Review Articles

PREVENTION OF COLORECTAL CANCER

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Colorectal cancer is one of the leading causes of mortality and morbidity. Cancers of the colon and rectum are rare in developing countries_ in Asia, Africa (among blacks), and South America (except Argentina and Uruguay), but are the second most frequent malignancy in industrialized regions (the United States, Canada, the Scandinavian countries, northern and western Europe, New Zealand, Australia). More than 940,000 cases occur annually worldwide, and nearly 500,000 die from it each year.

The American Cancer Society estimated that in 2006, 148,610 people were diagnosed with colorectal carcinoma (CRC), and 55,170 died of the disease. Colorectal cancer is the third most common type of cancer in both sexes (after prostate and lung cancers in men and lung and breast cancers in women) and the second most common cause of cancer death in the United States.

About 72% of new CRCs arise in the colon, and the remaining 28% arise in the rectum. The lifetime risk of being diagnosed with CRC in the United States is estimated to be 5.9% for men and 5.5% for women. Despite these daunting statistics, the incidence rates of CRC have been declining in both men and women since 1998, likely reflecting early detection efforts with removal of precancerous polyps.
In Portugal, the Instituto Nacional de Estatística estimated that in 2003**,** 22.711 portugueses died of the disease. Colorectal carcinoma is the second most common cause of death (after cerebrovascular and cardiovascular diseases). The colorectal cancer is the first cause of cancer death, about 14% of total cancer death (followed by pulmonary cancer 13,9 %, stomach cancer 11% and breast cancer 7%).

The aim of this review is to introduce the principles and applications of prevention in colorectal cancer.

Key words: Colorectal cancer; Risk factors; Prevention; Chemoprevention; Screening programs.

Epidemiology

Gender Overall the incidence of CRC and mortality rates are higher in men than in women; tumors of the colon are slightly more frequent in women than in men (1.2:1), whereas rectal carcinomas are more common in men than in women (1.7:1).

Age The vast majority, 91%, of all new CRC cases occur in individuals older than age 50. In the United States, the median age at presentation is 72 years.

Race The incidence and mortality rates of CRC are highest among African-American men and women compared with white men and women (15% higher and 40% higher, respectively). The incidence rates among Asian Americans, Hispanics/Latinos, and American Indians/Alaskan natives are lower than those among whites.

Geography The incidence of CRC is higher in industrialized regions (the United States, Canada, the Scandinavian countries, northern and western Europe, New Zealand, Australia) and lower in Asia, Africa (among blacks), and South America (except Argentina and Uruguay).

Survival Five-year survival rates (Table1) for patients with CRC have improved in recent years. This fact may be due to wider surgical resections, modern anesthetic techniques, and improved supportive care. In addition, better pathologic examination of resected specimens, preoperative staging, and abdominal exploration reveal clinically occult disease and allow treatment to be delivered more accurately. Survival also has improved through the use of adjuvant chemotherapy for colon cancer and adjuvant chemoradiation therapy for rectal cancer.

Table 1: Five-year relative survival rates in colorectal cancer[a] by stage at diagnosis (1995-200)

Time of detection	5 –year survival rate (%)
All stages	
In early, localized stage	64
After spread to adjacent organs or lymph nodes	67
After spread to distant sites	10
Unstaged	35

[a] Source: Cancer Facts & Figures – 2005. Atlanta: American Cancer Society; 2005. Surveillance, Epidemiology and End Results (SEER) Program.

Genetic changes and colon cancer carcinogenesis

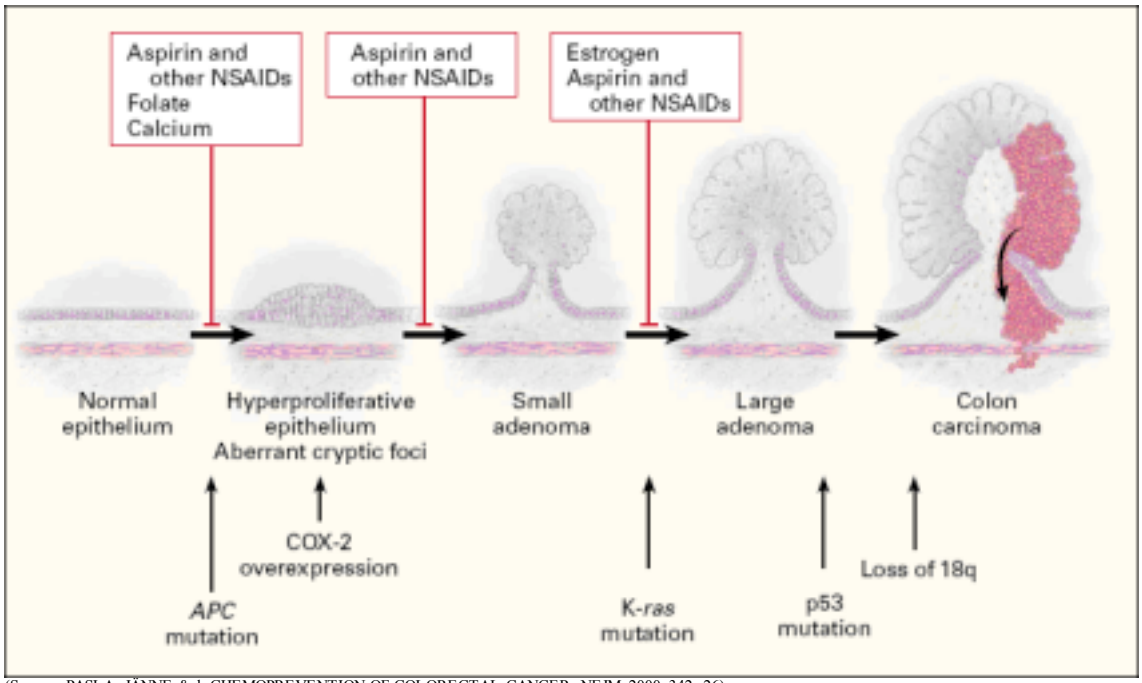
Colon cancers are thought to arise as the result of a series of histopathologic and molecular changes that transform normal colonic epithelial cells into a colorectal carcinoma, with an adenomatous polyp as an intermediate step in this process (Fig. 1)[1].
Adenomatous polyps are found in approximately 33 percent of the general population by the age of 50 years and in approximately 50 percent by the age of 70 years[2].Molecular analyses of colorectal adenomas and carcinomas have led to a genetic model of colon carcinogenesis, in which the development of cancer results not from any single genetic event but from the accumulation of a number of genetic alterations (Fig. 1)[1].
Numerous mutagenic events can occur throughout the colon cancer development including loss of heterozygosity in tumour suppressor genes such as APC, MCC, DCC, p53 and K-ras [3]. Colon cancer tumorigenesis is a step-wise process (Fig. 1) [4] in which mutations accumulate over time and oncogenes are activated while tumour suppressor genes are deactivated. Colon cancer mechanisms are discussed as common and alternate pathways.

Common pathway: Tumour suppressor genes make proteins that suppress tumour formation by limiting the cell growth. Mutations involving the tumour suppressor genes could result in a loss of their ability to restrict tumour growth [5,6]. Vogelstein et al (Fig 1) found that mutations involving a tumour suppressing gene called the adenomatous polyposis coli (APC) gene resulted in colon cancer [7]. Normally, APC binds to b-catenin and phosphorylates it. But when mutations occur, b-catenin interacts with transcription factors instead of stimulating growth. At present the transgene expression after gene therapy is short lived, therefore its role is limited in familial adenomatous polyposis where the colon cancer risk continues for life. P53 is another tumour suppressor gene which blocks the cell cycle and stimulates apoptosis. It is altered in more than 80% of colorectal cancers.

Alternate pathway: Hereditary non polyposis coli (HNPCC), sometimes called Lynch syndrome, accounts for approximately 5-10% of all colorectal cancer cases. Several genes have been identified that are linked to HNPCC. Mutations in the MLH1, MSH2, and MSH6 genes are the most frequent cause of HNPCC [8,9]. Although multiple genes have been linked to HNPCC, most families with HNPCC have only one mutated gene. Genetic testing is available for the MLH1, MSH2, and MSH6 genes. The HNPCC genes are part of a group of genes called mismatch repair genes. They make proteins which repair DNA mistakes that occur when cells divide. If one of these genes has a mutation, then DNA mistakes cannot be repaired, leading to damaged DNA and an increased risk of cancer. The risk of colorectal cancer in families with HNPCC is 70-90%, which is several times the risk in the general population. Women with HNPCC also have an increased risk of cancers of the uterus, ovaries, stomach, small intestine, kidney and breast [10].

MYH associated polyposis: This is a recently identified inheritable bowel cancer in which a person needs two faulty copies of the MYH gene to be at an increased risk of cancer.

Figure 1. Colon Carcinogenesis and the effects of Chemoprevention Agents.



(Source: PASI A. JÄNNE &al. CHEMOPREVENTION OF COLORECTAL CANCER. NEJM. 2000; 342: 26)

Etiology and risk factors

Environment Asians, Africans, and South Americans who emigrate from low-risk areas assume the colon cancer risk for their adopted country, suggesting the importance of environmental factors in CRC. Smoking and alcohol intake (four or more drinks per week) increase the risk of CRC [11-13].

Diet Epidemiologic and animal studies suggest that diet has a major role in colorectal carcinogenesis, that the consumption of dietary fiber, fruits and vegetables, wholegrain cereals, and calcium have a protective effect against colorectal cancer and adenomas; conversely, dietary fat, red meat, and high glycemic index foods might increase risk [14-16]. Diets rich in fat and cholesterol have been linked to an increased risk of colorectal tumors[17-20]. Dietary fat causes endogenous production of secondary bile acids and neutral steroids and increases bacterial degradation and excretion of these acids and steroids, thereby promoting colonic carcinogenesis. A protective role has been ascribed to calcium salts and calcium-rich foods, because they decrease colon-cell turnover and reduce the cancer-promoting effects of bile acid and fatty acids.
Historically, diets rich in cereal fiber or bran and yellow and green vegetables are said to have protective effects, fruit and vegetable intakes have been associated with a reduced risk of colon cancer; however, in more recent studies associations have been less consistent, with many case-control studies finding stronger associations for fat, fiber, and fruits and vegetables than the more recent larger cohort studies [21, 22].
Research in embryology, physiology, and epidemiology supports the notion that cancers of the proximal and distal colon may have different etiologies [23-25]. Recent evidence shows that two distinct kinds of genetic instability contribute to carcinogenesis in the colon; chromosomal instability occurs more often in distal colon cancers, whereas microsatellite instability predominates in proximal colon cancers [24,25]. Diet has been hypothesized to have more of a role in distal versus proximal colon cancers [26]. Fruits and vegetables are rich in many nutrients and bioactive compounds, such as vitamins, carotenoids, folate, and fiber, that may have cancer-preventive properties [27]. Nutrients that detoxify or deactivate carcinogens may act to prevent chromosomal instability whereas nutrients that function to regulate cell cycle progression and apoptosis may prevent the growth of chromosomally unstable cells. The relationship between fruit and vegetable intakes and the risk of colon cancer has been examined in many studies [28,29]. A review of 14 cohort studies concluded that fruit and vegetable intakes were not strongly associated with colon cancer risk overall but may be associated with a lower risk of distal colon cancer [30].

Insulin, Glucose , Insulin Resistance Data from a variety of sources suggest that insulin may play a functional role in colorectal carcinogenesis [31–33]. Insulin administration stimulates proliferation and reduces apoptosis in colorectal cancer (CRC) cell lines [34–36] and also promotes colorectal tumor growth in animal model systems [37–39]. In addition, multiple epidemiological studies have reported positive associations between type 2 diabetes mellitus (DM) and CRC risk, as recently reviewed [33, 40].
Insulin resistance (IR), defined as a subnormal glycemic response to endogenous insulin, precedes hyperinsulinemia among type 2 DM patients [41] and has been proposed as the primary mediator of increased CRC risk among obese individuals [31,42].
A prospective case-cohort study support the possibility that aberrant insulin and/or glucose homeostasis, perhaps as a consequence of insulin resistance, may be functionally related to CRC risk. [43]

Physical activity Several studies have reported a lower risk of CRC in individuals who participate in regular physical activity. High levels of physical activity may decrease the risk by as much as 50%. Being overweight or obese has been consistently associated with a higher risk of CRC. A year-long randomized controlled trial of moderate-to-vigorous intensity exercise intervention resulted in an increase in the potential for apoptosis at the bottom of the crypt in male exercisers compared with controls, whereas in contrast there was a decrease in the potential for apoptosis at the top and middle of the crypt in women. This pattern was also seen with improvements in aerobic fitness in men, whereas for women this pattern occurred only with increased minutes per week of exercise. [44].

Inflammatory bowel disease Patients with inflammatory bowel disease (ulcerative colitis, Crohn's disease) have a higher incidence of CRC. The risk of CRC in patients with ulcerative colitis is associated with the duration of active disease, extent of colitis, development of mucosal dysplasia, and duration of symptoms. The risk of CRC increases exponentially with the duration of colitis, from approximately 3% in the first decade to 20% in the second decade to > 30% in the third decade. CRC risk also is increased in patients with Crohn's disease, although to a lesser extent.

Adenomatous polyps Colorectal tumors develop more often in patients with adenomatous polyps than in those without polyps. There is approximately a 5% probability that carcinoma will be present in an adenoma; the risk correlates with the histology and size of the polyp. The potential for malignant transformation is higher for villous and tubulovillous adenomas than for tubular adenomas. Adenomatous polyps < 1 cm have a slightly greater than 1% chance of being malignant, in comparison with adenomas > 2 cm, which have up to a 40% likelihood of malignant transformation.

Cancer history Patients with a history of CRC are at increased risk of a second primary colon cancer or other malignancy. The risk of a second CRC is higher if the first diagnosis was made prior to age 60.

Prior surgery Following ureterosigmoidostomy, an increased incidence of colon cancer at or near the suture line has been reported. Cholecystectomy also has been associated with colon cancer in some studies but not in others.

Family history and genetic factors Individuals with a first-degree relative with the disease have an increased risk of developing CRC. Those with two or more relatives with the disease make up about 20% of all people with CRC. The risk of developing CRC is significantly increased in several forms of inherited susceptibility. About 5%–10% of all patients with CRC have an inherited susceptibility to the disease. The risks of developing CRC in the subgroups of familial or hereditary CRC vary from 15% in relatives of patients with CRC diagnosed before 45 years of age, through 20% for family members with two first-degree relatives with CRC, to approximately 70%–95% in patients with familial adenomatous polyposis and hereditary nonpolyposis CRC (HNPCC).

Chemoprevention

The pharmacologic prevention, known as chemoprevention, is directed at preventing the development of adenomatous polyps and their subsequent progression to colorectal cancers. Chemoprevention aims to block the action of carcinogens on cells before the development of cancer.

Antioxidants and calcium Controlled trials of vitamins C and E and calcium have produced mixed results. Clinical trials have shown that calcium supplementation modestly decreases the risk of colorectal adenomas.

Nonsteroidal anti-inflammatory drugs inhibit colorectal carcinogenesis, possibly by reducing endogenous prostaglandin production through COX inhibition. Sulindac (Clinoril) has induced regression of large bowel polyps in patients with FAP. Controlled studies have shown a reduction in the incidence of colorectal polyps with regular, long-term use of aspirin.
Results from the large-scale, The Women´s Health Study [45], long-term trial suggest that alternate day use of low-dose aspirin (100 mg) for an average 10 years of treatment does not lower risk of total, breast, colorectal, or other site-specific cancers.
Aspirin, however, has been found to be a more potent inhibitor of platelet COX-1 than of COX-2 activity in other cells,[46,47] which may be influenced by dose. Low-dose aspirin appears relatively specific for COX-1, although higher doses (1 g/d) inhibit both COX-1 and COX-2 and may have a stronger anti-inflammatory effect.[48] In addition, the required dosing interval for COX-2 inhibition may be shorter, due to the rapid resynthesis of the enzyme. [47] COX-2 expression has been found to be increased in colorectal neoplasia, [48] as well as in breast tumor cell tissue,[49] suggesting that higher and/or more frequent doses of aspirin may be more effective in cancer prevention.

In general, the effects of aspirin observed in studies of colon polyps appear to strengthen with increasing dose, and a meta-analysis found a lower risk of adenomatous polyps only at higher doses of aspirin and other NSAIDs.[50] However, the dose-response effect has not been consistent. Although some studies have found a reduction in risk of colorectal adenoma or cancer only with higher doses,[50-53] in the Aspirin/Folate Polyp Prevention Study,[54] effects on colorectal adenomas were observed for low dose (81 mg daily) but not for higherdose (325mgdaily) aspirin. In addition, in studies among healthy subjects using colorectal mucosal prostaglandin E2 levels as a biomarker, a daily dose of 81mg of aspirin was sufficient to suppress these levels after a 28-day period,[55,56] and the extent of reduction of prostaglandin E2 was not greater at higher doses.[56] Although the low alternate-day dose of aspirin used in the WHS could possibly explain the lack of effect on cancer, evidence for a dose-response effect remains inconsistent.

Aspirin appears to be effective at reducing the incidence of colonic adenoma and colorectal cancer, especially if used in high doses for more than 10 years. However, the possible harms of such a practice require careful consideration. Further evaluation of the cost-effectiveness of chemoprevention compared with, and in combination with, a screening strategy is required [57].

Cyclooxygenase-2 inhibitors and NSAIDs reduce the incidence of colonic adenomas. Nonsteroidal anti-inflammatory drugs also reduce the incidence of CRC. However, these agents are associated with important cardiovascular events and gastrointestinal harms. The balance of benefits to risk does not favor chemoprevention in average-risk individuals [58].

The U.S.Preventive Services Task Force recommends against the routine use of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) to prevent colorectal cancer in individuals at average risk for colorectal cancer [59].

Magnesium It is an essential ion that has an important role in regulating cell cycles and maintaining genomic stability [60]. Administration of supplemental magnesium in animals with experimentally induced colon cancer resulted in fewer colon tumors and smaller cryptal cells of the colon [61], suggesting an inhibitory role of magnesium in colon cancer cell proliferation. The mechanism by which magnesium prevents the growth of colon tumors was later found to be due to the inhibition of c-myc oncogene expression in the colon cancer cells [62] and the potentially reduced toxic effects of bile acids on colonic epithelial cells [63]. At the intracellular level, magnesium also effectively modulates insulin activity [64, 65]. Magnesium deficiency is often seen among patients with insulin resistance and type 2 diabetes [64, 65], which have also been linked to an increase in colorectal cancer incidence [66-68].
A cohort study [69] suggests little support for an inverse association between total magnesium intake and colorectal cancer incidence. Because data relating magnesium intake to colorectal cancer are sparse, more studies are warranted to elucidate the true role of magnesium in colorectal cancer development.

Postmenopausal hormones Women who use postmenopausal hormones appear to have a lower rate of CRC than do those who do not. A randomized trial [70] showed that the use of estrogen plus progestin was associated with a decreased risk of colorectal cancer. However, the cancers diagnosed in women who were using estrogen and progestin had greater lymph-node involvement and a more advanced stage than the cancers in the placebo group. These findings support wider implementation of bowel screening among postmenopausal women who are using hormone therapy. Current data are insufficient to support the use of estrogen plus progestin to reduce the risk of colorectal cancer in any population. Before therapy with estrogen plus progestin is used in any setting by postmenopausal women, all identified [71] and emerging [72,73] risks associated with these agents should be considered.
Possible mechanisms of the effect of postmenopausal hormone therapy on the risk of colorectal cancer include the influence of estrogen on bile acids [74] changes mediated by estrogen receptors on intestinal epithelium, [75,76] and alteration of insulin and insulin-like growth factor I [77,78].

The evidence supporting a role for hyperinsulinemia and hyperglycemia in the risk of colorectal cancer has recently been reviewed.[79] The reduction in the serum levels of fasting glucose and insulin with the use of estrogen plus progestin, as seen in this and other studies,[80] supports the idea that hyperglycemia and hyperinsulinemia contribute to the development of colorectal cancer.

Flavonoid A controlled, prospective and observational study suggests that long-term flavonoid treatment could reduce the recurrence rate of colon neoplasia in high risk patients particularly in those with resected colorectal cancer [81] Therefore flavonoid supplementation should be investigated by further clinical studies to prove the efficacy and validity of this concept. Flavonoids, indols, isothiocyanates, curcumin, resveratrol, glucosinolates and other plant products affect carcinogenic, mutagenic and neoplastic mechanisms [82], but could also induce protective enzymes of the intestinal mucosa [83]. Flavonoids are good candidates for primary and secondary prevention of colorectal cancer, since numerous *in vitro* studies and animal work report on their beneficial activities in terms of suppression of cancer proliferation, antioxidative and antiangiogenetic properties [82]. Epidemiological investigations [84-86], *in vivo* and *in vitro* experiments [87-91] and one clinical intervention study[92] support this concept. Other authors could not find protective effects of flavonoids on colorectal cancer incidence [93-95]. Flavonoids derived from tea plants can be used as a mean of bioprevention and have been manufactured and marketed as nutritional supplements [82].

Folic Acid A double-blind, placebo-controlled, randomized clinical trial of the efficacy of oral aspirin, folic acid, or both to prevent colorectal adenomas in persons with a history of adenomas concluded that folate, when administered as folic acid for up to 6 years, does not decrease the risk of adenoma formation in the large intestine among individuals with previously removed adenomas. The evidence for an increased risk of adenomas is equivocal and requires further research [96]. In view of the fortification of the US food supply with folate, and some suggestions that folate could conceivably increase the risk of neoplasia even outside the colorectum, [97-101] this line of investigation should have a high priority.

Lycopene Higher circulating insulin-like growth factor I (IGF-I) concentrations have been related to a greater risk of cancer. Lycopene intake is inversely associated with cancer risk, and experimental studies have shown that it may affect the IGF system, possibly through an effect on IGF-binding proteins (IGFBPs). A randomized, placebo-controlled, double-blinded crossover trial in a population at greater risk of colorectal cancer concluded that Lycopene supplementation did not influence serum total IGF-I and IGFBP-3 concentrations [102]. However, lycopene supplementation may decrease IGF-I bioavailability by increasing IGFBP-1 and -2 concentrations. Thus, it may provide a means of ultimately reducing colorectal cancer risk and potentially the risks of other major cancers such as prostate and premenopausal breast cancer. However, interindividual variation in IGFBP-1 and -2 effects was high, possibly complicated by differences in fasting duration and, consequently, insulin concentrations. Therefore, results must be confirmed in larger randomized intervention studies with control for the duration of fasting.

Vitamin D Epidemiological and clinical researchers have sought to investigate the potential association between vitamin D and risk of colorectal neoplasia. Low serum levels of 25(OH)D were found to be significantly associated with risk of both colorectal adenoma[103] and cancer[104] in two large cohort studies. Some studies have found an inverse nonsignificant association between dietary or total intake of vitamin D and colorectal adenomas or cancer[105–108], while others have not[109,110]. The most recent contribution to the vitamin D and colorectal neoplasia literature are results from the Women's Health Initiative (WHI) [111]. Therefore, the association between 25(OH)D levels and risk for colorectal neoplasia remains equivocal. A recent study show a moderate, nonsignificant inverse association between serum 25(OH) D levels and reduced risk for colorectal adenoma recurrence, particularly among women.[112]

Screening

Start screening at age 50 for people at average risk

National society guidelines recommend that people at average risk of colorectal cancer be screened starting at age 50 [113,114-117]. People are considered to be at average risk if they have no symptoms, do not have ulcerative colitis or Crohn's colitis, and do not have a personal or family history of colorectal neoplasia[118].

The US Multi-Society Task Force on Colorectal Cancer [115] suggests that people at average risk undergo one of the following:

Colonoscopy every 10 years

Flexible sigmoidoscopy every 5 years

Fecal occult blood testing every year

An air-contrast barium enema or computed tomographic (CT) colonography every 5 years

Fecal DNA testing, interval uncertain.

Anyone who has a positive result with any test other than colonoscopy should subsequently undergo colonoscopy.

Start screening sooner in people at higher risk:

African Americans should undergo screening for colorectal cancer under an average-risk strategy starting at age 45, according to a position paper from the American College of Gastroenterology [119].

People with a family history of colorectal polyps or cancer should also start screening earlier—as early as age 40, or 10 years younger than the age at which the relative was affected—and some should be tested more often than every 10 years (Table2).

Patients with ulcerative colitis or Crohn's colitis

Current multisociety guidelines for colorectal cancer screening and surveillance in patients with ulcerative colitis or Crohn's colitis are based on expert consensus and recommend a systematic biopsy protocol in some patients [115].

Recommendations for screening for colorectal cancer according to family history (Table 2):

FAMILY HISTORY	RECOMMENDATION
One first-degree relative with colorectal cancer or adenomatous polyp at age 60 or over, or Two second-degree relatives with colorectal cancer	Use an average-risk screening strategy starting at age 40
Two or more first-degree relatives with colorectal cancer, or	Colonoscopy at age 40, or 10 years younger than the age the earliest case in the family was diagnosed, whichever is earlier
Two second-degree relatives with colorectal cancer or adenomatous polyp before age 60	If normal, repeat every 5 years
Hereditary nonpolyposis colorectal cancer	Colonoscopy and endometrial biopsy at age 21–25, or 10 years younger than the age the earliest case in family was diagnosed Repeat every 2 years until age 40, then annually Refer to specialty center for genetic counseling and consideration of genetic testing
Familial adenomatous polyposis	Sigmoidoscopy or colonoscopy at age 10–12 Esophagogastroduodenoscopy at age 20 Refer to specialty center for genetic counseling and consideration of genetic testing

POST-POLYPECTOMY SURVEILLANCE:

After a polyp or polyps are discovered on colonoscopy, many patients are being told to come back for repeat colonoscopy unnecessarily soon, [120,121] thus diverting a scarce resource away from patients who may derive the most benefit—ie, those with high-risk polyps, those with a strong family history of colon cancer or an inherited predisposition to colon cancer, and those who have never undergone screening. Current evidence-based guidelines can be applied to several different patients. The histopathology report helps the clinician determine the appropriate post-polypectomy surveillance interval (Table 3).

Adenomas are precursors to colorectal cancer, progressing via the widely recognized adenoma-carcinoma sequence. [122]It is not unusual that both of our patients would have adenomatous polyps, since the prevalence of these polyps increases with age[123]. Adenomas are detected in 11% of average-risk people ages 50 to 54, increasing to 33% to 50% in people 65 to 75 years old[124,125].

Small, left-sided hyperplastic polyps, on the other hand, are considered nonneoplastic and do not require follow-up unless a patient meets the criteria for hyperplastic polyposis (table 3). While current guidelines do not take into account hyperplastic polyps when determining postpolypectomy surveillance, the clinical significance and possible neoplastic potential of large and right-sided hyperplastic polyps is an area of active research.

Adenomas: If adenomas are discovered, three key questions affect how soon the patient should undergo colonoscopy again (Table 3):

How many? Van Stolk et al [126] analyzed colonoscopy results from 479 participants in the Polyp Prevention Study and found at 3 years' follow-up that the strongest predictor of adenoma recurrence was the number of adenomas detected. Other studies also found that the number of adenomas predicts the subsequent development of more adenomas, and in particular advanced colorectal neoplasia [127-130].

How big? Noshirwani et al. [127] retrospectively analyzed data from their adenoma registry and found that polyps 1 cm or larger were significantly associated with the finding of advanced adenomas 3 years later.

What features? Tubulovillous or villous features in an adenoma have been shown to increase the risk of future advanced adenomas and cancer [131,132]. Similarly, high-grade dysplasia is associated with the subsequent development of advanced adenomas.

Recognizing advanced adenomas is important when interpreting a patient's colonoscopy results because multiple studies have shown them to predict recurrent advanced neoplasms or colorectal cancer [127,131-134].

Postpolypectomy surveillance strategies according to risk of recurrent advanced adenoma **(Table 3):**

COLONOSCOPIC FINDINGS	RECOMMENDATION
Above-average risk Small, left-sided hyperplastic polyps in a patient who does not meet criteria for hyperplastic polyposis syndrome [a]	Continue average-risk screening strategy
1–2 small (< 1 cm) tubular adenomas	Colonoscopy every 5–10 years
High risk 3–10 adenomas, or any adenoma > 1 cm with villous features or high-grade dysplasia	Colonoscopy every 3 years
> 10 adenomas	Colonoscopy more often than every 3 years, consider genetic counseling for familial syndrome
Hyperplastic polyposis syndrome	Colonoscopy, no clear recommendation on interval, further investigation needed

a Diagnostic criteria for hyperplastic polyposis syndrome according to the World Health Organization International Classification:

•At least five histologically diagnosed hyperplastic polyps proximal to the sigmoid colon, of which two are greater than 10 mm in diameter, or
•Any number of hyperplastic polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative with hyperplastic polyposis, or
•More than 30 hyperplastic polyps distributed throughout the colon.
ADAPTED FROM WINAWER SJ, ZAUBER AG, FLETCHER RH, ET AL. GUIDELINES FOR COLONOSCOPY SURVEILLANCE AFTER POLYPECTOMY:A CONSENSUS UPDATE BY THE US MULTI-SOCIETY TASK FORCE ON COLORECTAL CANCER AND THE AMERICAN CANCER SOCIETY. GASTROENTEROLOGY 2006;130:1872–1885.

Conclusions

Although the treatment of advanced colorectal câncer continues to improve, large-bowel câncer remains a major cause of illness and death. The specific causes of CRC are unknown, but environmental, nutritional, genetic, and familial factors, as well as preexisting diseases, have been found to be associated with this cancer.

Adenomas are thought to be precursors of most colorectal cancers, so they have been used as an intermediate end point in a number of randomized trials. However, adenoma recurrence trials on the effects of a low-fat, high-fiber diet, wheat bran supplementation, and low-fat, high-fiber, and highfruit and -vegetable diet have shown no effect on adenoma recurrence rates. One possible explanation for the lack of associations in trials is their short duration. Most of the adenoma recurrence trials have lasted 3to 4 years, whereas colorectal carcinogenesis in humans has been estimated to take 10 to 40 years. A dietary intervention could be protective at different stages of adenoma progression to cancer: (a) initial appearance, (b) growth, or (c) transformation into carcinoma. If diet affects early events in the neoplastic process, such as the initial growth of an adenoma, intervention effects might not emerge during the short duration of the original trial.

In future research, one important issue to consider is if fruit and vegetable intakes during childhood, adolescence, or early adulthood are more important determinants of colon cancer risk, than intakes in later adulthood then analysis of adult diet may not have captured the relevant exposure period.

In light of the emerging obesity epidemic in most industrialized societies, additional investigation is needed to determine whether or not CRC represents another disease entity associated with, or resulting from, the insulin resistance syndrome. Further development of quantitative IR biomarkers that accurately reflect long-term insulin and glucose exposure may also be rewarding with respect to identifying population subsets that are at increased CRC risk [40].

The difference in effect by gender and location of observed changes from moderate-to-vigorous intensity exercise intervention warrants further study. It is possible that Bcl-2 and Bax may be important biomarkers in providing mechanistic data to support the epidemiologic evidence for the role of physical activity in reduction of colon cancer risk.[44].

As evidence emerges of the efficacy of chemoprevention in persons at high risk for colorectal cancer, it seems appropriate to consider a similar strategy for the general population. Chemoprevention should not replace periodic fecal occult-blood tests and endoscopic screening, as well as modification in known risk factors for colorectal cancer, such as reduction in the intake of red meat, appropriate exercise, smoking cessation, and weight control.
The available data would suggest that for chemoprevention, aspirin would need to be used in doses greater than used for cardiovascular prevention and for a duration close to 10 years. Therefore, the potential benefit of aspirin chemoprevention would need to be carefully weighed against its harms. More information is still required to clarify the optimal dose, starting age, and duration of use of aspirin. In addition, its effect on colorectal cancer incidence and mortality should be clarified, particularly given the evidence that in patients at average cardiovascular risk, use of aspirin does not reduce all-cause mortality. Further evaluation of the cost-effectiveness of chemoprevention compared with, and in combination with, a screening strategy is required [57].
Non-ASA NSAIDs seem to be effective at reducing the incidence of colorectal adenomas and CRC in observational studies. Good-quality RCT data suggest that COX-2 inhibitors are effective at reducing the incidence of colorectal adenomas in patients with previous adenomas. However, positive data on the reduction of death is lacking for both non-ASA NSAIDs and COX-2 inhibitors. No quantitative data exist on the risk for gastrointestinal or cardiovascular harms associated with daily, multiyear use of non-ASA NSAIDs. Available data on COX-2 inhibitors suggest that absolute risk increases of over 1% for cardiovascular events and for clinically important gastrointestinal complications can be anticipated after only 2 to 3 years of use, and higher risks may accrue over longer periods. Furthermore, the cost-effectiveness of chemoprevention needs to be considered carefully and compared with other strategies, such as colorectal cancer screening alone. Therefore, the balance of benefits and risks does not appear to favor chemoprevention with non-ASA NSAIDs or COX-2 inhibitors in average-risk individuals or in those with a history of colorectal adenomas [58].

Surgical resection remains the only curative treatment, and the likelihood of cure is greater when the disease is detected at an earlier pathological stage. Early detection is the goal of screening programs that use periodic examination of stool for occult blood, with or without intermittent endoscopic examination of the bowel. Nevertheless, the optimal method for early detection remains uncertain, and despite widely published recommendations for such screening programs, compliance remains poor.

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