrointestinal immunology and gastrointestinal endoscopy. Competing interests: none declared.*

James E East MD (Res) FRCP *is a Consultant Gastroenterologist and Endoscopist, and Associate Professor, at the Translational Gastroenterology Unit, Nuffield Department of Clinical Medicine, and Oxford NIHR Biomedical Research Centre, University of Oxford, John Radcliffe Hospital, UK. His research interests are gastrointestinal endoscopy and early detection of colorectal cancer. Competing interests: JEE is on the Clinical Advisory Boards of Lumendi and Boston Scientific, and is a speaker for Olympus and Falk.*

Key points

- There is improved understanding of the serrated pathway in the development of colorectal cancer

- High-quality endoscopic examination is important to detect and remove both adenomas and sessile serrated polyps in the colon

- Advanced endoscopic techniques such as endoscopic mucosal resections performed in experienced centres increasingly lead to organ preservation and reduced need for surgical intervention

- Focus on optimal population screening strategy between colonoscopy, flexible sigmoidoscopy, and stool blood and DNA testing and ongoing research in these areas

- The faecal immunochemical test for haemoglobin and one-off flexible sigmoidoscopy form the pillars of the National Health Service bowel cancer screening programme, starting at age 60 and 55 years, respectively

CRC is more common in men than women, affecting 1 in 15 men and 1 in 18 women.

When detected early, CRC is curable, with survival rates of >90% at 5 years for patients diagnosed with early stage (stage I) disease. Patients with regional spread (stage IIIC) have a worse prognosis, with approximately 50% surviving at 5 years. Symptomatic patients are often diagnosed with advanced 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 high-risk patients and population-based screening programmes.

Aetiology and risk factors

CRC can develop over a number of years, with dysplastic adenomas the most common precursor lesion. Most 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*, *c-myc*), tumour suppressor genes (e.g. *APC*, 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 largely through studying familial instances of CRC, which make up 35% of cases. Hereditary non-polyposis CRC (Lynch syndrome) and familial adenomatous polyposis are the most common familial CRC syndromes but together account for <5% of all CRC. In 2017 the National Institute for Health and Care Excellence recommended that DNA mismatch repair testing be offered to all people with CRC when first diagnosed, to screen for Lynch syndrome.

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, thought to be the sole precursor of CRC; and hyperplastic polyps, believed to be benign. It has, however, become clear that another pathway involving serrated polyps (sessile serrated lesions) can result in progression to CRC via *BRAF* mutations and CPG island methylation. It is now thought that 15−30% of CRC cases arise through this 'serrated pathway', demonstrating the importance of recognizing and resecting these premalignant lesions in screening endoscopy.[2]

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 such as monogenetic predispositions or inflammatory bowel disease can lead to enhanced identification of high-risk individuals and subsequently stratification into appropriate surveillance programmes.

Diet, lifestyle and CRC

The relationship between diet and development of CRC is complex and has been examined in a number of studies. The European 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 CRC with increasing fibre intake, a finding confirmed by meta-analyses. Increased consumption of red and processed meat has previously been associated with an increased risk of CRC, although meta-analyses have suggested weak associations between red meat consumption and CRC risk. Increased fish consumption (80 g or more per week) is considered to be protective.

In epidemiological studies, obesity has been associated with increased risk of CRC. The underlying mechanisms are poorly understood but the metabolic syndrome, insulin resistance and modifications in adipocytokine concentrations are thought to play an important role. Conversely, increased physical activity protects against CRC, potentially because of increased gut motility, decreased insulin and insulin-like growth factor concentrations, reduction and prevention of obesity, and modification of prostaglandin concentrations.

It is becoming increasingly evident that the gut microbiome has a substantial impact on intestinal health. Pre-clinical data provide evidence that the microbiome influences gut inflammation and carcinogenesis. As highlighted above, diet is a contributing factor to CRC development, and the gut flora is strongly modified by a person's diet. Further evidence is needed to decipher the specific role of the microbiota in CRC and how this could potentially be therapeutically manipulated to prevent CRC.

In the USA, the incidence and mortality rates for CRC are highest among the African−American population However, the causes underlying these higher rates are not fully understood and are currently mainly attributed to differences in diet, access to healthcare and health literary among this section of the US population. Research is currently underway to improve our understanding of the complex interplay between genetic predisposition and the above-mentioned lifestyle factors in African−American individuals.

As with many other cancers, smoking is a risk factor for the development of CRC. The risk of CRC was increased in current and former smokers compared with those who had never smoked according to the results of the prospective EPIC cohort study, which investigated modifiable risk factors in CRC. However, EPIC also highlighted that the risk of developing CRC in former smokers returned to levels similar to those of non-smokers after 20 years' abstinence.

Research into diet, smoking and lifestyle has helped to guide public health messages for the primary prevention of CRC.

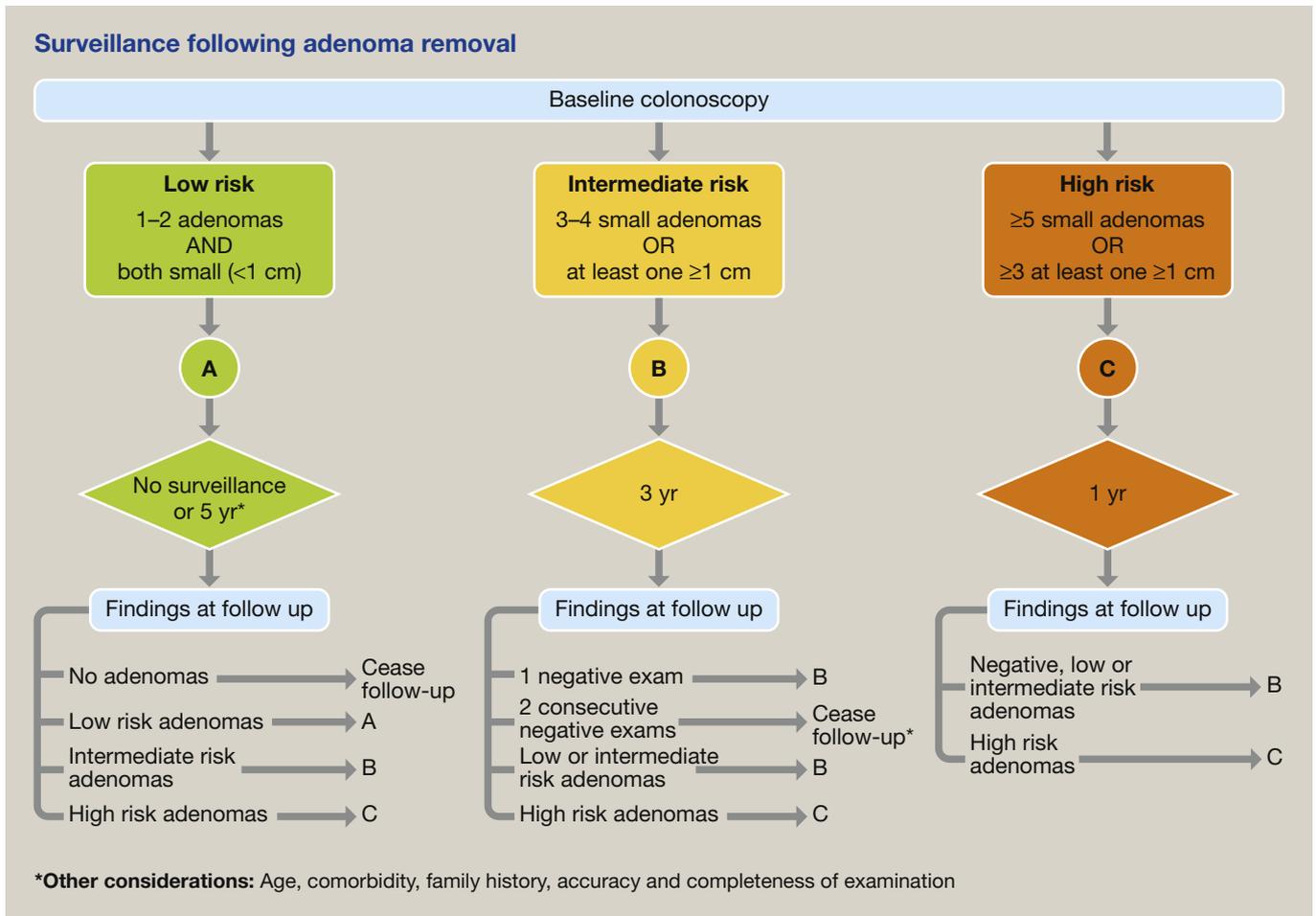### Surveillance of high-risk groups

Colonoscopic surveillance is recommended in individuals known to be at higher risk of developing CRC. Guidelines currently recommend surveillance in individuals with known monogenetic predisposition such as Lynch syndrome or familial adenomatous polyposis, a strong family history of CRC or long-standing colitis. Surveillance intervals vary according to individual risk, with patients deemed to be at higher risk of CRC development being most frequently surveyed. For example, in patients with long-standing ulcerative colitis a surveillance colonoscopy is initially offered after 10 years, with subsequent surveillance every 1−5 years depending on the severity and extent of colitis. Patients with previous CRC can be offered surveillance in an attempt to identify tumour recurrence or *de novo* premalignant lesions; however, the evidence of clear clinical benefit from these strategies is weak.

Surveillance after removal of adenoma

Patients with previously detected adenomas are at risk of developing further adenomas and are usually offered endoscopic surveillance every 1−5 years based on the size and number of polyps detected (Figure 1). The practice of endoscopically removing 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 both reduce both the incidence of subsequent CRC and mortality from CRC.[3] More recent studies have shown that the quality of endoscopic examination is likely to be important; this is measured by adenoma detection rate. In a US study, an increased adenoma

Risk factors for CRC		
	Increased risk	**Decreased risk**
Modifiable	Smoking	Dietary fibre
	Excess alcohol	Large bowel endoscopy
	Obesity (metabolic syndrome)	Aspirin
	Red and processed meat	Physical activity
Non-modifiable	Increased age	
	Male sex	
	Family history/mendelian genetic risk	
	Inflammatory bowel disease	
	Acromegaly	

Table 1

MEDICINE 47:7   396

Surveillance following adenoma removal

Baseline colonoscopy

Low risk 1–2 adenomas AND both small (<1 cm)	**Intermediate risk** 3–4 small adenomas OR at least one ≥1 cm	**High risk** ≥5 small adenomas OR ≥3 at least one ≥1 cm
A	B	C
No surveillance or 5 yr*	3 yr	1 yr

Findings at follow up

Low risk:
- No adenomas → Cease follow-up
- Low risk adenomas → A
- Intermediate risk adenomas → B
- High risk adenomas → C

Intermediate risk:
- 1 negative exam → B
- 2 consecutive negative exams → Cease follow-up*
- Low or intermediate risk adenomas → B
- High risk adenomas → C

High risk:
- Negative, low or intermediate risk adenomas → B
- High risk adenomas → C

***Other considerations:** Age, comorbidity, family history, accuracy and completeness of examination

Figure 1 Summary of British guidelines for endoscopic surveillance after adenoma removal. Reproduced from Atkin WS, Saunders BP. Surveillance guidelines after removal of colorectal adenomatous polyps. *Gut* 2002; **51**(Suppl V): v6–v9 with permission from BMJ Publishing Group Ltd.

detection rate was inversely associated with risk of subsequent development of CRC.

Advanced polypectomy removal techniques such as endoscopic mucosal resection allow the safe endoscopic removal of very large polyps of up to 10 cm in size, which would previously have required surgical resection. These advanced techniques allow organ preservation in patients who might otherwise have been at high risk of perioperative mortality and a deterioration in quality of life.[4] It is recommended that these complex procedures are carried out at high-volume tertiary centres.

Endoscopic follow-up after polyp detection at index colonoscopy can be based on polyp type, size, dysplasia and quantity of detected lesions. The European Society of Gastrointestinal Endoscopy recommends that follow-up for high-risk patients should occur at intervals of between 3 and 5 years. However, it recommends that patients with low-risk lesions such as one or two tubular adenomas <10 mm, or low-grade dysplasia or serrated adenomas <10 mm without dysplasia, can be referred to standard national screening programmes. This approach may be incorporated into future UK guidelines.
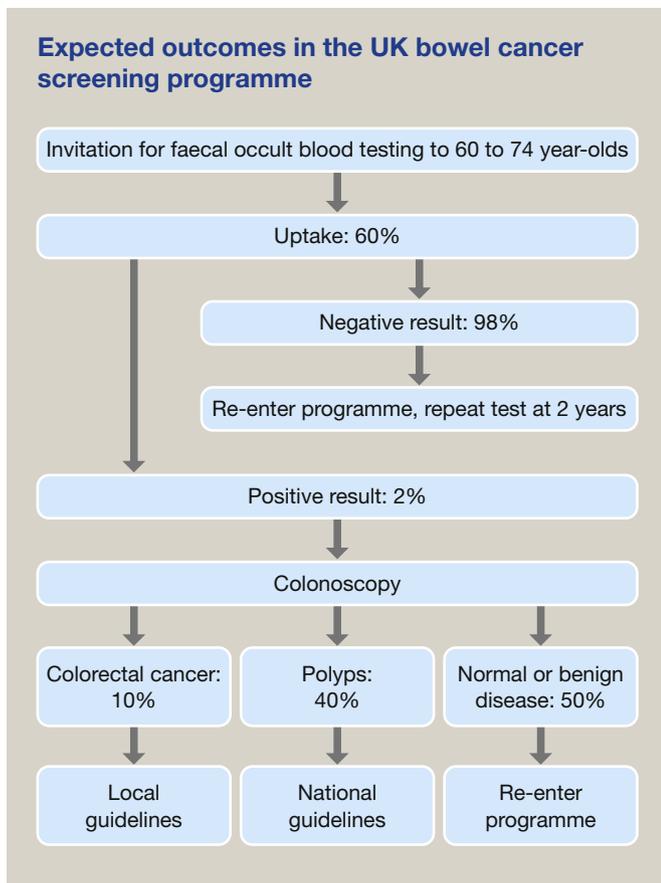
Prevention of CRC through screening

Many countries worldwide now employ a population-based screening programme for CRC. The UK bowel cancer screening programme began in England in 2006 with the aim of identifying CRC at an earlier stage when curative treatments are most effective, thus improving clinical outcome and survival. Screening also identifies colorectal polyps before transition to malignant tumours and allows for polypectomy during endoscopy. This potentially reduces the risk of CRC development in screened individuals.

Stool screening with guaiac faecal occult blood testing (gFOBT) or faecal immunochemical testing (FIT) for human haemoglobin in stool detects individuals at risk of CRC, and those with positive tests are invited for colonoscopy. FIT may be able to detect more individuals with adenomas and therefore have a greater preventive role than gFOBT. A systematic review demonstrated an approximately 25% reduction in relative risk of CRC mortality in individuals screened with gFOBT compared with the unscreened population.

In England until 2018, screening using gFOBT testing was offered every 2 years to men and women in the general population who were aged 60–74 years; however, other UK nations have variations in their entry criteria (Figure 2). Recent studies and cost-effectiveness analyses have demonstrated that FIT has a higher sensitivity as well as better acceptance among the general population due to ease of use and single stool sample requirement. FIT is now replacing gFOBT in the NHS bowel cancer

Expected outcomes in the UK bowel cancer screening programme

Invitation for faecal occult blood testing to 60 to 74 year-olds

↓

Uptake: 60%

↓

Negative result: 98%

↓

Re-enter programme, repeat test at 2 years

Positive result: 2%

↓

Colonoscopy

↓ ↓ ↓

| Colorectal cancer: 10% | Polyps: 40% | Normal or benign disease: 50% |

↓ ↓ ↓

| Local guidelines | National guidelines | Re-enter programme |

Figure 2 . Adapted from Ballinger AB, Anggiansah C. Colorectal cancer. *Br Med J* 2007; **335**: 715—8 with permission from BMJ Publishing Group Ltd.

screening programme, to eventually include individuals between 50 and 74 years of age.

Methods of screening

All methods used in CRC screening have advantages and disadvantages. Depending on the type of stool test, the detection rate varies, leading to either missed cancers or false-positive results; individuals are therefore subjected to further colonoscopies, with their attendant (albeit small) complication rate. FIT cut-off levels differ internationally in terms of the concentration of haemoglobin at which the results is considered positive. However, the overall benefits of these simple tests are the relative low cost and good population uptake. gFOBT and FIT rely on the detection of blood in stool; however, not all pre-cancerous and cancerous colonic lesions bleed.

There are benefits to an initial use of structural screening tests such as colonoscopy or flexible sigmoidoscopy, which allow the detection and removal of polyps regardless of their propensity to bleed. A large multicentre study performed in the UK suggested that a once-only flexible sigmoidoscopy performed in men and women between the ages of 55 and 64 was effective at reducing the incidence and mortality of CRC, continuing to reduce the incidence and mortality of CRC almost two decades later.[5]

The roll-out of a flexible sigmoidoscopy screening programme in the UK (bowel scope) is currently underway. The rationale for this approach is that approximately two-thirds of CRCs, and the preceding adenomas, in younger patients are located in the rectum or sigmoid colon, making these detectable by flexible sigmoidoscopy. Furthermore, for individuals being screened, it is a quicker investigation than colonoscopy and does not require full bowel preparation or sedation.

Chemoprevention

Chemoprevention refers to the use of oral medication to reduce the risk of CRC development. Aspirin and other non-steroidal anti-inflammatory agents are the most widely studied agents that can be used for CRC prevention. These drugs inhibit the enzymes cyclooxygenase-1 and cyclooxygenase-2. These enzymes are part of a pathway thought to play a role in the development of adenomatous polyps.

Studies have suggested that long-term aspirin use might be of benefit in reducing the occurrence of CRC; however, the greater risk of bleeding with high-dose aspirin and the short follow-up time within the trials have limited the use of aspirin in the primary prevention of CRC. In a larger study that followed up the outcomes of four trials of the use of low-dose aspirin for vascular events over a 20-year period, aspirin was found to reduce both the incidence of and mortality from CRC. Because of the unclear benefit, aspirin is not currently routinely recommended for the chemoprevention of sporadic CRC; however, the Colorectal Adenoma/Carcinoma Prevention Project 2 CAPP2 study suggested a chemopreventive effect of aspirin in Lynch syndrome.

Prevention and early diagnosis − the future

Future research into improving CRC outcomes will undoubtedly concentrate on prevention and early diagnosis. Uncertainty remains around specific aspects of diet, nutrition and lifestyle that could allow a further reduction of CRC incidence through a population-wide optimization of these risk factors.

Population screening has already demonstrated substantial benefits for detection of early-stage disease and mortality from CRC. Improvements have been made to screening techniques, uptake of screening and the target population screened. Research into blood-based or other stool-based screening methods such as blood-based DNA methylation or stool methylation might further improve both the uptake of screening and the sensitivity of testing. A better understanding of the serrated pathway for CRC development has led to an increase in efforts to identify and remove serrated lesions at endoscopy. Advances in endoscopic equipment and technique have improved adenoma detection rates and led to the possibility of *in vivo* polyp characterization with 'optical biopsy'; with this, the endoscopist would determine the pathology and not send lesions for pathological examination, with cost savings.

The role of artificial intelligence and computer vision supported by deep-learning algorithms promises a revolution in endoscopy practice. These have the potential to increase polyp detection rates, and also assist the endoscopist with decisions of when to leave lesions *in situ*, when to remove them without sending the tissue for histology, and when to proceed with conventional removal and pathohistological analysis. However,

398

these novel techniques require in-depth validation, further research and operator training before they can be routinely recommended.

KEY REFERENCES
1 Siegel R, DeSantis C, Virgo K, et al. Cancer treatment and survivorship statistics. *CA Cancer J Clin* 2012; **62:** 220—41.
2 East JE, Atkin WS, Bateman AC, et al. British Society of Gastroenterology position statement on serrated polyps in the colon and rectum. *Gut* 2017; **66:** 1181—96.
3 Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med* 2012; **366:** 687—96.
4 Moss A, Bourke MJ, Williams SJ, et al. Endoscopic mucosal resection outcomes and prediction of submucosal cancer from advanced colonic mucosal neoplasia. *Gastroenterol* 2011; **140:** 1909—18.
5 Atkin W, Wooldrage K, Parkin DM, et al. Long term effects of once-only flexible sigmoidoscopy screening after 17 years of follow-up: the UK Flexible Sigmoidoscopy Screening randomised controlled trial. *Lancet* 2017; **389:** 1299—311.

TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1
A 65-year-old man underwent a follow-up colonoscopy. Three years previously he participated in the UK bowel cancer screening programme and had a positive test for faecal occult blood. At colonoscopy 3 adenomas, all <1 cm in size, were detected and successfully removed. The follow-up colonoscopy was now normal.

What is now the most appropriate follow-up plan for this patient?
A) No further follow-up required
B) Follow-up colonoscopy in 5 years
C) Yearly tests with faecal immunochemical test (FIT)
D) Follow-up colonoscopy in 3 years
E) Follow-up colonoscopy in 10 years

Question 2
A middle-aged woman presented with a 2-month history of altered bowel habits. She had no significant medical history. Her father was found to have colorectal cancer, aged 80.

Investigations
Colonoscopy, 15 mm polyp removed. Histology confirmed colorectal cancer.

Under which circumstances should testing for Lynch syndrome be offered?
A) This should be routinely offered
B) Lynch syndrome should be tested for if she was under 50 years of age
C) This should be offered if she was aged over 60 with a family history of 2 or more close relatives with colorectal cancer
D) If she was over 50 with a family history of 1 or more close relatives with colorectal cancer diagnosed under 60
E) If she had a medical history of cancer

Question 3
A 45-year-old woman consulted her GP as she was concerned about her risk of future colorectal cancer. Her father had been diagnosed with colorectal cancer is his 70s.

Which intervention would most reduce her chance of developing colorectal cancer in the future?
A) Dietary fibre
B) Large bowel endoscopy
C) Aspirin
D) Physical activity
E) Smoking cessation

399