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Chapter 1

Colorectal Cancer

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Additional information is available at the end of the chapter

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1. Introduction

1.1. Epidemiology – Clinical presentation-screening

Colorectal cancer (CRC) is a common and lethal disease. The risk of developing CRC is influenced by both environmental and genetic factors. Colorectal cancer is the third most common cancer worldwide. Clinical symptoms develop late in the course of the disease, and precursor lesions (adenomas) can be easily detected and removed. The disease is a candidate for early detection and prevention by screening. The epidemiology of CRC and risk factors for its development will be discussed here.

Epidemiology — CRC incidence and mortality rates vary markedly around the world [1]. Globally, CRC is the third most commonly diagnosed cancer in males and the second in females, with over 1.2 million new cases and 608,700 deaths estimated to have occurred in 2008.Incidence and mortality rates are substantially higher in males than in females [2]. It is the fourth most common cause of cancer death after lung, stomach, and liver cancer. It is more common in developed than developing countries.

In the United States, both the incidence and mortality have been slowly but steadily decreasing. Annually approximately 143,460 new cases of large bowel cancer are diagnosed, of which 103,170 are colon and the remainder rectal cancers. Annually, approximately 51,690 Americans die of CRC, accounting for approximately 9 percent of all cancer deaths [6].

Incidence — There is significant geographical variation in age-standardized and cumulative, 0-74 year incidence and mortality rates. Globally, the incidence of CRC varies over 10-fold. The highest incidence rates are in Australia and New Zealand, Europe and North America, and the lowest rates are found in Africa and South-Central Asia [5]. The highest incidence rate of CRC is estimated in the Czech Republic [39-42]. These geographic differences appear to be

attributable to differences in dietary and environmental exposures that are imposed upon a background of genetically determined susceptibility.

In Europe, the incidence of colorectal cancer is increasing, particularly in Southern and Eastern Europe, where rates were originally lower than in Western Europe [7]. In the USA, incidence rose until the mid-1980s but in the last two decades the rates have fallen for both men and women. Countries that have had a rapid 'westernization' of diet, such as Japan, have seen a rapid increase in incidence of colorectal cancer. Consumption of meat and dairy products in Japan increased tenfold between the 1950s and 1990s.

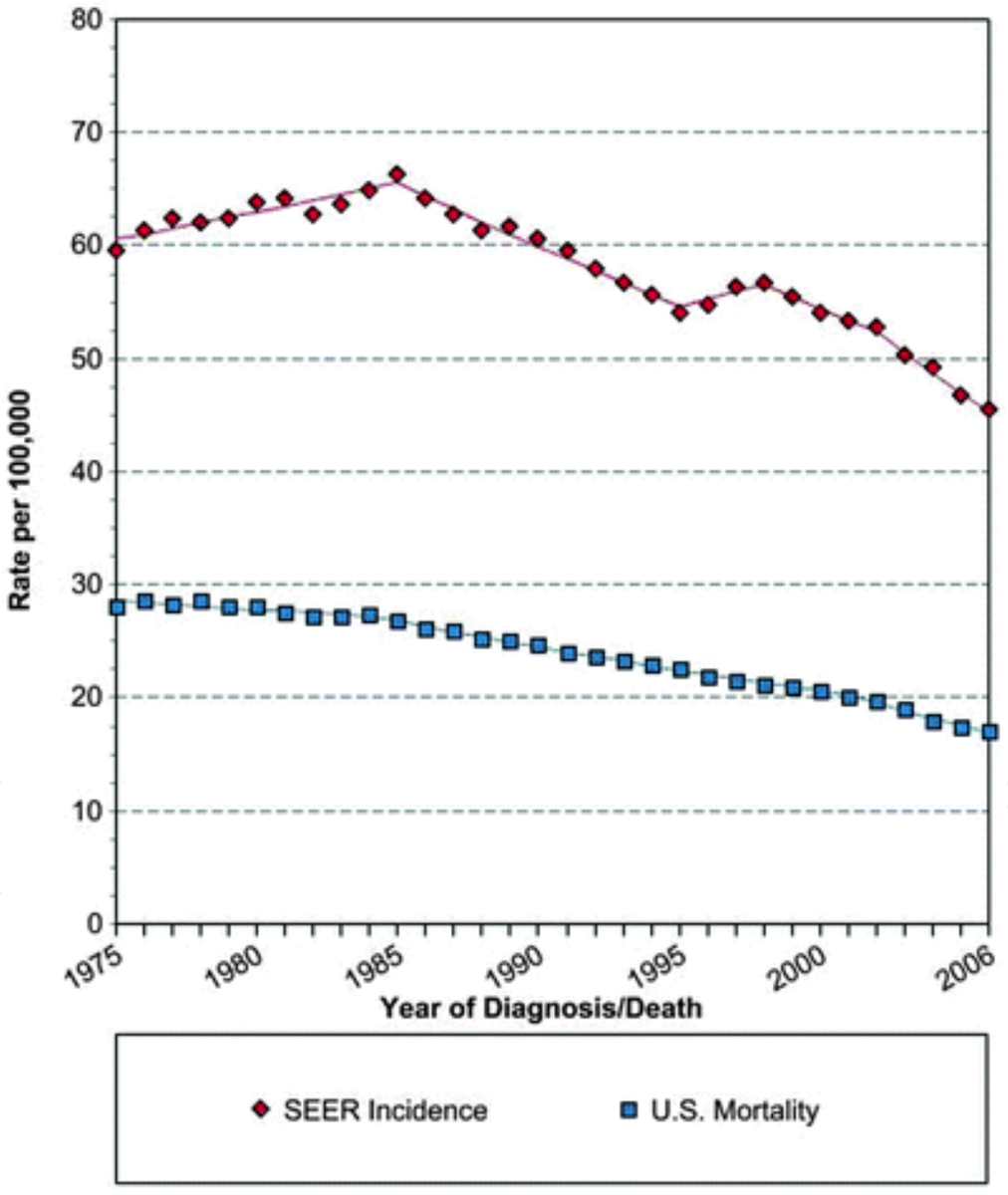

Figure 1. Age-adjusted colorectal cancer incidence and death rates in the United States 1975–2006.

Colorectal cancer (CRC) is a disease with a major worldwide burden. The worldwide incidence of CRC is increasing. In 1975, the worldwide incidence of CRC was only 500,000.In western countries, some of the increase is due to the aging of the population. However, in countries with a low baseline rate of CRC, the incidence is increasing even after age-adjustment. Prior to 1985, the age-adjusted incidence of CRC in the USA also increased (figure 1). However, since this time the rates have declined an average of −1.6% per year. In the time period 1998–2005, the rate of decline accelerated; −2.8% per year in men and −2.3% per year in women. This reduction has been mainly confined to those of white race and is largely limited to a decrease in the incidence of distal cancers. Although the cause of the decrease in incidence is unknown, and may have been influenced by many factors, it is likely that much may be attributable to screening by sigmoidoscopy and colonoscopy. In contrast, the incidence of proximal cancers has remained relatively stable over the same time period. Currently, the overall probability of an individual developing CRC in the USA over a lifetime is 5.5% in men and 5.1% in women.

From a population perspective, age is the most important risk factor for CRC. CRC is predominantly a disease of older individuals. 90% of cases are diagnosed over the age of 50. The risk of CRC continues to increase with age (Figure 2). The incidence per 100,000 people age 80–84 is over seven times the incidence in people age 50–54. However, CRC can occur at any age and the incidence of CRC occurring before age 40 may be increasing.

In the USA, the risk of CRC differs by sex. The age-adjusted incidence of CRC is over 40% higher in men than women [8]. Overall, the incidence of CRC in men is 61 per 100,000 males as compared to 45 per 100,000 females. In addition, the ratio of colon to rectal cancer differs by sex; the ratio of colon to rectal cases for women is 3:1 as compared to 2:1 for males.

Race and ethnicity influence CRC risk [20]. Ashkenazi Jewish individuals appear to be at a slightly increased risk of CRC. At least part of this increased incidence may be due to a higher prevalence of the *I1307K* mutation of the adenomatous polyposis gene (*APC*), a mutation that confers an increased risk of CRC development (18–30% lifetime risk). The *I1307K* mutation is found in 6.1% of unselected Ashkenazi Jewish individuals and 28% of Jewish individuals with CRC, while the mutation is rare in other populations. In the USA, the incidence of CRC is higher in African Americans of either sex as compared to white Americans. Asian American/Pacific Islanders, Native Americans, and Hispanic Americans experience a lower incidence of CRC than Caucasians (Table 1).African Americans have not experienced the substantial reduction in incidence of CRC found to have occurred in whites; prior to 1980 incidence in African Americans was actually lower than in white Americans. In African Americans, the increased rate of cancer is predominantly due to a higher rate of proximal cancers.

There is substantial geographic variation in the incidence of CRC, with relatively high rates in North America, Western Europe, and Australia and relatively low rates in Africa and Asia (Figure 3) Such observations led to Burkitt's hypothesis; that dietary differences, specifically fiber and fat intake, between populations were responsible for the marked variation in rates of CRC found around the world. Burkitt observed that populations in low-risk areas of the third world had greater stool bulk, a faster colonic transit time, and higher dietary fiber intake

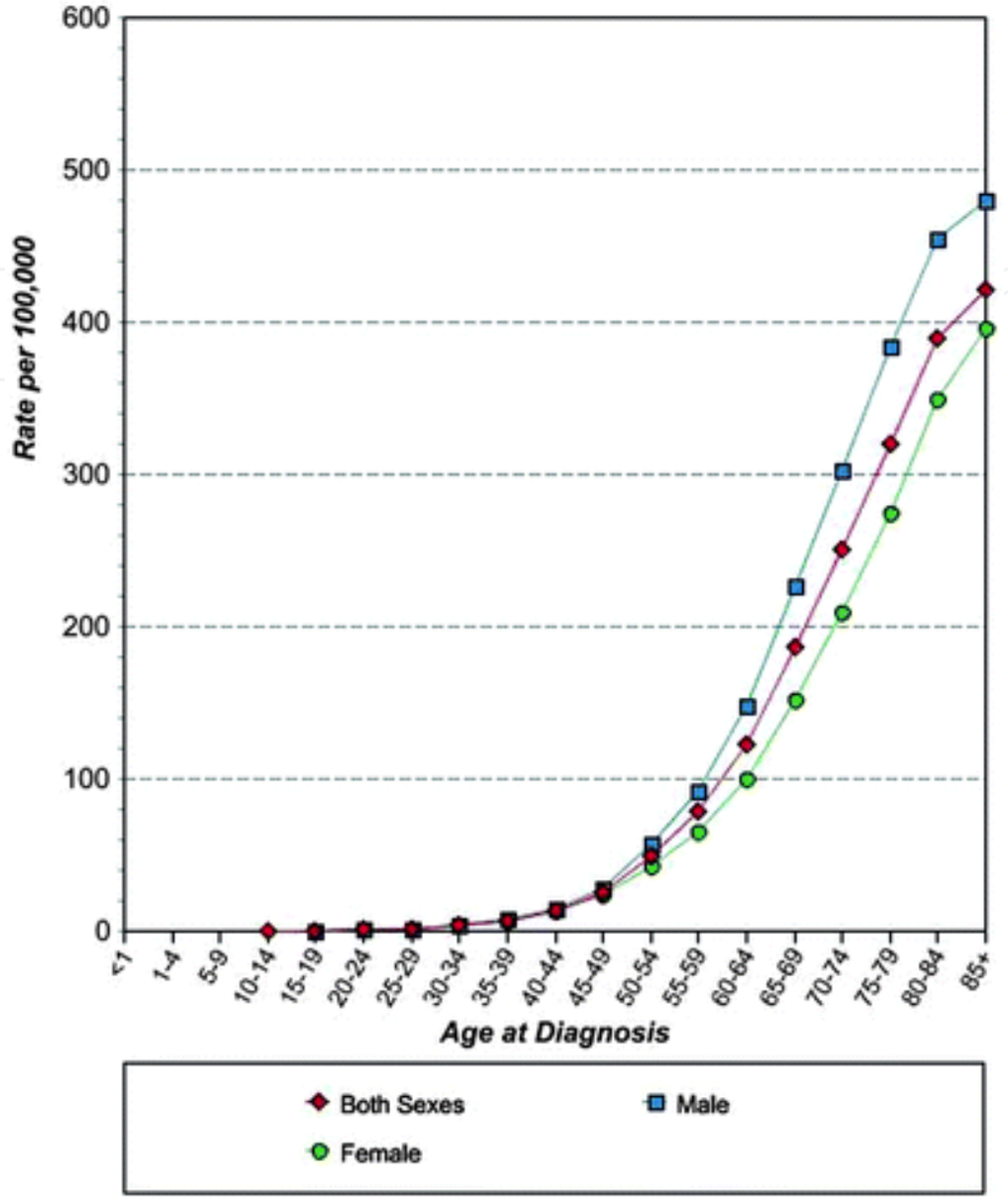

Figure 2. Age-specific SEER incidence rates in the United States 1992–2006.

		White	African American	Asian American and Pacific Islander	American Indian/ Alaska Native	Hispanic/ Latino
Incidence	Male	58.9	71.2	48.0	46.0	47.3
	Female	43.2	54.5	35.4	41.2	32.8
Mortality	Male	22.1	31.8	14.4	20.5	16.5
	Female	15.3	22.4	10.2	14.2	10.8

*per 100,000 age-adjusted to the 2000 US standard population

Table 1. Incidence and mortality rates* for CRC by site, race and ethnicity, US 2001–2005

than populations in high-risk, westernized regions. Although such ecological studies are confounded by numerous factors (for example, variations in average life expectancy, cancer detection methods, etc.), environmental factors (most prominently dietary factors) are still considered to have a major role in this disease. This is supported by studies of migrants from low prevalence areas to high prevalence areas. Such studies generally demonstrate that the incidence of CRC in the migrants increases rapidly to become similar and in some cases to exceed the incidence of the high-risk area. Interestingly, there is less variation in the incidence of rectal cancer between countries as compared to the incidence of colon cancer.

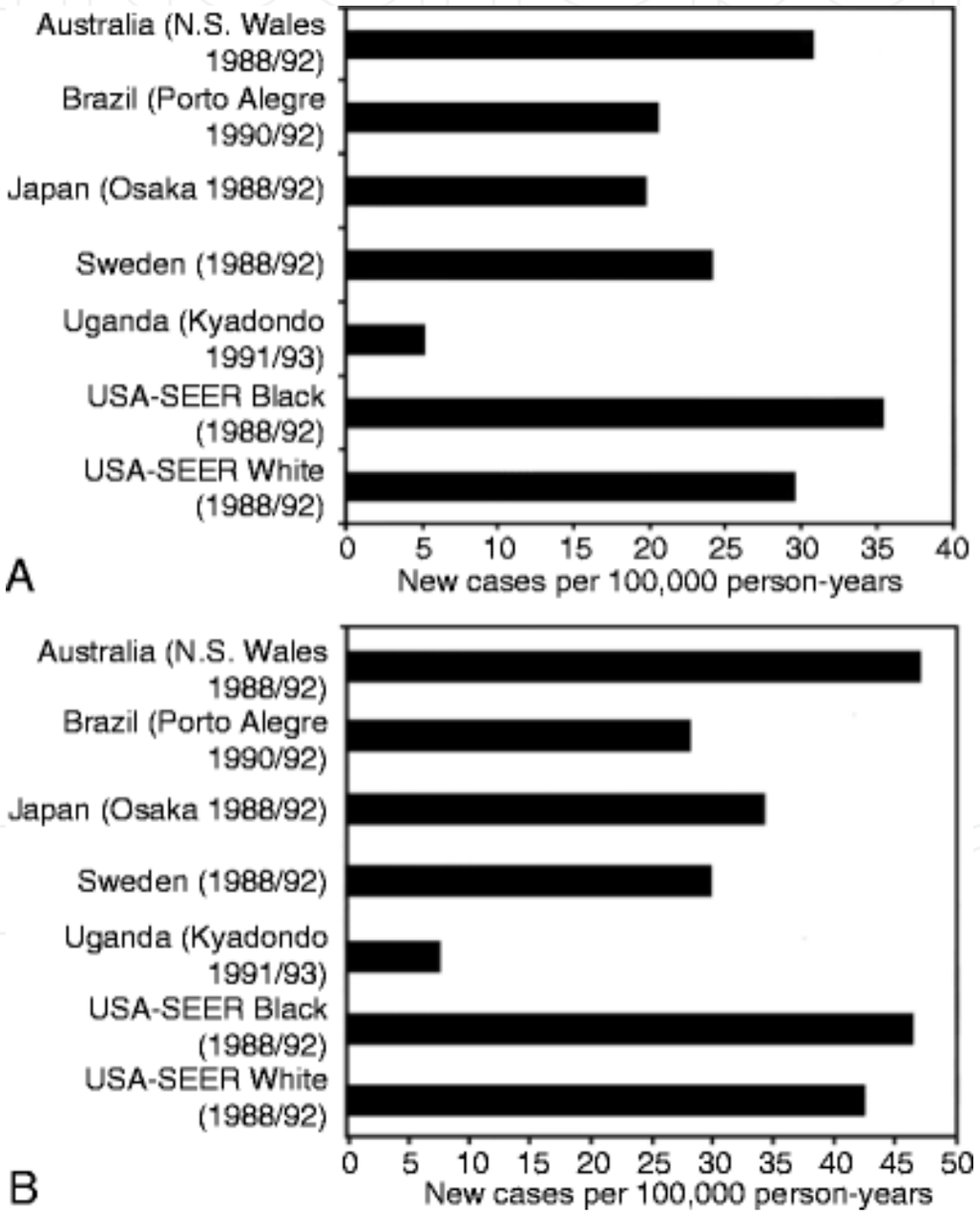

Figure 3. A Age-Standardized (to the world population) incidence rates of cancer of the large bowel among females, B Age-standardized (to the world population) incidence rates of cancer of the large bowel among males

The lifetime incidence of CRC in patients at average risk is about 5 percent, with 90 percent of cases occurring after age 50. In the US, CRC incidence is about 25 percent higher in men than in women and is about 20 percent higher in African Americans than in whites. The incidence is higher in patients with specific inherited conditions that predispose them to the development of CRC.

Mortality — Death rates from CRC have declined progressively since the mid-1980s in the United States and in many other western countries. This improvement in outcome can be attributed, at least in part, to detection and removal of colonic polyps, detection of CRCs at an earlier stage, and more effective treatments, particularly adjuvant therapy. Globally, the United States has one of the highest survival rates from CRC. However, mortality rates continue to increase in many countries with more limited resources and health infrastructure, particularly in Central and South America and Eastern Europe [43-44]. African Americans suffer the highest mortality rate from CRC in the USA (Table 1).The reasons for the higher mortality rate are likely multifactorial, including the higher incidence of CRC, and the differences in stage distribution. Differences in incidence, stage distribution and survival of CRC between white and African Americans are in part due to differences in socioeconomic status, screening rates and treatment. However, the differences may also be due to genetic and environmental factors that have yet to be elucidated. The highest mortality rates in both sexes are estimated in Central Europe (20.3/100000 for male patients, 12.1/100000 for female patients), and the lowest in the Middle Africa (3.5 and 2.7 respectively). The majority of deaths of CRC occur in older people, around 80% in people aged 65 and above and almost two-fifths of deaths appear in the group with age over 80.

Because CRC is a survivable cancer, with a 5-year survival rates adjusted for life expectancy of 64% the prevalence of people living with a diagnosis of CRC in the population is substantial.

Factors that may have contributed to the worldwide variation in colorectal cancer incidence patterns include differences in the prevalence of risk factors and screening practices. Established and suspected modifiable risk factors for colorectal cancer, including obesity, physical inactivity, smoking, heavy alcohol consumption, a diet high in red or processed meats, and inadequate consumption of fruits and vegetables, are also factors associated with economic development or westernization [35]·This partially explains the historically high albeit decreasing colorectal cancer incidence rates observed in long-standing developed countries such as the United States, Canada, and New Zealand over the past several years [36]. Colorectal cancer screening can also influence colorectal cancer incidence rates. All screening tests including stool blood tests (e.g. fecal occult blood test) and structural screening tests (e.g. sigmoidoscopy and colonoscopy) may increase colorectal cancer incidence rates initially as they detect previously undiagnosed cases.

Riskfactors-Although the exact cause for the development of colorectal cancer is not known, there are factors that increase risk for developing adenomas, polyps and cancer. These include numerous suspect factors.

Environmental and genetic factors can increase the likelihood of developing CRC. Although inherited susceptibility results in the most striking increases in risk, the majority of CRCs are sporadic rather than familial. These include:

1. **HereditaryCRCsyndromes** such as: Familial adenomatous polyposis (FAP) and Lynch Syndrome (hereditary nonpolyposis colorectal cancer (HNPCC)) which are the most common of the familial colon cancer syndromes, but together these two conditions account for only about 5 percent of CRC cases.

a. **Familialadenomatouspolyposis(FAP)** and its variants (Gardner's syndrome, Turcot's syndrome, and attenuated adenomatous polyposis coli) account for less than 1 percent of colorectal cancers. In typical FAP, numerous colonic adenomas appear during childhood. Symptoms appear at an average age of approximately 16 years and colonic cancer occurs in 90 percent of untreated individuals by age 45**.** An attenuated form of APC (AAPC) carries a similarly high risk of colon cancer but is characterized by fewer adenomas and an older average age of cancer diagnosis of 54 years.

FAP is caused by germline mutations in the adenomatous polyposis coli (APC) gene which is located on chromosome 5. The same gene is involved in the attenuated form of FAP, but the sites of the APC gene mutations are different.

b. **Lynchsyndrome** — Lynch syndrome is an autosomal dominant syndrome, which is more common than FAP, and accounts for approximately 3 to 5 percent of all colonic adenocarcinomas. The name Lynch syndrome honors the pioneering work of Dr. Henry Lynch in drawing attention to the syndrome. The term Lynch syndrome is now commonly used for families who have been genetically determined to have a disease-causing defect in one of the mismatch repair genes, most commonly hMLH1, hMSH2, hMSH6, or PMS2. As a general rule, patients with Lynch syndrome have a germline mutation in one allele of a MMR gene and the second allele is inactivated in the colorectal cancers by somatic mutation, loss of heterozygosity, or epigenetic silencing by promoter hypermethylation.

The colorectal tumors that develop in patients with Lynch syndrome are characterized by early age of onset and predominance of right-sided lesions [21]. The mean age at initial cancer diagnosis is 48 years, with some patients presenting in their 20s. Nearly 70 percent of first lesions arise proximal to the splenic flexure, and approximately 10 percent will have synchronous (simultaneous onset of two or more distinct tumors separated by normal bowel) or metachronous cancers (non-anastomotic new tumors developing at least six months after the initial diagnosis).

Extracolonic cancers are very common in Lynch syndrome, particularly endometrial carcinoma, which may occur in up to 60 percent of female mutation carriers in some families. Other sites at increased risk of neoplasm formation include the ovary, stomach, small bowel, hepatobiliary system, brain and renal pelvis or ureter.

2. Personal or family history of sporadic CRCs or adenomatous polyps

Patients with a personal history of CRC or adenomatous polyps of the colon are at risk for the future development of colon cancer. The clustering of risk in families may be attributed to an inherited susceptibility, common environmental exposures, or a combination of both. The

influence of a more distant family history of CRC on individual risk has not been determined with certainty. Some of the increased risk attributed to family history is due to inheritance of known susceptibility genes, such as mutations in the *APC* gene, *p53* gene, or in MMR genes, particularly *MSH2*, *MLH1*, and *MSH6*.

Importantly, the majority of cases of CRC cannot be attributed to known genetic defects even when associated with a family history of CRC as recognized genetic syndromes account for only a small proportion of all cases of CRC. Additional autosomal dominant genetic defects conferring a high risk of CRC almost certainly is found. However, at least some of the increased risk of CRC associated with a family history is likely attributable to other genetic factors, such as recessive susceptibility genes, autosomal dominant genes with low penetrance, or complex interactions between an individual's genetic makeup and environmental factors.

Despite the importance of family history on the risk of CRC, up to 25% of individuals with a first-degree relative with confirmed CRC do not report having such a family history and even those that do report a history may not be aware of the increased risk associated with this. This has important implications for the assessment of family history as well as patient and family counseling.

3. Inflammatory bowel disease

Patients with long-standing inflammatory bowel disease (IBD) are known to be at an elevated risk of CRC, although it is difficult to precisely estimate the risk. The magnitude of the risk has been studied extensively in ulcerative colitis (UC).

Ulcerativecolitis— There is a well documented association between chronic ulcerative colitis and colonic neoplasia, with the extent, duration, and activity of disease being the primary determinants while for Crohn's disease there are less data. However, there is an association between pancolitis due to Crohn's disease and the risk of colon malignancy. The extent of disease does appear to have a significant influence on CRC risk in UC [38]. Other factors that may modify the risk of CRC in patients with UC include the coexistence of primary sclerosing colangitis (PSC), presence of inflammatory pseudopolyps, and severity of inflammation. For patients with long-standing, extensive UC, colectomy is an effective strategy for the prevention of CRC. Other strategies include endoscopic surveillance for dysplasia and/or the use of chemopreventive agents.

The relationship between Crohn's disease and the development of CRC has been less consistently demonstrated. In studies using data from referral-based practices, the risk of development of CRC appears to be significantly increased in patients with extensive Crohn's colitis. Finally, the risk of CRC in patients with Crohn's disease is elevated, but the exact magnitude of increased risk remains unclear and requires further investigation.

Several additional risk factors have been identified mostly in observational studies. These may include: race/ethnicity and gender, acromegaly, renal transplantation, diabetes mellitus and insulin resistance, use of androgen deprivation therapy, cholecystectomy, alcohol, obesity.

Protectivefactors — A large number of factors have been reported by at least some studies to be associated with a decreased risk of CRC. These *include* regular physical activity, a variety of dietary factors, the regular use of aspirin or nonsteroidal antiinflammatory drugs (NSAIDs), and hormone replacement therapy in postmenopausal women. None of these factors are currently used to stratify CRC screening recommendations.

1. Physical Activity

Over 50 studies have been conducted to evaluate the influence of physical activity on CRC risk. Overall, the literature is relatively consistent with respect to the effect: Greater physical activity (occupational, recreational, or total activity) is associated with a reduced risk of CRC. The effect is relatively small; the estimated increased risk of colon cancer in the sedentary ranges from 1.6 to 2.0. The biological mechanisms that explain the relationship between physical activity and CRC risk are unclear. Increased physical activity leads to changes in insulin sensitivity and IGF levels, and both insulin and IGF are potentially involved with colorectal carcinogenesis. Additional proposed mechanisms include effects of physical activity on prostaglandin synthesis, effects on antitumor immune defenses, and the reduction in percent body fat associated with exercise. The mechanism is almost certainly multifactorial. Nonetheless, for a host of health-related reasons, frequent moderate to vigorous physical activity can be recommended to most patients without hesitation.

2. Fruit and Vegetable Intake

The effect of dietary intake of fruit and vegetables on CRC risk has been evaluated extensively [22]. Fruits and vegetables are a source of antioxidants, including carotenoids and ascorbate. Other bioactive constituents in fruits and vegetables that may protect against carcinogenesis include the indoles and isothiocyanates. The evidence for an association between fruit and vegetable intake and the risk of CRC is inconsistent [23]. Given this, it is unlikely that a large number of cases of CRC can be attributed directly to a lack of intake of fruits or vegetables, or that major additional interventions to increase consumption would lead to a substantial reduction in the incidence of CRC.

3. Aspirin and Nonsteroidal Anti-inflammatory Drugs

There is considerable observational evidence that the use of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) has protective effects at all stages of colorectal carcinogenesis (aberrant crypt foci, adenoma, carcinoma, and death from CRC [14]. The mechanism of antineoplastic action of NSAIDs is incompletely understood, but it is believed that both cyclooxygenase (COX)-dependent and COX-independent pathways may be involved. NSAIDs and aspirin may play an important role in secondary chemoprevention of colorectal adenomas and cancer. Because chemopreventive agents must be used in the general population to substantially reduce the burden of disease, the risks of chemoprophylaxis with aspirin or NSAIDs may outweigh the benefits. Serious GI complications occur in regular users of aspirin and NSAIDs although rare.

4. Hormone Replacement Therapy

Observational studies have demonstrated an association between hormone replacement therapy (HRT) in women and a reduction in both incidence and mortality from CRC. Possible mechanisms for the effect of HRT include a reduction in bile acid secretion (a potential promoter or initiator of CRC), as well as estrogen effects on colonic epithelium, both directly and through alterations in insulin-like growth factor with the use of estrogens. Overall, there appears to be a consistent reduction in the risk of CRC with the use of HRT. However, given the potential adverse effect of HRT, this should not be used as a primary preventive strategy for CRC.

4. Clinical presentation

4.1. Symptoms

Symptoms are common and prominent late in colon cancer when the prognosis is poor but are less common and less obvious early in the disease. Common symptoms include abdominal pain, rectal bleeding, altered bowel habits, and involuntary weight loss [58]. Although colon cancer can present with either diarrhea or constipation, a recent change in bowel habits is much more likely to be from colon cancer than chronically abnormal bowel habits. Less common symptoms include nausea and vomiting, malaise, anorexia, and abdominal distention.

Symptoms depend on cancer location, cancer size, and presence of metastases. Left colonic cancers are more likely than right colon cancers to cause partial or complete intestinal obstruction because the left colonic lumen is narrower and the stool in the left colon tends to be better formed because of reabsorption of water in the proximal colon [59]. Large exophytic cancers are also more likely to obstruct the colonic lumen. Partial obstruction produces constipation, nausea, abdominal distention, and abdominal pain. Partial obstruction occasionally paradoxically produces intermittent diarrhea as stool moves beyond the obstruction.

Distal cancers sometimes cause gross rectal bleeding, but proximal cancers rarely produce this symptom because the blood becomes mixed with stool and chemically degraded during colonic transit. Bleeding from proximal cancers tends to be occult, and the patient may present with iron deficiency anemia without gross rectal bleeding. The anemia may produce weakness, fatigue, dyspnea, or palpitations. Advanced cancer, particularly with metastasis, can cause cancer cachexia, characterized by a symptomatic tetrad of involuntary weight loss, anorexia, muscle weakness, and a feeling of poor health.

4.2. Signs

Just as with symptoms, colon cancer tends not to produce signs until advanced. Anemia from gastrointestinal bleeding may produce pallor. Iron deficiency anemia can cause koilonychia manifested by brittle, longitudinally furrowed, and spooned nails; glossitis manifested by lingual erythema and papillae loss; and cheilitis manifested by scaling or fissuring of the lips. Hypoalbuminemia may clinically manifest as peripheral edema, ascites, or anasarca. Hypo-

active or high-pitched bowel sounds suggest gastrointestinal obstruction. A palpable abdominal mass is a rare finding that suggests advanced disease. Rectal examination, including fecal occult blood testing (FOBT), is important in the evaluation of possible colon cancer. Rectal cancer may be palpable by digital rectal examination. Other physical findings, although rare, should be systematically searched for, including peripheral lymphadenopathy, especially a Virchow's node in the left supraclavicular space; hepatomegaly from hepatic metastases; and temporal or intercostal muscle wasting from cancer cachexia. Very rare findings with colon cancer include a Sister Mary Joseph node caused by metastases to a periumbilical node, and a Blumer's shelf caused by perirectal extension of the primary tumor.

4.3. Laboratory abnormalities

Patients with suspected colon cancer should have routine blood tests including a hemogram with platelet count determination, serum electrolytes and glucose determination, evaluation of routine serum biochemical parameters of liver function, and a routine coagulation profile. About half of patients with colon cancer are anemic. Anemia, however, is very common, so that only a small minority of patients with anemia have colon cancer. Iron deficiency anemia of undetermined etiology, however, warrants evaluation for colon cancer, particularly in the elderly [60]. Hypoalbuminemia is uncommon, but not rare, in colon cancer. It usually indicates poor nutritional status from advanced cancer. Routine serum biochemical parameters of liver function are usually within normal limits in patients with colon cancer. Abnormalities, particularly elevation of the alkaline phosphatase level, often indicate hepatic metastases. The serum lactate dehydrogenase level may increase with colon cancer. Diarrhea associated with colon cancer can rarely produce electrolyte derangements or dehydration. Nausea and vomiting from colon cancer can rarely produce metabolic derangements of hypovolemia, hypokalemia, or alkalosis.

The serum carcinoembryonic antigen level is not useful to screen for colon cancer. It is only moderately sensitive. Although patients with very advanced cancer tend to have highly elevated levels, patients with early and highly curable colon cancer tend to have only minimally elevated levels, with considerable overlap with the levels of patients without colon cancer. It is poorly specific. Other colonic diseases or systemic disorders can cause a carcinoembryonic antigen elevation. Preoperative testing is, however, useful to determine cancer prognosis and to provide a baseline for comparison with postoperative levels. An elevated serum level preoperatively is a poor prognostic indicator: the higher the serum level the more likely the cancer is extensive and will recur postoperatively. After apparently complete colon cancer resection the serum level almost always normalizes; failure to normalize postoperatively suggests incomplete resection. A sustained and progressive rise after postoperative normalization strongly suggests cancer recurrence. Patients with this finding require prompt surveillance colonoscopy to exclude colonic recurrence and abdominal imaging to exclude metastases.

4.4. Unusual clinical syndromes caused by colon cancer

Colon cancer can cause acute colonic obstruction, most commonly from exophytic intraluminal growth, and most uncommonly from intussusception or volvulus. Obstruction typically occurs in the sigmoid colon because of the narrow lumen and hard stool in this region. Patients present with abdominal pain, nausea and vomiting, obstipation, abdominal tenderness, abdominal distention, and hypoactive bowel sounds. Colon cancer can rarely perforate acutely through the colonic wall and cause acute generalized peritonitis, and can rarely perforate slowly to form a walled-off inflammatory mass or abscess with localized peritoneal signs [61]. Factors promoting colonic perforation include disruption of mucosal integrity because of transmural malignant extension or colonic ischemia, and increased intraluminal pressure because of colonic obstruction. Presentation with colonic obstruction or perforation indicates a poor prognosis. Colon cancer rarely causes ischemic colitis because of colonic dilatation proximal to malignant obstruction or malignant infiltration of blood vessels. Colon cancer occasionally causes gross rectal bleeding because of cancerous mucosal ulceration.

5. Colorectal cancer (crc) – screening

Colorectal cancer is theoretically a preventable disease and is ideally suited to a population screening programme, as there is a long premalignant phase, during which there is ample opportunity to intervene with a variety of different screening modalities.

Most CRCs are thought to arise from benign adenomatous polyps, a process that takes approximately five to ten years. This long premalignant phase makes the disease ideally suited to a population screening programme.

Early detection and removal of precancerous colon polyps and CRC may reduce both incidence and death rates related of CRC. It is recommended to begin screening at age 50 for asymptomatic persons who are at average risk. High-risk patients should have regular colorectal surveillance [45]. Several screening methods are used to detect CRC lesions. Colonoscopy is the best method and final assessment step for detection of CRC.

The ultimate aim of a screening programme for CRC is to reduce mortality from the disease, which may be achieved in two ways. As five-year survival is closely related to the stage at which the cancer is detected (patients with Dukes' stage A cancer have a greater than 90 per cent five-year survival rate, while those with Dukes' stage D disease have a 7 per cent five-year survival rate), any screening modality that results in early detection of the disease will have a beneficial effect on survival through more effective treatment (figure 5). Additionally, if benign adenomatous polyps are removed, cancer development is prevented, resulting in decreased mortality.

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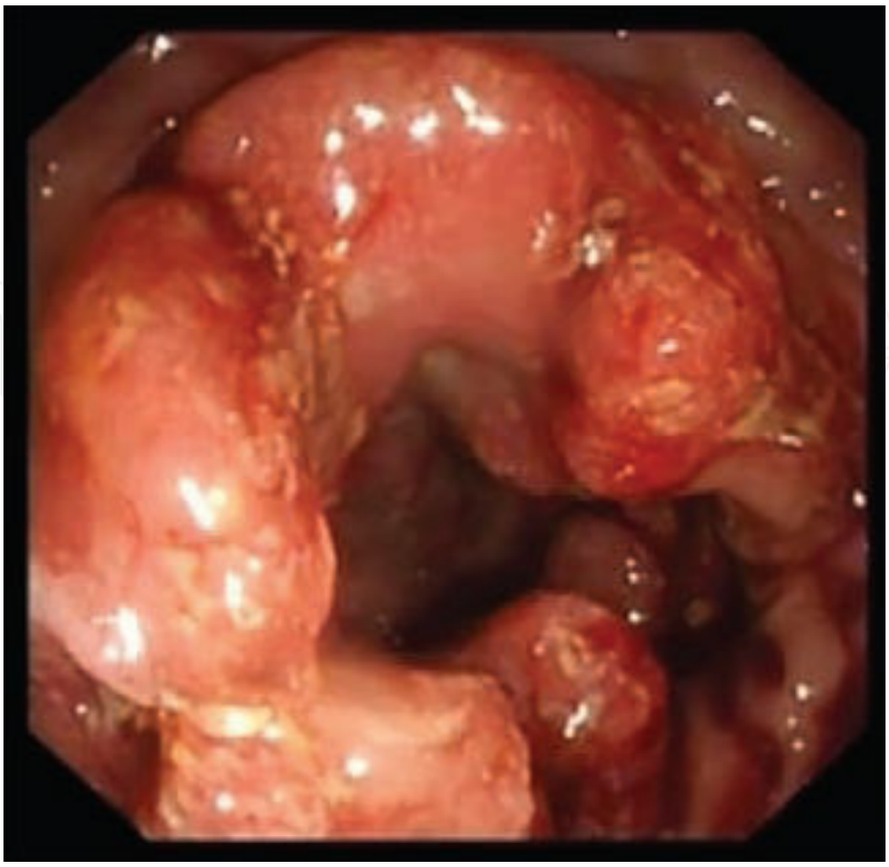

Figure 4. Colorectal cancer

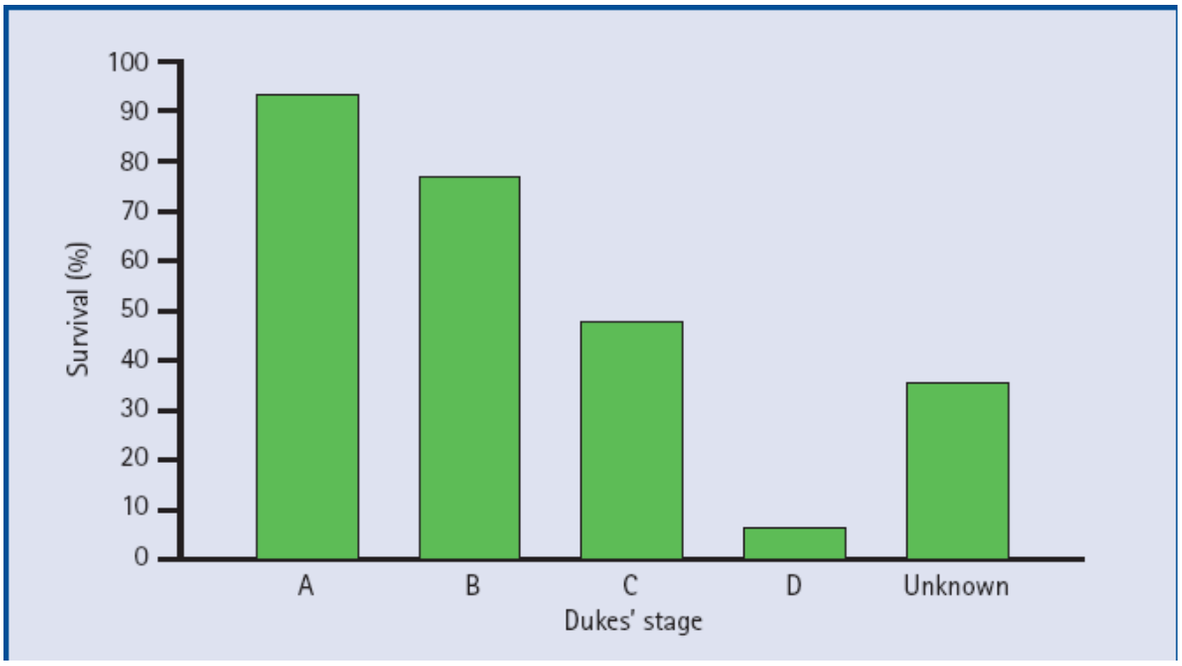

Figure 5. Five-year survival of colorectal cancer for each Dukes' stage at diagnosis

6. Who is at risk of developing colorectal cancer

There is strong tendency that countries with an obviously rising CRC incidence are more "Westernized" in lifestyle, especially in dietary habits, with increased consumption of high fat and protein but less fiber in diet. The change is more evident in urban areas than rural areas of the same country. Most of CRC is sporadic, i.e., caused by the interaction of genetic and environmental factors via the adenomacarcinoma sequence, and cancer may take up to ten years to develop in this way. Adenomas are more common with age, and one in four of the population aged over 50 will develop one or more polyps, with 10% of these polyps progressing to cancer over time.The most common indicator of high risk is a first-degree relative with CRC.

7. Tests for colorectal cancer screening

Tests for CRC include: colonoscopy, flexible sigmoidoscopy (FS), virtual colonoscopy and faecal occult blood testing (FOBt).

7.1. Faecal Occult Blood testing (FOBt)

FOBt has been used widely in CRC screening for several decades. Screening at age 50 for asymptomatic persons who are at average risk with annual and biennial FOBt has been shown in multiple randomized trails to reduce CRC incidence and mortality rates [49].

FOBt can detect occult blood in a small amount of stool sample. It is cheap, non-invasive and easily performed at home. FOBt is based on the propensity of CRC and adenomas to bleed microscopically.

There are two different types of FOBT, guaiac FOBT (gFOBT) and immunochemical FOBT (iFOBT). The gFOBT uses a guaiac-impregnated card to detect heme. The basis of the test involves the detection of the peroxidase activity of heme when a hydrogen peroxide developer is added. Therefore, the presence of any other peroxidases, e.g. from fruit/ vegetables, can result in a false positive test, as can the presence of heme in red meat. There can also be bleeding within the intestine for other reasons, again resulting in false positive results. False negative results can occur due to the irregular nature of the bleeding from the tumor; several samples are usually requested to attempt to overcome this problem [50]. The sensitivity of gFOBT is about only 50% of cancers will be picked up in population screening (figure 6).

iFOBT test have been developed which specifically detect the hemoglobin in human feces by antibodies and is widely available now [51]. It is more sensitive and specific for human hemoglobin than gFOBT and thus does not require dietary or drug restriction. However, iFOBT is more expensive than gFOBT and the high analytical sensitivity of most of the commercially available tests results in a greater number of participants requiring colonoscopy and a greater false positive rate [54]. However, recent developments in quantitative iFOBT may overcome this problem, asthe trigger for investigation can be set at any concentration of fecal hemoglobin. Clinical trials have shown that persons with positive occult-blood tests have

a risk of cancer that is three to four times as high as that among persons with negative tests, and that colonoscopy should be recommended for persons with these positive tests. In a recent study (Quintero et al) it has been shown that both iFOBT and colonoscopy are effective for detecting colorectal cancer but iFOBT is less effective for early detection of premalignant lesions (adenomas) than colonoscopy or sigmoidoscopy [57]. However, comparative studies have shown that iFOBT is more accurate than the gFOBT for the detection of colorectal cancer and advanced adenomas and this new test is now recommended as the first-choice fecal occult blood test in colorectal-cancer screening.

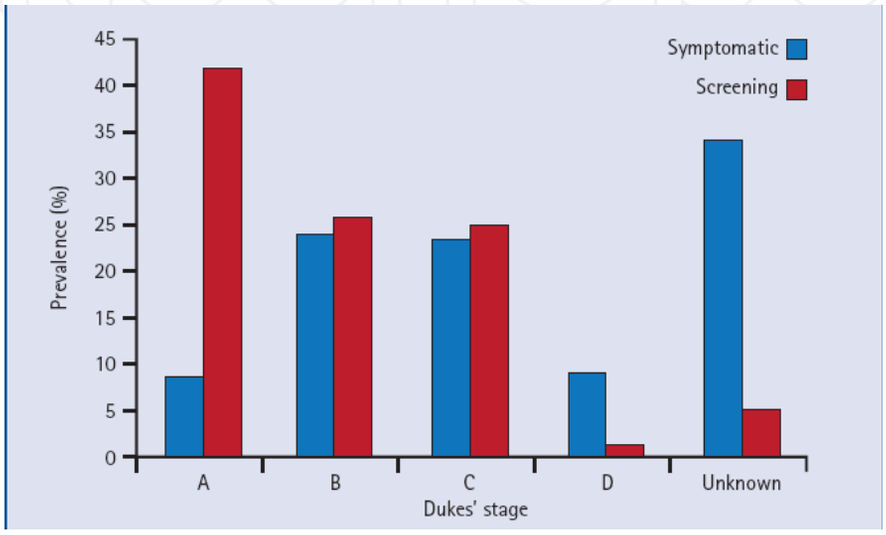

Figure 6. Dukes' stage of colorectal cancers detected by faecal occult blood test screening compared to those diagnosed in patients presenting with symptoms

7.2. Flexible sigmoidoscopy

Flexible sigmoidoscopy has also been used as a screening tool for CRC detection, as half of all cancers are seen in the rectum or sigmoid colon. There have been several studies suggesting benefit from flexible sigmoidoscopy, and their data suggest that flexible sigmoidoscopy would be an effective screening tool. Flexible sigmoidoscopy as an alternative to colonoscopy has the advantage that no oral bowel preparation is required, as the subject uses an enema that can be taken at home.The procedure is quick, requires no sedation and examines the left colon, which is the site of 75 per cent of all colorectal neoplasia. If CO_2 insufflation is used, adenomas can be resected at the initial screening examination. This procedure does not, however, examine the right colon. For many clinicians and patients, colonoscopy is more appealing than flexible sigmoidoscopy because patients can be sedated and undergo a complete colon examination with polypectomy.

7.3. Virtual colonoscopy

Virtual colonoscopy, or computed tomography colonography (CTC), is another modality used to examine the colon. It has been suggested that this examination has fewer complications and

increased patient satisfaction when compared to colonoscopy, but with similar sensitivity and specificity for the detection of pathology. There is no requirement for sedation and it has the advantage of detecting extracolonic pathology. It does, however, still require bowel preparation and colonic insufflation with CO_2, the latter still causing discomfort. Furthermore, it is not therapeutic and the lesions detected require endoscopic evaluation and resection.

7.4. Colonoscopy

Colonoscopy is the gold standard investigation for the diagnosis of CRC. It is highly sensitive and specific for detecting both cancers and adenomas of at least 1 cm in diameter and has the added benefit not only of providing tissue for diagnostic purposes, but also affords the opportunity of removing adenomas by polypectomy and hence preventing colorectal cancer (CRC). Several large cohort studies show that among patients at average risk who undergo screening colonoscopy, 0.5 to 1.0% have colon cancer and 5 to 10% have advanced neoplasia that can be removed. Several studies have shown that among patients with an adenoma that is detected and removed at screening colonoscopy, colorectal cancer may develop in 0.3 to 0.9% within 3 to 5 years after screening. In a recent study (Zauber et al) it has been evaluated the long -term effect of colonoscopic polypectomy on mortality from colorectal cancer. According to the results of this study, the endoscopic removal of adenomas ends in reduced mortality from colorectal cancer [56]. To sum up, this procedure is considered the most accurate test for early detection and prevention of colorectal cancer as it markedly reduces the risk of CRC and death. Unfortunately, there are limitations to its use as a screening modality on a population level, although it may be the ideal choice of examination for an individual. Colonoscopy is invasive and time consuming,and requires full bowel preparation; the complication rate, although low, may still be unacceptable within a screening population.

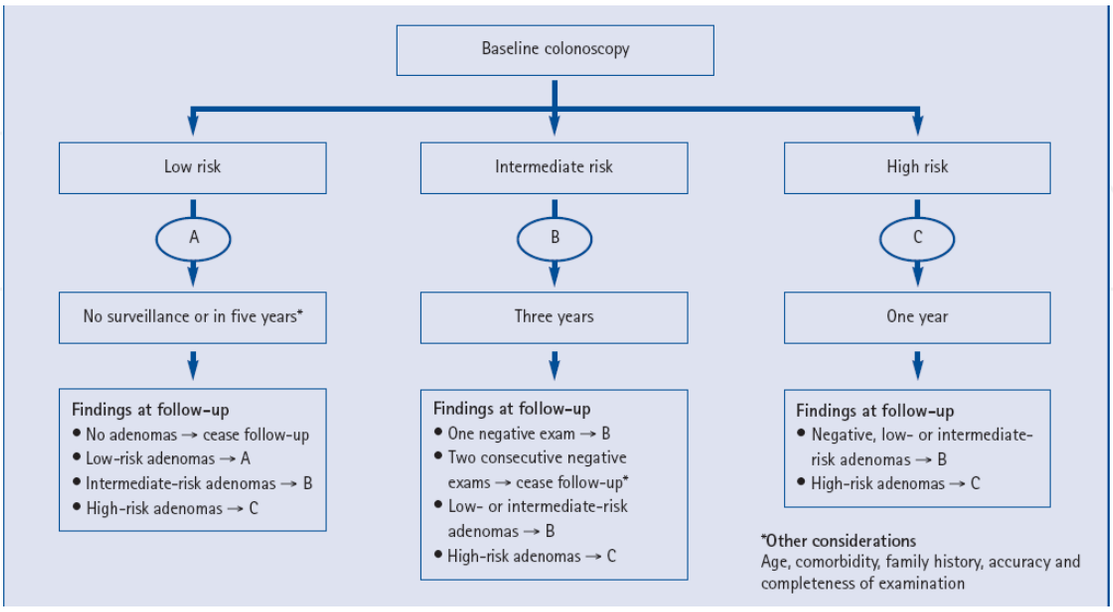

Figure 7. British Society of Gastroenterology guidelines for follow-up of adenoma removal.

8. Conclusions and recommendations

Although there are several methods available for CRC screening, none is optimal. Patients at average risk for CRC should begin screening at age 50 with either annual FOBT, flexible sigmoidoscopy every 5 years or colonoscopy every 10 years. Evidence does not show any strategy as optimal, so clinicians should discuss the advantages and disadvantages of the various screening techniques with patients. Patients with a family history of CRC or adenomas or a personal history of high-risk polyps or inflammatory bowel disease should begin screening earlier (figure 7). Routine screening in persons older than 75 years of age is not recommended. Life expectancy, rather than age alone, should guide decisions about when to stop CRC screening.

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