Abstract. Colorectal cancer (CRC) is an important public health problem: there are nearly one million new cases of CRC diagnosed world-wide each year and half a million deaths. Recent reports show that it is one of the most frequent form of cancer among people aged 75 years and older. Given that the majority of cancers occur in elderly people and with the ageing of the population in mind, this observation gives further impetus to investigating prevention and treatment strategies among this subgroup of the population. Screening recommendations and implementation is nowadays a priority and achieving CRC control is the immediate challenge.

Introduction

Most CRC, at least two-thirds and perhaps as much as 90%, arise from benign, adenomatous polyps lining the wall of the bowel. Those which grow to a large size and have a villous appearance or contain dysplastic cells are the most likely to progress to cancer.
The natural history and the role of several risk factors in the aetiology of CRC are becoming more clearly understood and the genetic events involved in this disease susceptibility are more clear for us.

While there are many questions to be solved, it is apparent that many facets of CRC are becoming increasingly understood and prospects for prevention are becoming apparent.

1. Epidemiology of colorectal cancer

Colorectal carcinoma (CRC) is the fourth most common cancer in men and the third most common cancer in women worldwide. In 2002, cancers of the colon and rectum accounted for around 1 million of all new cancer cases (9.4% of the world total), and in contrast to cancers in most other sites, only a minimal difference in incidence was observed between men and women (ratio, 1.2:1) (1).

More than 142,000 cases of CRC will have been diagnosed in the United States in 2010. These will have included around 40,000 cases of rectal carcinoma. In 2008, the age-standardised incidence rates were 34.1 per 100,000 men and 25 per 100,000 women (2).

In the European Union, 332,000 new cases were reported in 2008. Age-standardised incidence rates ranged between 27.6 per 100,000 men in Finland and 60.7 per 100,000 men in the Czech Republic (3).

Five year survival rates as high as 90% have been reported when CRC is diagnosed at an early stage. In general, the mortality rate is around half of the incidence rate. In 2002, for example, approximately 529,000 CRC-related deaths occurred in the world. Worldwide, the prevalence of CRC is second only to that of breast cancer. Research has estimated that 2.8 million CRC patients are still alive within 5 years of diagnosis (1). It is estimated that a total of 51,370 deaths will have occurred secondary to CRC in the United States in 2010, and these will have accounted for 9% of all cancer deaths. Mortality rates for CRC have decreased over the past two decades, particularly in recent years, as a result of improvements in early detection and treatment (2).

The most recent data from the European Union are those from 2008, during which 148,000 deaths occurred secondary to CRC.

A recent study compared population-based data from the 109,953 colon cancer patients of the Surveillance, Epidemiology, and End Results (SEER) programme with those from the 134,206 colon cancer patients of the National Cancer Data Base (NCDB) (4). This demonstrated that 5-year survival ranged between 76% +/- 0.3% for patients with stage I (T1-2N0) disease, and was
26.5% for patients with stage IIIC (T4N2) disease. The relative survival (i.e., cancer survival in the absence of other causes of death) was longer in cases with early stage disease, and reached a level of 97.1% +/- 0.4% for stage I. These data indicate that most patients with stage I disease in this cohort died from non-CRC related causes.

An analysis of data from the population-based registries of the National Cancer Institute (NCI) SEER programme yielded an adjusted 5-year conditional probability of survival (i.e., the probability of survival following a 5-year survival period) in which the greatest improvement was seen in cases with an advanced stage of CRC disease, and in which the rates of survival reached ≥ 80%. One exception was stage IV disease, for which the adjusted 5-year conditional probability of survival was 48% (5).

• Subsite distribution

Approximately 70% of all CRCs are located in the distal or left large bowel. However, several studies have demonstrated a shift towards an increase in proximal lesions, particularly in the incidence of right-sided cancers (6-8). It is unclear whether this is a genuine phenomenon or simply an artefact of factors such as lack of consensus across studies concerning the most appropriate division of the colorectum into anatomical subsites, or an increase in the excision of adenomatous polyps in the descending colon following screening with flexible sigmoidoscopy. An alternative hypothesis is that screening colonoscopy is more effective in protecting the left colon from cancer compared with the right colon (9). However, this effect may also be related to particular aspects of the colonoscopy procedure, such as poor right-sided bowel preparation, incomplete colonoscopy, and the presence of anatomical configurations which compromise visibility.

Research suggests that there are biological differences between right- and left-sided colon cancers. In a recent study, Meza et al. reported that adenoma initiation rates were highest for right-sided lesions, whereas adenoma growth rates were highest for left-sided lesions. This would explain why the incidence of right-sided colon cancer shows the greatest increase after the age of 70 years (10). Histological and molecular differences have also been described, including a higher incidence of the mucinous histotype, microsatellite instability, and defects in mismatch repair genes (11-13). Although the biological characteristics of proximal tumours are associated with a more favourable prognosis than those of distal lesions, proximal lesions are usually diagnosed at more advanced stages (14-15). This explains the discrepancy in survival rates across studies (14-20).
• **Age**

The risk of developing CRC increases with age. Diagnosis is rare before the age of 40 years, and incidence begins to increase significantly between the ages of 40 and 50. Around 91% of cases are diagnosed in individuals aged 50 years and above. In the United States, the probability of developing invasive CRC in individuals aged between 40 and 59 years is 1 in 110 for males and 1 in 139 for females. In individuals above the age of 70 years, the incidence increases to 1 in 22 for males and 1 in 24 for females (2).

• **Gender**

Although the incidence of CRC is similar in men and women, some gender-related differences have been reported. Studies have shown that compared to men, female colon cancer patients tend to be significantly older at presentation (21-23), have longer survival in the case of advanced disease (23-24), present more frequently in an emergency setting (23), and are more likely to develop a right-side tumour (14). These findings have implications for screening, diagnosis, and prognosis.

• **Geographical distribution**

The incidence and mortality of CRC vary markedly between countries, as shown in Figures 1 and 2. Center *et al.* analyzed variations in the rate of CRC across countries from 1953–1957 through to 1998–2002 using data from the Cancer Incidence in Five Continents databases (25). The registries with the highest incidence of CRC were located predominantly in Europe, North America, and Oceania, which probably reflects the influence of dietary and lifestyle factors. In these regions, CRC represents 12.6% of all incident cancer cases in men and 14.1% of all incident cancer cases in women (26). From 1983–1987 to 1998–2002, the incidence rates from registries in Western Europe remained stable or showed only a slight increase with the exception of Spain, where the incidence of CRC showed a marked increase. Age-standardised incidence rates of fewer than 25 per 100,000 men 20 years ago had increased to 39.7 per 100,000 men by 2008 (3, 25). This increase may be partly attributable to a change in dietary habits from a “Mediterranean” diet rich in fruits and vegetables to a western diet containing a higher proportion of red meat and saturated fat.

In men and women in the United States, the incidence of CRC increased during the period 1975–1985, and then showed a marked decline during
1985–1995. This was followed by a short and non-significant increase during the period 1995–1998. A marked decline was observed during 1998–2006, which was probably due to the initiation of large-scale screening programmes. The most rapid annual rate of decline occurred among men and women aged ≥65 years. By contrast, short-term incidence trends showed an annual increase in individuals aged <50 years (27).

The lowest rates were observed in registries from Asia, Africa, and South America. However, from 1983–1987 through to 1998–2001, the incidence of CRC increased in regions undergoing economic transition, such as countries in Eastern Europe, most parts of Asia, and certain countries in South America. These increases were mainly observed in men. Asian registries also recorded high rates in Japan, Singapore, and Israel. The recent increase in the incidence of CRC in these three countries is probably attributable to changes in environment and/or lifestyle (25).

Variation in 5-year survival has also been observed between continents. This has been estimated to be 65% in North America, 54% in Western Europe, 34% in Eastern Europe, and 30% in India (1).

**Race**

The influence of race on the incidence of CRC and survival remains unclear, although studies of migrants have suggested that environmental factors play a major role in disease aetiology (28). From 1999 to 2004, a total of 814,697 cases of invasive CRC were reported in the United States. A recent analysis of these cases revealed that the incidence was higher among black migrants (57.2 per 100,000) compared with white- (50.8 per 100,000) or Asian migrants (38.9 per 100,000). This effect was most pronounced in individuals aged <65 years. In all age groups, localized and regional cancers were diagnosed most frequently in whites and non-Hispanics, and least frequently in blacks. Conversely, distant or unstaged cancers were diagnosed more frequently in blacks (29). It is probable that these discrepancies arise from a complex interplay between genetic and environmental risk factors as well as variability in population-level screening rates and access to care.

2. **Non genetic risk factors**

a. **Behavioural risk factors**

Numerous epidemiological studies have suggested that dietary and lifestyle factors influence the risk of colon cancer. However, their findings should be interpreted with caution, since many of these studies involved
small sample sizes and sources of bias. Most of the studies performed to investigate dietary risk factors for colon cancer have used an ecological or case-control design. The cohort method is considered to be the most valid design for an observational epidemiological study. However, its use is less common in this particular field of research due to the relatively low incidence of colon cancer and the requirement for prolonged monitoring. Furthermore, many risk factors, such as obesity, a high fat diet, lack of physical activity, alcohol consumption and smoking, are intercorrelated, and thus caution should be exercised when interpreting the results for possible confounding factors.

• **Behavioural factors that may increase the risk of CRC**

  ○ **Body mass index (BMI).** Ecological studies have reported higher rates of obesity and CRC in industrialised countries. CRC ranks second in terms of both incidence and mortality in industrialised nations, compared with fifth in less developed countries (30). Two recent meta-analyses have reported an association between high BMI and CRC. The first included data from 23 cohort studies and eight case-control studies, which included a total of 70,906 CRC patients (31). Most of the study populations were from western countries. The pooled estimate indicated that individuals with a BMI of $\geq 30$ kg/m$^2$ had a 40% greater risk of CRC compared with individuals with a BMI of $<25$ kg/m$^2$ (Relative risk (RR): 1.40; 95% CI: 0.31–1.51). Evidence was found for both significant heterogeneity across cohort studies and publication bias, and the true estimate of effect for the association between obesity and CRC in this analysis was around 20% (RR: 1.19; 95% CI: 1.11–1.29). A proportion of the observed heterogeneity in estimates across studies was explained by differences in cancer location (higher association with colon cancer than with rectal cancer) and gender (higher association in men than in women). No substantial change in the results was observed following adjustment for potential confounders such as diet and physical activity.

  The second meta-analysis involved cohort studies only. This analyzed data from 15 studies and a total of 1,058,883 participants, including 6,458 CRC patients (32). The pooled RR for CRC was 1.37 (95% CI: 1.21–1.56) for men who were overweight (BMI = 25–29.9) or obese (BMI $\geq 30$), and 1.07 (95% CI: 0.97–1.18) for women.

  Available studies also suggest that obesity and obesity-related inflammation and metabolic disorders may affect the prognosis of CRC (33-34), although further research is necessary to confirm this hypothesis.
○ **Cigarette smoking.** Three recent meta-analyses have investigated the association between cigarette smoking and CRC (35-37). The first included observational studies. The other meta-analyses included prospective studies only, the majority of which were cohort studies. Compared to never-smokers, current smokers had a 7–17% higher risk of developing CRC. However, this association only reached significance in the study by Huxley *et al.* The RR for CRC mortality was significantly higher in ever-smokers compared to never-smokers in the studies of Botteri (RR: 1.28; 95% CI: 1.15–1.42) and Liang (RR: 1.40; 95% CI: 1.06–1.84). In both studies, comparisons between former-smokers and never-smokers revealed a significantly higher incidence of CRC (17–25%) and mortality (15–23%) in former smokers. In general, smokers showed a high tendency to an increased risk of rectal rather than colon cancer. The risk of CRC was also found to increase with the number of cigarettes smoked daily and the duration of smoking.

○ **Diabetes mellitus.** Most epidemiological studies investigating the relationship between diabetes and the risk of CRC have reported a positive association. Furthermore, insulin resistance and type 2 diabetes are known to be correlated with calorie-high diet, physical inactivity, and obesity, all of which are known risk factors for CRC. A meta-analysis published in 2005 included six case-control studies and nine cohort studies (38). This found that individuals with diabetes had a significant 30% increase in risk (RR: 1.30; 95% CI: 1.20–1.40). No heterogeneity across studies was found. The subgroup meta-analysis revealed similar results across studies for women and in men, and that the estimated risk was similar for colon cancer and rectal cancer. An analysis restricted to studies that had controlled for obesity and physical activity revealed a positive association between diabetes and CRC (summary RR: 1.34; 95% CI: 1.20–1.49), with no statistically significant heterogeneity across studies.

A second meta-analysis of 15 cohort studies also suggested that the risk of CRC was 23% higher in individuals with diabetes compared with unaffected individuals (RR: 1.23; 95% CI: 1.17–1.30) (35).

○ **Western diet.** In 1971, Burkitt observed that the diet and stools of native South Africans differed from those of westerners, and that these two groups showed a marked difference in the incidence of colon cancer. He proposed that the high fibre content of the native diet had a protective effect (39). A formal analysis of first epidemiological data suggested a positive association between the risk of colon cancer and dietary fat and meat, and a negative association with dietary fibre (40-43).
However, more recent studies and one meta-analysis have indicated that dietary fat \textit{per se} is not associated with an increased risk of CRC (44-45).

In a large cohort study of nearly 149,000 men and women, participants were asked to complete a questionnaire concerning their eating habits at two time-points, \textit{i.e.}, 1982 and 1992/1993 (46). A high intake of red and processed meat in 1992/1993 was associated with a higher risk of colon cancer after adjusting for age and energy intake. However, this association was not found after adjustment for BMI, cigarette smoking, and other covariates.

In terms of long-term consumption, individuals who had reported the highest intake of processed meat (1 oz of processed meat 5 or 6 days per week for men, and 2 or 3 days per week for women) in both 1982 and 1992/1993 had a higher risk of distal colon cancer (RR: 1.50; 95% CI: 1.04–2.17) compared to individuals who were in the lowest tertile of consumption at both time-points. This was also the case for the ratio of red meat to poultry and fish (RR: 1.53; 95% CI: 1.08–2.18). The most recently published meta-analysis included 26 cohort studies and data from more than 15,000 CRC cases (35). The pooled estimate for the highest vs. the lowest level of consumption was RR 1.21 (95% CI: 1.13–1.29) for red meat intake, and RR 1.19 (95% CI: 1.12–1.27) for processed meat intake. No evidence of heterogeneity across studies was found (P=0.72), and there was no significant difference in the estimates for colon cancer and rectal cancer.

These results are similar to those of a meta-analysis published in 2006. Interestingly, the authors of the 2006 meta-analysis found no change in their results after adjusting for potentially confounding factors such as physical activity, BMI, smoking, alcohol intake, total energy, and calcium (47).

\textbf{Alcohol consumption.} Alcohol consumption is one of the most important known causes of human cancer, and several studies have suggested that increased alcohol intake is a risk factor for CRC. The most recently published meta-analysis included data from 21 cohort studies (35). The authors estimated that the risk of developing a malignant tumour in the colorectum was 56% greater in individuals who were categorized as “heavy drinkers” (RR: 1.56; 95% CI: 1.42–1.70), although the criterion for inclusion in this category (\textit{i.e.}, the level of alcohol intake) was not specified. No evidence of heterogeneity across studies was found. The effect size estimates for colon and rectal cancer were similar, and both were statistically significant.

A previous meta-analysis of data from 16 cohort studies reported a 15% increase in the risk of CRC for every 100 g increase in alcohol intake per week. This association was found for both colon and rectal cancer (48).
**Behavioural factors that may reduce the risk of CRC**

- **Intake of dietary fibre, fruit, and vegetables.** Although early observations suggested that a diet rich in fibre exerted a protective effect, subsequent studies have yielded conflicting results. A large cohort study of 76,947 women and 47,279 men (49) and a meta-analysis of 13 prospective cohort studies (50) found only a minimal association between high fibre intake and a lower risk of CRC. However, this result was not statistically significant after adjustment for potential confounding variables. The meta-analysis found no association between CRC risk and the consumption of fruit or vegetables.

  In 2000, the results of a randomised trial performed to determine whether dietary supplementation with wheat-bran fibre reduces the rate of recurrence of colorectal adenomas were published (51). This had involved 1,429 adenoma patients who had undergone the removal of one or more histologically confirmed colorectal adenomas during the 3-month period before recruitment. The patients had been randomised to receive either a high- or low-fibre cereal supplement for a period of 6 weeks. Although compliance with the study protocol was high, no significant differences in recurrence rates were observed between the experimental and placebo subjects, even after adjustment for known risk factors such as randomisation period, sex, smoking status, alcohol consumption, and energy intake. Possible causes of this negative finding include an imbalance in other risk factors, the short intervention period, or the possibility that fibre may only protect against malignant change in the case of large adenomas.

- **Physical activity.** A sedentary lifestyle is associated with a higher risk of obesity, which is a known risk factor for CRC. It may also promote the development of cancer through its effects on immune function and on hormone and growth factor levels. Two meta-analyses of epidemiological studies have been published to date. The first included case-control studies and cohort studies (52), whereas the most recent meta-analysis included 27 cohort studies (35). Both meta-analyses found that the estimated reduction in colon cancer risk secondary to physical activity was around 20%. The protective effect conferred by physical activity appeared to be stronger for men than women, and for colon cancer rather than rectal cancer, and recreational physical activity rather than occupational physical activity.

- **Calcium and vitamin D.** Most epidemiological studies performed to date have suggested that increased calcium consumption (either dietary
or as a supplement) is associated with a slight decrease in CRC risk. Cho et al. performed a meta-analysis of 10 cohort studies. The pooled multivariate RR for CRC was 0.85 (95% CI: 0.78–0.94) for individuals who consumed 250 g/day of milk or more compared with participants who consumed less than 70 g/day. Every 500-g/day increase in milk consumption was associated with a 12% reduction in the risk of CRC (53). This association was found in both sexes, and was restricted to cancers of the distal colon and rectum.

Grau et al. performed a large multicentre trial to investigate the effect of calcium supplementation on the recurrence of large bowel adenomas in patients with a recently diagnosed colorectal adenoma. A total of 930 subjects were randomised to either placebo or calcium (3 g of calcium carbonate, or 1200 mg of elemental calcium) (54-55). Among subjects assigned to calcium supplementation, a statistically significant reduction in the risk of one or more recurrent adenomas was only observed in those with a baseline 25-(OH) vitamin D level that was above the median (RR: 0.71; 95% CI: 0.57–0.89; P for interaction =0.012). Calcium supplementation had no effect in subjects whose baseline 25-(OH) vitamin D levels were at or below the overall median (29.1 ng/mL). The calcium risk ratio was higher for histologically advanced neoplasms (0.65; 95% CI: 0.46–0.93) than for hyperplastic polyps (0.82; 95% CI: 0.67–1.00) or tubular adenomas (0.89; 95% CI: 0.77–1.03). The preventive effect was most pronounced in individuals with a high dietary intake of calcium and fibre and a low intake of fat. However, these interactions were not statistically significant.

A meta-analysis of 17 epidemiological studies showed an inverse association between the level of circulating 25-(OH) vitamin D and the risk of developing colorectal adenomas (Odds Ratio (OR): 0.7; 95% CI: 0.56–0.87) (56).

b. Inflammatory bowel disease

In 1925, Crohn and Rosenberg were the first to describe a case of CRC in association with inflammatory bowel disease (IBD) (57). Many subsequent studies have produced evidence in support of an association between IBD and CRC risk. Early studies may have overestimated the risk associated with IBD, since their results were frequently based upon data from hospitalised patients.

Although estimates of cancer risk in patients with ulcerative colitis (UC) differ between studies, almost all studies have demonstrated a significant association between UC and CRC. The standardised incidence ratio (SIR) ranges from 2 to 30. The cumulative incidence 25–35 years following the
assignment of a diagnosis of UC ranges from 8% to 43% (58-71). These wide differences are probably attributable to a range of factors, such as variation in dietary patterns, genetic factors, use of colonoscopy surveillance, the frequency of prophylactic colectomy, and treatment with aminosalicylates, which appear to have a protective effect.

In 2001, Eaden et al. published a meta-analysis of 116 studies which had investigated the risk of CRC in patients with UC. These studies included a total of 54,478 patients, of whom 1,698 had a diagnosis of CRC (72). The overall estimate of the prevalence of CRC was 3.7% (95% CI: 3.2–4.2) for any UC patient, and 5.4% (95% CI: 4.4–6.5) for patients with pancolitis. The incidence was higher than that in the general population. The CRC incidence rate was 3 per 1000 person years duration (pyd) (95% CI: 2/1000–4/1000) for any UC patient, and 4 per 1000 pyd (95% CI: 3/1000–6/1000) for patients with pancolitis. The CRC incidence rate in the general population was estimated to be 0.6 per 1000 pyd. No publication bias was found. For the first decade of UC, the overall incidence rate was 2 per1000 pyd (95% CI: 1/1000–2/1000). For the second and third decades, the estimated overall incidence rates were 7 per 1000 pyd (95% CI: 4/1000–12/1000) and 12 per 1000 pyd (95% CI: 7/1000–19/1000), respectively. Thus, the risk of CRC in UC was estimated to be 2% at 10 years, 8% at 20 years, and 18% at 30 years. These rates were very similar for patients with pancolitis. However, the CIs were wide, which is probably attributable to the small number of studies in the pancolitis group (n=6). In adult UC patients, the age-at-onset had no statistically significant bearing on cancer risk.

A study of 723 UC patients identified longer disease duration, extensive colitis, primary sclerosing cholangitis (PSC), and the presence of dysplasia in the biopsy specimen as risk factors for CRC (73).

Several studies have reported that PSC is a risk factor for CRC in patients with UC. However, these studies generally involved small sample sizes (74-75). The cumulative risk for CRC has been reported to be 14–16% after 10 years of IBD (74,76) and 31% after 20 years (76).

The underlying biological mechanism remains unknown, although several hypotheses have been proposed. One such hypothesis is that the abnormal bile composition in PSC exerts a carcinogenic effect (77-78). An alternative hypothesis is that since UC and PSC are often characterised by low disease activity (79); these patients tend to undergo colectomy and sulphasalazine therapy less frequently than other IBD patients.

The results of several epidemiological studies suggest that patients with Crohn’s disease (CD) have a 1.5–20-fold increase in CRC risk (80-83). In a meta-analysis of 12 studies, the overall pooled estimate for the colon cancer RR was 2.5 (95% CI: 1.3–4.7) (84). After selecting studies performed
in patients with colonic or ileal disease, the only statistically significant association was between colonic disease and CRC (RR: 4.5; 95% CI: 1.3–14.9), with no association being found with ileal disease (RR: 1.1; 95% CI: 0.8–1.5). The cumulative risk of CRC in CD patients was 2.9% (1.5–5.3%) at 10 years; 5.6% (3.1–10.4%) at 20 years; and 8.3% (4.5–15.1%) at 30 years.

Patients with IBD tend to develop CRC 15–20 years earlier than patients with sporadic cancers. In a study of 80 IBD cases, the median age at CRC diagnosis was 54.5 years (range, 32–76 years) in patients with CD, and 43 years (range, 17–75 years) in patients with UC. During the same period, the median age at diagnosis of sporadic CRC in 5,266 patients with no history of IBD (P<0.001) was 65 years (range, 7–99) (P<0.001) (85).

Patients with UC and CD tend to develop CRC in differing anatomical locations. Patients with UC develop tumours predominantly in the rectosigmoid area, whereas patients with CD frequently develop tumours in the right rectosigmoid colon. Patients with CD also have a higher risk of small bowel carcinoma compared with UC patients (84-85).

In a cohort of 920 IBD patients who were followed up for a median period of 14.8 years (86), the occurrence of CRC was not associated with an increase in mortality.

c. Colonic polyps

Adenomatous polyps have malignant potential and therefore require clinical intervention (87-88). They are classified histologically as: 1) tubular, 2) tubulovillous, or 3) villous. The reported frequency of each histological subtype varies across studies. In two large case series, tubular adenomas were the most frequent subtype (65–75%), followed by the tubulovillous (20–25%), and villous (5–9%) subtypes (89-90).

The risk of invasive malignancy was also found to differ according to histological subtype. Malignant potential was reported to be rare in tubular adenomas (2–3%), but higher in tubulovillous (6–8%) and villous adenomas (10–18%). Cancer risk also increased with polyp size, reaching 6.5–17% for adenomas that were larger than 2 cm. The most frequent anatomical location was the sigmoid colon, followed by the descending colon (89-90).

In 1992, Atkin et al. investigated a cohort of 1,618 rectosigmoid adenoma patients to assess the long-term risk of CRC following endoscopic polypectomy (91). Each patient was followed up for a mean period of 13.8 years. The incidence of CRC was found to be significantly increased in patients with a history of a rectosigmoid tubulovillous or villous adenoma, or an adenoma that was larger than 1 cm (SIR: 3.6; 95% CI: 2.4–5.0). In patients with multiple adenomas, the SIR reached 6.6 (95% CI: 3.3–11.8).
3. Inherited risk factors

The aetiology of CRC involves both genetic and environmental factors. Although some specific genetic disorders are associated with a particularly high risk of CRC, they account for less than 5% of all cases. The majority of cases have a multifactorial aetiology. Approximately 20% to 25% of cases occur in patients with a positive family history of CRC, and the remaining cases are sporadic.

• Familial adenomatous polyposis

Familial adenomatous polyposis (FAP) is an autosomal dominant disease that is characterized by the presence of hundreds of adenomatous polyps in the colon and rectum. If left untreated, this disorder can progress to CRC. FAP accounts for 1% of all CRC cases, and affects around 1 per 10,000 individuals. The penetrance of the disease approaches 100% by the age of 40 years (92).

Attenuated FAP (AFAP) is a less aggressive variant of FAP. It is characterised by the presence of fewer colorectal adenomatous polyps (usually 10 to 100), a later age-at-onset, and a lower cancer risk. Certain types of lesions (skull and mandible osteomas, dental abnormalities, and fibromas on the scalp, shoulders, arms, and back) are indicative of the Gardner variant of FAP. Patients with Turcot syndrome present with FAP and a medulloblastoma of the brain (93).

In 1991, the gene responsible for the vast majority of FAP cases, the adenomatous polyposis coli (APC) gene, was identified. In 5–30% of FAP patients, no APC mutation is identifiable through currently available genetic tests. In 2003, Varesco et al. showed that 'APC-negative' FAP patients may carry biallelic mutations in the MYH gene (94).

Until the 1950s, almost all untreated FAP patients died from CRC between the ages of 40 and 50 years. FAP also involves a variety of extracolonic manifestations. These include osteomas, epidermoid cysts, desmoid tumours, upper gastrointestinal polyps, congenital hypertrophy of the retinal pigment epithelium, and other malignancies (duodenal carcinoma, thyroid carcinoma, and hepatoblastoma). The introduction of screening programmes has reduced the prevalence of CRC and improved survival in the majority of FAP patients. It has also led to a substantial change in the pattern of mortality. At the time of writing, the most frequent causes of death in patients detected through screening programmes are duodenal cancer and desmoid tumours (95-98).
**Hereditary nonpolyposis colorectal cancer**

Hereditary nonpolyposis colorectal cancer (HNPCC) is also known as Lynch syndrome. This disorder has an autosomal dominant mode of inheritance, and is associated with an increased risk of CRC and other neoplasias, including cancers of the endometrium, stomach, ovary, urinary tract, hepatobiliary tract, pancreas, and small bowel (99). HNPCC accounts for around 2% to 3% of all CRC cases (100) and is caused by germline mutations in DNA mismatch repair (MMR) genes, in particular MLH1, MSH2, and MSH6 (101).

A study in Finland compared cancer incidence in the general population with that of a cohort of 1,763 members of 50 HNPCC families. In all cases, the diagnosis had been established through genetic testing. In mutation carriers, the authors reported an SIR for CRC of 68 (95% CI: 56–81) (102). The SIR for CRC was higher in men (SIR=83) than in women (SIR=48). The male-to-female ratio was 1.7 (95% CI: 1.2–2.7). An increased SIR was also observed for cancers of the endometrium (62; 95% CI: 44–86), ovaries (13; 95% CI: 5.3–25), biliary-tract (9.1; 95% CI: 1.1–33), uro-epithelium (7.6; 95% CI: 2.5–18), stomach (6.9; 95% CI: 3.6–12), and kidney (renal-cell adenocarcinoma) (4.7; 95% CI: 1–14), as well as for tumours of the central nervous system (4.5; 95% CI: 1.2–12). In mutation carriers, the cumulative incidence rates for CRC at 70 years were 100% in men and 54% in women.

Lynch syndrome is characterised by an early age-at-onset and a predominance of right-sided colonic tumours (103). In a cohort of mutation carriers who were participating in a surveillance programme, the mean age at initial cancer diagnosis was 40 years (104). Most first lesions arise proximal to the splenic flexure, and are usually synchronous (two or more distinct tumours separated by normal bowel) or metachronous (new nonanastomotic tumours which develop at least 6 months after the initial diagnosis) (105).

**Family history of CRC**

In a survey of around 36,000 households in the United States, approximately 5% of respondents reported having one or more first-degree relatives with CRC (106). The number of affected family members, their degree of kinship, and the age-at-onset in relatives are all factors which influence the risk of CRC. Two meta-analyses estimated familial CRC risk in first-degree relatives of CRC- and colorectal adenoma patients (107-108). Both of these studies generated a pooled estimate of RR in the presence of a first degree relative with CRC of around 2.25. This increased to 3.87 in cases in which the relative had been diagnosed with CRC before the age of 45.
years. The RR increased to 3.97–4.25 in cases with at least two affected relatives. The CRC risk was found to be greater for the relatives of patients with colon cancer compared to the relatives of patients with rectal cancer.

4. Prevention

In 1990, Fearon and Vogelstein described the molecular basis of colorectal neoplasia as a multistep, multipathway and multifocal process that ultimately requires cumulative damage to several genes within and across cellular generations (109). Research into the pathogenesis of CRC has shown that the progression from normal epithelium to adenoma and carcinoma may occur over a period of decades. It is generally accepted that most CRC evolve from adenomatous polyps, and that the removal of such polyps can prevent the transition to CRC. In the National Polyp Study, a cohort of 1,418 patients who had undergone complete colonoscopy involving the removal of a minimum of one adenomatous polyp were followed up with periodic colonoscopy for an average of 5.9 years (110). The incidence of colon cancer was 88% to 90% lower than in patients from other studies who had not undergone polyp excision, and 76% lower than in the general population.

Two main strategies to prevent CRC have been described. The first is the introduction of screening programmes for the detection and removal of precancerous adenomas. The second is chemoprevention, which involves the use of dietary substances or medications to avoid either the development of adenomas or the transition to adenocarcinoma.

a. Chemoprevention

A simple first step towards the prevention of CRC is the adoption of a series of healthy dietary and lifestyle habits. Epidemiological studies have identified several dietary and lifestyle factors that confer risk or protective effects in CRC, as described in the section “non-inherited risk factors”. The World Health Organisation recommends the avoidance of alcohol and tobacco, fatty foods and the excessive consumption of red meat, and advocates foods rich in calcium or fibre, fresh vegetables and fruit, and daily physical exercise as being beneficial (111).

A number of medications have been shown to confer a potential preventive effect. However, since studies have shown that simple biannual faecal occult blood testing achieved a 21% reduction in mortality at 18-year follow-up, and that one-off screening with sigmoidoscopy, led to a decrease in mortality of 31% after 10 years compared to no screening, the risk-benefit ratio of the use of a chemopreventive drug needs to be carefully evaluated
Furthermore, as with screening programmes, the long-term prescription of a chemopreventive agent to otherwise healthy individuals may be associated with poor compliance. Finally, the cost-effectiveness of this strategy has not yet been demonstrated.

**Non-steroidal anti-inflammatory drugs**

Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to suppress malignant transformation and tumour growth experimentally, principally by inhibiting cyclooxygenase-2 (COX-2)-mediated prostaglandin E (PGE)-2 synthesis in neoplastic tissues. Several hypotheses concerning the contribution of COX-2 to tumourigenesis have been proposed. These include the inhibition of apoptosis, an increase in angiogenesis or invasiveness, modulation of inflammation/immune suppression, upregulation of PGE, and conversion of procarcinogens to carcinogens (114-116).

Dubé *et al.* carried out a systematic review of studies assessing the effect of chemoprophylaxis on the incidence of adenoma and CRC and on CRC mortality in populations without genetic risk factors (117). The authors identified significant heterogeneity across studies in terms of dosage as well as the duration and frequency of administration which necessitated careful consideration in the formation of subgroups for the analyses. An analysis of randomised clinical trials showed that regular ingestion of aspirin reduced the incidence of new colonic adenomas in patients with a previous history of colonic adenomas (RR: 0.82; 95% CI: 0.7–0.95), but not in the average-risk population. The analysis of cohort studies showed that regular ingestion of aspirin was associated with a reduction of 22% in the RR for CCR incidence. However, two randomised clinical trials of low-dose aspirin failed to show any protective effect. Only one study assessed mortality rates, and this identified no difference between patients assigned to low-dose aspirin and those assigned to placebo. The benefits of chemoprevention were most pronounced when high dose aspirin was used for a period of more than 10 years. However, aspirin use was associated with a dose-related increase in the incidence of gastrointestinal complications.

The same group reported similar findings from a systematic review of case-control and cohort studies of non-aspirin-NSAIDs chemoprophylaxis (118). One cohort study showed that non-aspirin-NSAIDs significantly reduced the incidence of colorectal adenomas in patients with a previous history of adenomas (RR: 0.64; CI: 0.48–0.85). Several case control studies showed that NSAIDs reduced the incidence of colorectal adenomas in average-risk populations (RR: 0.54; CI: 0.4–0.74). This analysis also showed that non-aspirin NSAIDs had a statistically significant dose-dependent and
duration-dependent effect on CRC risk. A risk reduction of up to 30% was found for colon cancer, whereas no benefit was observed for rectal cancer alone. A single study investigated the effect of ibuprofen on CRC mortality. This demonstrated no protective effect for ibuprofen, but rather a statistically significant increase in all-cause mortality (119).

Although no statistically significant increase in all-cause mortality was observed for NSAID use, these drugs were associated with a greatest risk of peptic ulceration and gastrointestinal haemorrhage, as well as cardiovascular events in patients at high risk of cardiovascular disease.

In patients with a history of colorectal adenomas, COX-2 inhibitors (mainly celecoxib) were found to reduce the incidence of all adenomas and advanced adenomas over a 3-year period of follow-up (pooled RR: 0.72; 95% CI: 0.68–0.77 vs. RR: 0.56; CI: 0.42–0.75). Although COX-2 inhibitors were associated with fewer gastrointestinal adverse effects than non-aspirin NSAIDs, data from the APPROVe study demonstrated that they were associated with an increased risk of peptic ulceration compared with placebo (120). This trial also demonstrated an association between the use of rofecoxib vs. placebo and an increase in the risk of cardiovascular events (16 per 1000 events). This finding led to the withdrawal of rofecoxib from the market. A subsequent polyp prevention study (Adenoma Prevention with Celecoxib [APC]) also found that celecoxib was associated with an increased risk of cardiovascular events (risk relative to placebo: 1.6; 95% CI: 1.0–2.5), in particular for those patients with pre-existing atherosclerotic heart disease (121).

It may therefore be concluded that the risk-benefit ratio for chemoprevention with non-aspirin NSAIDs or COX-2 inhibitors is non-favourable in average-risk individuals and patients with a history of colorectal adenomas.

In 2000, Steinbach et al. conducted a randomised clinical trial in patients with FAP to investigate the effect of two doses of celecoxib on colorectal polyps (122). After 6 months, the authors observed a 28% reduction in the mean number of colorectal polyps (P=0.003 for the comparison with placebo), and a 30.7% reduction in the polyp burden (the sum of polyp diameters) (P=0.001) in patients receiving the higher dose of celecoxib (400 mg twice daily). In the placebo group, respective reductions of 4.5% and 4.9% were observed. The lower dose of 100 mg twice daily was associated with a less pronounced effect. The authors reported an 11.9% reduction in the mean number of colorectal polyps (P=0.33 for the comparison with placebo) and a 14.6% reduction in the polyp burden (P=0.09).

In 2002, a randomised controlled trial of patients with FAP reported a significant reduction in the number of areas affected by duodenal polyps following 6 months treatment with 400 mg of celecoxib administered twice daily (123).
• **5-aminosalicylic acid**

CRC is one of the most serious complications of IBD. 5-aminosalicylic acid (5-ASA) is an anti-inflammatory agent which is used in the treatment of mild to moderate active UC. It is usually well tolerated and is associated with minimal systemic adverse effects and gastrointestinal toxicity (124). Epidemiological studies performed in the early 1990s suggested that the chronic consumption of aminosalicylates, such as sulphasalazine, may also confer a degree of protection against CRC in patients with UC, and that this effect may be mediated, at least in part, via a similar mechanism to that of NSAIDs (125).

A meta-analysis of nine studies (three cohort studies and six case-control studies) involving a total of 1,932 patients reported an association between 5-ASA use and a significant reduction in CRC risk (OR: 0.51; 95% CI: 0.37–0.69), as well as a protective effect against a combined endpoint of CRC and dysplasia (OR: 0.51; 95% CI: 0.38–0.69) (126). Two studies analyzing the duration and frequency of 5-ASA use concluded that there was a dose-response effect, and that regular use was associated with a lower risk of CRC (OR: 0.28; 95% CI: 0.10–0.81).

• **Ursodeoxycholic acid**

Ursodeoxycholic acid (UDCA) is a well-tolerated, low-risk agent that is used in the clinical management of primary biliary cirrhosis (PBC) and PSC. Tung et al. performed a cross-sectional survey of 59 patients with co-morbid UC and PBC who were undergoing colonoscopic surveillance (127). A significant association was found between UDCA use and a decrease in the risk of colonic dysplasia (OR: 0.18; 95% CI: 0.05–0.61; P=0.005). This association was also found after adjustment for the use of sulphasalazine or 5-ASA.

Pardi et al. followed up a cohort of patients with comorbid UC and PBC who had participated in a randomised, placebo-controlled trial of UDCA therapy assessing the effect of UDCA on the development of colorectal dysplasia and CRC compared to that of a placebo (128). UDCA therapy was found to be associated with a reduction in the risk of both colorectal dysplasia and CRC (RR: 0.26; 95% CI: 0.06–0.92; P=0.034). Although many patients assigned to the placebo group eventually received open-label UDCA, this did not significantly alter the results.

• **Folic acid**

The results of early epidemiological studies suggested that there is an inverse association between folate levels and the risk of CRC. Although more
than 20 case control studies have been performed, the findings have been inconsistent. A meta-analysis of cohort studies reported an association between reduced CRC risk and dietary folate \textit{(i.e., folate from food alone; RR for high vs. low intake: 0.75; 95% CI: 0.64–0.89) but not with total folate \textit{(i.e., folate from both food and supplements; RR for high vs. low intake: 0.95; 95% CI: 0.81–1.11)} (130). The authors found no significant heterogeneity between studies.

However, recent research in patients with a history of colorectal polyps has suggested that folate supplements may induce a transition to malignancy in undetected precursor lesions. This hypothesis is consistent with the role of folate in nucleotide synthesis and cell proliferation (130).

It is therefore possible that folate acts as a ‘dual-modulator’ in colorectal carcinogenesis. According to this hypothesis, moderate dietary increments initiated before the establishment of neoplastic foci may exert a protective effect, whereas excessive folate intake in individuals with early undetected lesions may increase the risk of tumourigenesis (131).

b. Screening for colorectal cancer

The risk of CRC is higher in individuals with a history of adenomatous polyps, IBD, or inherited genetic disorders. Given that most CRCs arise from adenomatous polyps, and that the progression to carcinoma may take several years, the early detection and removal of adenomas is probably the most effective method of reducing the incidence and mortality of CRC, as suggested by the results of several studies (132-134).

Available screening tests:

- **Stool-based tests**

  Screening for the presence of occult blood in the stool exploits the fact that most cancers, and some adenomatous polyps, tend to bleed. Faecal occult blood testing (FOBT) detects faecal hemoglobin, and employs a variety of techniques including immunochemical or DNA analysis and guaiac-testing. Stool DNA testing is expensive, and its suitability as a screening strategy has not yet been assessed within the context of large-scale prospective trials. Several factors may affect the accuracy of FOBT. These include stool rehydration (increases sensitivity; decreases specificity and positive predictive value), heme degradation, medications, and dietary substances such as peroxidases and heme from meat. Current recommendations state that testing should be conducted on two or three samples taken from stool specimens on consecutive days, since multiple consecutive sampling
increases the likelihood of detecting blood. Following a positive test, diagnostic endoscopy must be performed to determine the source of the occult blood (135).

Three large prospective randomised trials have been performed in average-risk populations to assess the effect on mortality of FOBT-based screening programmes. The programmes examined in these studies were conducted on an annual or biennial basis, and all subjects with positive results were examined by colonoscopy (136-139). A systematic review of these three studies and data from a Swedish trial estimated an overall significant reduction in CRC mortality of 16% (RR: 0.84; 95% CI: 0.77–0.93) (140). This increased to 23% when the estimated RR was adjusted for attendance for screening in individual studies. A shift to the detection of earlier stage disease, which is associated with superior clinical outcome, was observed in all four studies.

• **Sigmoidoscopy**

Sigmoidoscopy is a procedure which involves direct endoscopic examination of the distal part of the colon. Diagnostic biopsies can be obtained during its performance. If a neoplastic lesion is found during sigmoidoscopy, the entire large bowel should be evaluated by colonoscopy. Nonprospective, case-control studies have indicated that screening sigmoidoscopy can reduce the incidence of distal CRC by 50% to 66% (141-143), and reduce overall CRC mortality by up to 79% (142).

A prospective controlled trial in Norway offered sigmoidoscopic screening to 400 randomly selected individuals from the general population. A control group of 399 individuals from the same population did not undergo screening (144). In cases in which polyps were discovered, a colonoscopy was performed and during this procedure, all polyps were removed. Colonoscopy was repeated 2 and then 6 years later. After 13 years of follow up, the authors found a significant reduction in the incidence of CRC (risk ratio: 0.2; 95% CI: 0.03–0.96; P=0.02). However, the study found a higher overall mortality among patients who had undergone screening (risk ratio: 1.57; 95% CI: 1.03–2.4; P=0.03). Further studies are warranted to investigate this finding.

• **Colonoscopy**

Colonoscopy is regarded as the gold-standard for the diagnosis of CRC since it allows direct examination of the full length of the large bowel as well
as the excision of polyps and biopsy sampling. A recent systematic review found that the ability to detect adenomas was directly correlated with adenoma size. The sensitivity of a single colonoscopy was 97.8% for adenomas $\geq 10$ mm. This was reduced to 87% and 74% for adenomas sized 5–10 mm and 1–5 mm, respectively (145).

No published prospective study has demonstrated a direct reduction in CRC mortality secondary to primary screening colonoscopy. However, much of the demonstrated benefit of other screening techniques such as FOBT or sigmoidoscopy is attributable to the use of colonoscopy in cases with abnormal results. This is also illustrated by the reduction in mortality following colonoscopy and polypectomy that was observed in the study by the National Polyp Study Workgroup (132).

A retrospective study of 1,177 average-risk and asymptomatic individuals who had undergone colonoscopy in a medical centre in Israel reported prevalence rates of 20.9%, 6.3%, and 1.1%, for colorectal neoplasia, advanced neoplasia, and cancer, respectively (146). Detection of proximal neoplasia was particularly frequent among patients aged 65 to 75 years. In this age-group, the prevalence of proximal neoplasia in the absence of distal lesions reached 60%. This finding suggests that colonoscopy could be of particular benefit in this population.

By contrast, a recent Canadian case-control study reported an association between colonoscopy and fewer deaths from left-sided CRC (adjusted conditional OR: 0.33; CI: 0.28–0.39). This association was not found for right-sided CRC (adjusted conditional OR: 0.99; CI: 0.86–1.14) (147).

- “Virtual Colonoscopy” (computed tomographic colonography)

Computed tomographic colonography (CTC) is a minimally invasive procedure in which two-dimensional (2D) or three-dimensional (3D) images of the entire colon are generated from a spiral computed tomographic scan. If a suspected colorectal lesion is detected, a conventional colonoscopy may be performed.

Kim et al. compared patients who had undergone screening with CTC or conventional colonoscopy (148). Each group was comprised of more than 3,000 patients. Similar detection rates for advanced neoplasia were found (3.2% vs. 3.4%, respectively). However, polypectomy and complications were less common in the CTC group.

The ACRIN (American College of Radiology Imaging Network) National CT Colonography Trial involved a total of 2,600 participants, all of whom underwent CTC followed by conventional colonoscopy (149). The physician who performed the colonoscopy was blind to the CTC results. For
Table 1. Recommendations for screening in average-risk populations.

<table>
<thead>
<tr>
<th>Organisation</th>
<th>Countries with a relatively high level of resources and high CRC incidence and mortality</th>
<th>Recommendations</th>
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<tbody>
<tr>
<td>World Gastroenterology Organisation (152)</td>
<td>Colonoscopy starting at the age of 50 and repeated every 10 years in the absence of factors that would place the individual at increased risk.</td>
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<tr>
<td></td>
<td>Colonoscopy at the age 50 only, in the absence of factors that would place the individual at increased risk.</td>
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<td></td>
<td>Flexible sigmoidoscopy starting at the age of 50, and repeated every 5 years, in the absence of factors that would place the individual at increased risk. Diagnostic work-up with colonoscopy following a positive sigmoidoscopy.</td>
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<tr>
<td></td>
<td>Flexible sigmoidoscopy at the age of 50 only, in the absence of factors that would place the individual at increased risk. Diagnostic colonoscopy work-up in cases of a positive sigmoidoscopy or advanced neoplasia, depending on the available colonoscopy resources.</td>
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<tr>
<td></td>
<td>Flexible sigmoidoscopy at the age of 50 only. Diagnostic colonoscopy only indicated in cases in which advanced neoplasia is detected</td>
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<td></td>
<td>Annual fecal blood testing every year from the age of 50, in the absence of factors that would place the individual at increased risk. The type of test used depends on colonoscopy resources and the dietary habits of the population. Diagnostic work-up can involve colonoscopy, if available, or barium enema if colonoscopy is not readily available.</td>
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<tr>
<td>American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology (153)</td>
<td>Tests that primarily detect adenomatous polyps and cancer (acceptable options)</td>
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<tr>
<td></td>
<td>From the age of 50 years: Flexible sigmoidoscopy every 5 years. Colonoscopy every 10 years. Double contrast barium enema every 5 years. Computed tomography colonography every 5 years.</td>
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<tr>
<td></td>
<td>Tests that primarily detect cancer (acceptable options)</td>
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<tr>
<td></td>
<td>From the age of 50 years: Annual guaiac-FOBT with high sensitivity for cancer. Annual fecal immunochemical test with high sensitivity for cancer. Stool DNA with high sensitivity for cancer, interval uncertain.</td>
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<tr>
<td>American College of Gastroenterology (154)</td>
<td>Colonoscopy is the preferred modality for CRC screening (B level of evidence)</td>
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<td></td>
<td>Alternative methods for CRC screening include annual FOBT (A level of evidence), flexible sigmoidoscopy every 5 years or combined annual FOBT and flexible sigmoidoscopy every 5 years.</td>
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large adenomas (>10 mm) and cancers, the mean (±SE) per patient estimates of the sensitivity, specificity, and positive and negative predictive values were 0.90±0.03, 0.86±0.02, 0.23±0.02, and 0.99±<0.01, respectively.

This technique may be limited to the identification of flat and depressed adenomas and polyps that are smaller than 10 mm in diameter, and two

### Table 2. Recommendations for screening in high-risk populations.

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<tbody>
<tr>
<td>Familial adenomatous polyposis</td>
<td>Annual sigmoidoscopy</td>
<td>Annual flexible sigmoidoscopy starting at the age of 10 to 12 years.</td>
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<tr>
<td>Hereditary nonpolyposis colorectal cancer</td>
<td>Colonoscopy every 1 to 2 years, starting at the age of 20 to 25 years, or 10 years earlier than the youngest age at CRC diagnosis in the family, whichever is earliest.</td>
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<tr>
<td>Inflammatory bowel disease</td>
<td>Colonoscopy with biopsies for dysplasia starting 8 years after the onset of pancolitis or 12 to 15 years after the onset of left-sided colitis.</td>
<td>Colonoscopy including the extraction of multiple biopsy specimens should be performed every 1 to 2 years beginning after 8 to 10 years of disease onset.</td>
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<td>Family history of one or more first-degree relatives with sporadic CRC</td>
<td>A first-degree relative with CRC or adenomatous polyp diagnosed before the age of 60, or with two first-degree relatives diagnosed with CRC at any age: colonoscopy starting at the age of 40, or 10 years younger than the earliest diagnosis in their family, whichever is earliest, and repeated every 5 years.</td>
<td>Family history of one or more first-degree relatives with sporadic CRC regardless of age: colonoscopy beginning at age 40 years or 10 years younger than the affected relative, whichever is earliest. If the index colonoscopy is normal, repeat colonoscopy should be performed according to the age of the affected relative.</td>
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<tr>
<td></td>
<td>A first-degree relative with a CRC or adenomatous polyp diagnosed after the age of 60, or with two second-degree relatives with colorectal cancer: screening as for average-risk persons, but starting at the age of 40.</td>
<td>First-degree relative aged &lt;60 years with adenomatous polyps: colonoscopy beginning at the age of 40 years or 10 years younger than the affected relative, whichever is earliest. If the index examination is normal, it is recommended that colonoscopy is repeated every 5 years.</td>
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studies have estimated that CTC is less cost-effective than standard colonoscopy (150-151).

These methods must be organised into a screening programme that targets appropriately aged individuals and identifies those with an increased likelihood of disease. The interval between repeat screening should be clearly defined for individuals with negative initial findings. When an abnormal result is obtained, additional diagnostic testing including biopsy or excision should be performed as appropriate. Furthermore, a surveillance programme should be in place for patients who have undergone the removal of a polyp or cancer.

Screening guidelines have been established for average-risk populations (asymptomatic and without a personal or family history of adenomatous polyps or other illness, e.g., IBD, FAP, HNPCC, that predispose to CRC) and individuals who are at high risk.

Recommendations for CRC screening need to take multiple factors into account. These include effectiveness, sensitivity, false-positive rate, safety, cost, cost-effectiveness, and patient preference.

The guidelines of the World Gastroenterology Organisation (WGO) propose different approaches depending upon local resources, cultural preferences, and national health policies (152). The guidelines of the American Cancer Society and the United States Multi-Society Task Force on Colorectal Cancer (ACS-MSTF) distinguish between tests that can detect cancers at an early and treatable stage (e.g., stool tests), and tests that can also detect adenomas and thus lead to cancer prevention (e.g., sigmoidoscopy, colonoscopy, CTC) (153).

The American College of Gastroenterology advocates colonoscopy as the preferred screening/prevention test and faecal immunochemical testing as the preferred method of screening/detection in patients who decline cancer prevention tests (154).

A summary of the recommendations of each set of guidelines for average- and high-risk populations is provided in Tables 1 and 2 respectively.

**Conclusion**

CRC is a common and lethal disease. The risk of developing CRC is influenced by both environmental and genetic factors and the most relevant risk factor is older age.

The transition from identification of theoretically avoidable causes of this disease to implementation of preventive strategies depends on the delineation of exposures considered to be causally associated with development of CRC.
There are several factors considered to be associated with the development of CRC. In this way, the risk is clearly increased by a Western diet but also there are genes responsible for the most common forms of inherited CRC which have also been identified.

With this background it seems appropriate to change dietary habits, to practice regular physical activity and maintain a healthy weight, together with targeted screening programs and early therapeutic intervention. All these measures could, in time, substantially reduce the morbidity and mortality associated with CRC.

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