Strategies for colon cancer prevention

Jan Björk

Abstract Colorectal cancer (CRC) is common and is associated with a considerable mortality. Morbidity and thereby mortality can be reduced by using different prevention strategies such as lifestyle interventions and chemoprevention. Endoscopic surveillance of high-risk individuals and population-based endoscopic screening of average-risk individuals enables detection and removal of premalignant lesions (adenomas) as well as presymptomatic detection of cancer. Implementation of cancer detection tests such as fecal occult blood tests (FOBTs) is another strategy to reduce cancer mortality by early detection of CRC. Personalized management, based on estimates of the individual risk using information concerning environmental factors, lifestyle, family history, personality, social background and phenotype in combination with a variety of biomarkers such as genotype, will become more important as a strategy to optimize CRC prevention in the future.

Keywords Colorectal cancer · Prevention · Screening · Surveillance

Introduction

Colorectal cancer (CRC) is one of the most prevalent malignancies in Western countries with a life-time risk of 5% to 6% [1]. Global statistics shows that European countries have a leading position, both in terms of incidence and mortality of CRC. It has been estimated that approximately 50% die of the disease. The incidence and mortality in CRC varies over countries even within Europe indicating an influence of other factors such as lifestyle and screening practices [2]. CRC could be divided into at least three types: sporadic, hereditary and colitis-associated. A large body of evidence indicates that diet and lifestyle, family history and chronic inflammation are risk factors for CRC. Thus, primary prevention by modification of environmental factors and lifestyle, identification, surveillance and prophylactic treatment of high-risk individuals and the use of chemoprevention are important. However, the most efficient way to prevent CRC or death from CRC among the general population is screening targeting the average risk individuals. Therefore population-based screening programs, including all people eligible to attend screening on the basis of age and geographical area of residence, are currently being implemented in several European countries and more will follow. In the United States there is a trend towards a decrease in CRC morbidity and mortality. Microsimulation modeling demonstrates that declines in CRC death rates are explained to a small but demonstrable extent by risk factor reductions and improved treatments and to a great extent by screening [3]. The aim of population-based screening is to discover latent disease in the average risk population in order to detect early stages which can be cured by treatment before it poses a threat to the individual and/or the community [4]. CRC is particularly suitable for screening since it is common and believed to develop gradually according to the adenoma-carcinoma sequence [5]. The time-span from an early adenoma to an established CRC is unobserved, but is estimated to take at least 10 years [6], thus providing an opportunity for early detection and intervention. Moreover, removal of colorectal adenomas has a preventive effect on CRC [7] and detection of CRC at an earlier stage.
affects mortality [8] which indicates that interventions along the adenoma-carcinoma pathway have a positive impact on outcome. Identification and surveillance of high-risk populations such as individuals belonging to families with hereditary CRC syndromes and patients with inflammatory bowel disease (IBD) are other measures of great importance. Individuals with a family history of CRC indicating a genetic predisposition but without detectable genetic markers or individuals with a phenotypic appearance indicating high-risk is a third group where surveillance is justified. There are several screening options for CRC available where fecal occult blood tests (FOBTs) and lower endoscopy are the most commonly used.

**Primary prevention**

Primary prevention strategies are targeted to prevent CRC in an otherwise healthy population. The decline in CRC seen in the United States is prognosticated to continue if risk factor modification remains at current rates. With favorable trends in risk factor exposure decrease could probably be even more pronounced. Many cancers have modifiable risk factors, although risk factor reduction usually results in long-term, not short-term, improvements in cancer incidence. Thus, the impact of changing prevalence of CRC risk factors must be assessed over a long time to observe impact [9].

**Physical inactivity**

Lifestyle such as lack of physical exercise is a risk factor for CRC [10] and decreased occupational physical activity increases the risk for colon cancer [11].

**Obesity**

There is considerable evidence supporting the concept that both overweight and obesity are associated with an increased risk of CRC. Obesity also increases the risk of colon adenomas [12]. Overall, obesity approximately doubles the relative risk of adenomas. A meta-analysis of six studies estimated a 3% increase in CRC risk per one unit increase in body mass index (BMI). Abdominal obesity is a stronger risk factor than truncal obesity or BMI [13, 14].

**Smoking**

Smoking is a strong predictor of CRC [15, 16]. A history of more than 20 pack-years of smoking increases the risk for colorectal adenomas and CRC [17, 18] and has been shown to account for 12% of all deaths from CRC [19, 20]. Based on these data, special efforts may be justified to ensure that screening takes place in active smokers and in former who have smoked for more than 20 pack-years.

**Diet**

The geographic differences in CRC incidence could, at least to some extent, be attributed to differences in diet habits. The association of high incidence of CRC with diets containing large amount of red meat emphasises the impact of diet [21]. The WCRF [22] recognizes that there is limited but suggestive evidence that food containing animal fat increases the risk of CRC. But there is also data suggestive of a causal relationship between high intake of n-3 long-chain polyunsaturated fatty acids (LC-PUFA) and reduced risk of CRC, indicating that fish intake probably have a CRC protective effect [23]. A systematic review of five studies failed to show any benefit of increased dietary fiber intake for reducing incidence or recurrence of adenomatous polyps [24]. The role of nutritional supplementation is difficult to assess. Nutritional chemoprevention trials had to be carried out with large number of patients studied for long duration, measuring CRC as an end point. Folic acid has been identified as possible agents for the chemoprevention of CRC. However, a recent meta-analysis showed no such evidence [25]. Pooled data from 60 epidemiological studies on CRC cases showed that higher consumption of milk/dairy products reduces the risk of colon cancer, and high calcium intake reduces the risk of CRC. Evidence from two randomized controlled trials suggests that calcium supplementation contribute to a moderate degree to the prevention of colorectal adenomas. Vitamin D was associated with a non significant reduction in CRC risk [26]. The Polyp Prevention Study was a clinical trial of antioxidant vitamins (ß-carotene, vitamins C and E). No effect was seen on recurrence of colorectal adenomas compared to placebo [27]. A high-quality meta-analysis of eight trials found that, compared with no treatment or placebo, there was no benefit of antioxidants (beta-carotene, vitamin A, vitamin C, vitamin E, or selenium) in decreasing the risk of CRC. Vitamin E was, in fact, found to increase the risk of colorectal adenomas [28].

**Chemoprevention**

Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs including selective cyclooxygenase-2 inhibitors (COXIBs) have a chemopreventive effect on CRC [29]. Elevated cyclooxygenase-2 (COX-2) expression is found in most CRC tissue and is associated with poor outcome in terms of survival among CRC patients. NSAIDs exert their anti-inflammatory and antitumor effects primarily by
reducing prostaglandin production by inhibition of COX-2 activity [30]. It has been possible to reduce the formation of colorectal adenomas of both familial and sporadic origin by treating with NSAIDs [29, 31]. COXIBs have also been shown to cause regression of polyps in randomized studies on patients with familial adenomatous polyposis (FAP) [32, 33]. Evidence of long-term efficacy of NSAIDs is, however, currently lacking and potential severe adverse events must be taken into account [29]. Moreover, the use of NSAIDs in FAP patients does not replace prophylactic colorectal surgery. Currently, the use of NSAIDs is restricted as adjunctive treatment in FAP patients with ileorectal anastomosis in order to reduce polyp burden. However, endoscopic surveillance of the rectum is still advocated [34].

Aminosalicylic acid (ASA)

ASA has in observational studies been associated with significant reductions in colorectal adenoma recurrence, CRC incidence, and CRC mortality [35, 36].

5-Aminosalicylate (5-ASA)

Pooled results of observational studies support a protective association between 5-ASA and CRC or a combined endpoint of CRC/dysplasia in patients with ulcerative colitis (UC) [37–39].

Ursodeoxycholic acid (UDCA)

UDCA was one of the earliest agents investigated as a drug for CRC prevention. In a randomized controlled trial in patients with colorectal adenomas UDCA significantly lowered the odds of advanced lesions in men, but not women [40]. UDCA also has been shown to reduce the risk of colorectal dysplasia or CRC in patients with primary sclerosing cholangitis (PSC) and UC [41, 42].

Statins

A population-based case-control study found that CRC was 30% less likely to occur in patients who took statins for at least 5 years but data from randomized controlled trials are lacking [43].

Hormon therapy

Two meta-analyses of mostly observational cohort studies reported a 20–30% reduction in colon cancer incidence in women who had ever used hormone therapy [44, 45]. However, data from the Women’s Health Initiative study showed that, although women were at decreased risk of developing colon cancer, those women who did develop colon cancer were diagnosed at a more advanced stage than women who took placebo [46].

Family history

Inherited susceptibility plays an important role in the pathogenesis of CRC. Thus, it is recommended that a careful family history always should be obtained. Where a positive history is presented the empirical risks for the development of CRC can be determined. When no hereditary CRC syndrome is evident, screening is based on empiric risk estimates. For instance, the CRC risk is increased twofold [47] and the odds ratio is 2.6 for high-risk adenomas defined as adenomas ≥1 cm in size and/or villous elements in individuals with only one affected first-degree relative with CRC which further emphasize the close relationship between adenomas and CRC and the importance of the adenoma-carcinoma sequence [48]. The American College of Gastroenterology (ACG) recommendations are colonoscopy every 10 years beginning at age 50 years when following criteria are fulfilled: a single first-degree relative with CRC or high-risk adenoma, defined as adenoma ≥1 cm in size, or with high-grade dysplasia or villous elements, diagnosed at age ≥60 years (Grade 2 B). The recommendations are colonoscopy every 5 years beginning at age 40, or 10 years younger than age at diagnosis of the youngest affected relative if the following criteria are fulfilled: single first-degree relative with CRC or advanced adenoma diagnosed at age <60 years or two first-degree relatives with CRC or high-risk adenomas (Grade 2 B) [49].

If phenotype and/or inheritance pattern indicate an inherited CRC syndrome, genetic counseling, presymptomatic endoscopic screening and, if appropriate, molecular genetic testing should be advised. It is possible to test selected subjects for carriage of germline mutations in genes responsible for Lynch syndrome/hereditary non-polyposis colorectal cancer (HNPCC), familial adenomatous polyposis (FAP), Peutz-Jeghers syndrome, and juvenile polyposis which are all autosomal dominant hereditary syndromes with CRC predisposition. Molecular genetic testing is also possible for MUTYH- associated polyposis (MAP), a syndrome resembling FAP but, unlike FAP, inherited in an autosomal recessive fashion. Once the mutation has been found selected members of the family (at risk individuals), who are identified from the pedigree, can be offered genetic testing.

Before genetic testing is performed in patients who meet the criteria for Lynch syndrome microsatellite instability testing and / or tumor immunohistochemical staining for mismatch repair proteins should be performed. Patients with positive tests can be offered genetic testing and, if the mutation is found, all family members at risk can be offered
genetic testing. ACG recommends that patients with positive genetic testing and those at risk in families where genetic testing is unsuccessful should be offered colonoscopy every 1 year to 2 years beginning at age 20–25 years, until age 40 years, then annually thereafter (Grade 2 B) [49].

The European guidelines recommend that individuals with a FAP-phenotype should undergo APC-mutation testing and, if negative, MUTHY-mutation testing. Patients with FAP or at risk of FAP should undergo annual flexible sigmoidoscopy or colonoscopy until preventive surgery is performed [50]. Despite surgical procedure used postsurgical endoscopic surveillance is mandatory. Patients with ileorectal anastomosis, ileal pouch, or an ileostomy, should undergo endoscopic surveillance approximately every 6–12 months according to the ACG recommendations (Grade 2 B). Individuals with less dense polyp burden (<100 colorectal polyps) should be offered genetic counseling, consideration of APC- and MUTYH-mutation testing, and individualized colonoscopy surveillance depending on the size, number, and pathology of polyps seen according to the same recommendations (Grade 2 C) [49]. Despite of phenotype it is not always possible to find the mutation causing the syndrome. In these families endoscopic surveillance of at risk individuals is recommended. Screening strategies targeting risk populations based on family history of CRC have been estimated to prevent up to 15–20% of all CRC [51].

Inflammatory bowel disease (IBD)

It was shown decades ago that longstanding extensive ulcerative colitis (UC) was associated with an increased risk of CRC [52, 53]. UC-associated CRC are more often multiple, broadly infiltrating, anaplastic, and uniformly distributed throughout the colon, and seem to arise from flat mucosa and not from adenomas in comparison with noncolitis-associated CRC [54]. After 10 years of extensive UC, the cancer risk has been reported to increase with 0.5–1% per year [55]. Even patients with left-sided UC reach similar levels of cumulative cancer risk but first after 30–40 years of disease [56]. Regular surveillance colonoscopy has been proposed after 8–10 years of colitis with multiple biopsies at regular intervals. The finding of high grade dysplasia (HGD) in flat mucosa is an indication for prophylactic colectomy or proctocolectomy. Patients especially at risk for CRC are those with primary sclerosing cholangitis (PSC) [57]. It is therefore justified to start colonoscopic surveillance as soon as the coexisting diagnoses of UC and PSC are established and offer this patients treatment with UCDA [42]. In addition, a family history of CRC is also an independent risk factor [58]. Only indirect evidence indicate that surveillance colonoscopy is likely to be effective at reducing the risk of death from UC-associated carcinoma, particularly in those with long-standing extensive colitis [59]. Pharmacological intervention with 5-ASA has been shown to reduce the risk of CRC and dysplasia up to 50% [37]. Previous epidemiological studies imply that an increased risk of CRC is valid for Crohn’s disease as well [59, 60].

Screening

Population based CRC screening has been introduced in several countries throughout the world. The age range for a screening program should include a cohort of the population fulfilling the criteria of both high incidence of CRC and still a considerable life-expectancy. Colonoscopic detection of CRC is uncommon in asymptomatic individuals below 50 years of age. The low yield of screening colonoscopy in younger adults is consistent with current recommendations, not starting screening before age 50 in individuals at average risk [61]. CRC screening tests could be divided into cancer prevention and cancer detection tests. Cancer prevention tests have the potential to detect both cancer and adenomas, whereas cancer detection tests have low sensitivity for adenomas but also lower sensitivity for cancer compared with that in cancer prevention tests (imaging tests).

Imaging tests

Endoscopic screening examination could be performed either as a flexible sigmoidoscopy or as a colonoscopy. In CRC screening of average-risk individuals both methods are used. Sigmoidoscopy is easier to perform and less time consuming and is associated with less complications compared to colonoscopy [62]. Case-control studies of sigmoidoscopy, have shown morbidity and mortality reductions of distal CRC of 80% [63] and 60% [64], respectively, in screening populations. Overall, flexible sigmoidoscopy detects 60–70% of the significant lesions detected by colonoscopy [65]. The Telemark Polyp Study conducted in Norway was a randomized controlled trial where flexible sigmoidoscopy was used demonstrated a significant reduction in the incidence of CRC [66]. A similar study from the United Kingdom presented data on the attendance rate which was only 45% [31]. The evidence that colonoscopy prevents incident CRCs and reduces the mortality from CRC is indirect but substantial. Notably, no prospective randomized controlled trial, comparing colonoscopy with no screening, has been carried out. However, cohort studies containing patients, who have undergone colonoscopy and polypectomy have shown a 76–90% reduction in CRC morbidity compared to reference pop-
Fecal bleeding tests

Guaiac-based fecal occult bleeding test (gFOBT) has so far been the most frequently used test in screening programs. It detects the peroxidase reaction of hemoglobin, which causes the detection paper impregnated with guaiac resin to turn blue. Diet restrictions are necessary to avoid false positive results. There is good evidence that gFOBT reduces mortality of CRC by 15–33% [87]. There is still no clear recommendation regarding optimal time interval since only the interval up to 2 years has been investigated. The immunochemical FOBT (iFOBT) is more expensive than the gFOBT but the adherence is better [88, 89]. iFOBT reacts exclusively to human hemoglobin. Several qualitative and quantitative tests are presently available, with varying levels of sensitivity and specificity.

New screening methods include tests which examine the stool for the presence of abnormal DNA are commercially available. Generally, these tests have higher sensitivity but lower specificity than gFOBT [90]. Fecal DNA testing is also more expensive. Additional disadvantages of fecal DNA testing include no established data on which to determine an optimal interval, and the lack of clinical recommendations on how to respond to patients who have positive DNA tests and negative colonoscopies. Introduction of organized, population-based, colorectal cancer screening using FOBT has the potential to reduce overall CRC cancer mortality. However, a recent study from the United Kingdom shows that socio-economic variation in screening participation could exacerbate existing inequalities in mortality. The results showed a strong socio-economic gradient in FOBT uptake, which declined from 49% in the least deprived quintile of postcodes to 38% in the middle quintile and 32% in the most deprived quintile. Variation in socio-economic deprivation between sectors accounted for 62% of the variance in return rates, with little attenuation as a result of controlling for ethnicity, household mobility or health status. These results highlight the need to understand the causes of socio-economic gradients in screening participation and address barriers that could otherwise influence outcome in CRC survival [91]. ACG recommends a preferred cancer prevention test with colonoscopy every 10 years (Grade 1 B) starting at age 50 years in those without a family history of colorectal neoplasia and a preferred cancer detection test using annual iFOBT to detect occult bleeding (Grade 1 B). In clinical settings, in which economic issues preclude primary screening with colonoscopy, or for patients who decline colonoscopy, one of either flexible sigmoidoscopy every 5–10 years or CT colonography every 5 years should be offered. As cancer detection test, occult blood detection through the iFOBT is recommended [49].

### Surveillance

Colonoscopy is used for early detection and prevention of CRC by identification of CRC and removal of colorectal polyps. An autopsy survey and a prospective necropsy study of the colon and rectum showed that adenomas were
very common lesions occurring in approximately 50% and 30% of the patients, respectively [92, 93]. Approximately 70% of colonoscopically removed polyps are adenomas [94]. Adenomas are benign lesions that, by definition, display dysplasia. It is postulated that almost all CRCs arise from adenomas but only a small fraction of them undergo malignant transformation. It is estimated that the development from normal mucosa via adenoma to CRC takes several years [5]. The purpose of surveillance endoscopy is to detect and resect synchronous adenomas missed during the initial colonoscopy and to remove metachronous lesions before they get malignant. Several studies have been performed investigating the recurrence rate of adenomas in patient with adenomas at previous colonoscopy. The risk of metachronous adenomas is high, between 42% and 60% after 3 years and 4 years, respectively according to two previous studies [95, 96]. The majority of these lesions are small and probably of low clinical significance. The National Polyp Study (NPS) has shown that only 3.3% of the patients with colorectal adenomas had advanced lesions including 2 early CRCs 3 years after the index colonoscopy. Based on this an endoscopic surveillance interval of at least 3 years was recommended [97]. The miss rate of synchronous polyps at colonoscopy is not neglectable [98]. It is however clear that that some individuals are predisposed to a faster rate of polyph development. Predictors of adenoma recurrence are number and size of adenomas. Patients with up to 2 adenomas measuring less than 1 cm at initial colonoscopy have a low risk of developing adenomas of clinical importance within 3 years whereas patients with 3 or more adenomas with at least one measuring 1 cm or more is a high-risk population which is recommended follow-up colonoscopy at 3 years [99]. Predictors of colorectal cancer are, except for number and size, the histological features of tubulovillous or villous growth [100]. Colonoscopic removal of at least 1 adenoma larger than 5 mm reduced the risk of subsequent CRC development compared with that expected in the general population indicating that endoscopic intervention is efficient in reducing morbidity in CRC in patients under regular colonoscopic surveillance [101]. Moreover, prevalence of left-sided advanced colorectal lesions, but not right-sided advanced lesions, has been shown to be reduced within a 10-year period after colonoscopy, even in the community setting [102]. Resources in terms of money and accessibility as well as compliance rate have to be taken into account when designing the endoscopic surveillance setting.

Outlook

CRC morbidity and mortality can be reduced. A concerted action including lifestyle changes, chemoprevention, surveillance of high-risk individuals, and population-based screening of average-risk individuals is at present the most efficient strategy. Factors that have to be taken into account are compliance, sensitivity, specificity, cost, and safety. Insufficient adherence to lifestyle recommendations and low attendance to screening programs are important factors that affect the outcome of CRC prevention in the general population and must by all means be improved. As predictive diagnostics, such as genetic testing using advanced molecular technologies, develop and become more widely used the population of well defined and more motivated high-risk individuals will increase in size compared with today. Once a high-risk individual has been identified targeted preventive measures and treatment can be implemented. In the future, personalized surveillance and treatment based on the risk profile involving the genetic background, a variety of biomarkers, phenotype, lifestyle, personality and social background probably will become more important as a strategy to optimize CRC prevention.

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