Colorectal Cancer

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ACP Medicine. 2005;

Epidemiology

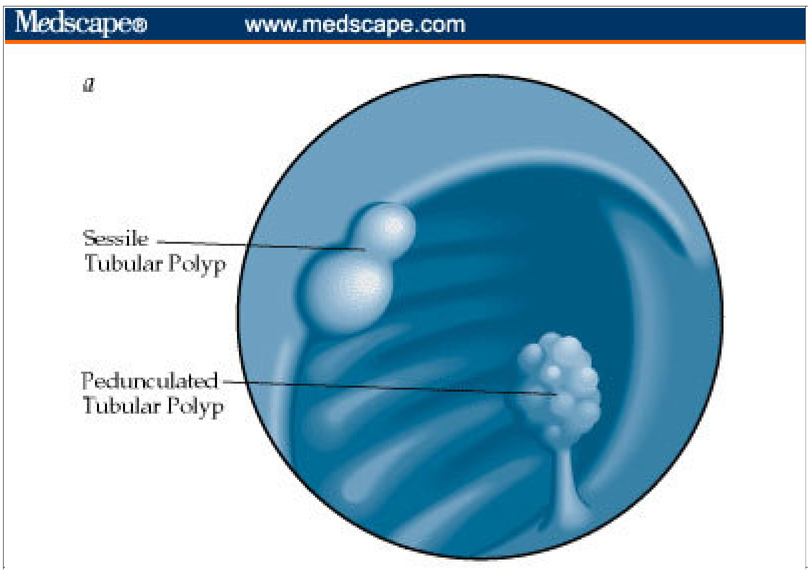
Colorectal cancer is the second most common cancer and the second leading cause of cancer death in the United States.[1] It is estimated that 147,500 new cases and 57,100 deaths from colorectal cancer occurred in 2003. Worldwide, the mortality from colorectal cancer is estimated to have been 500,000. The incidence and mortality of colorectal cancer increase with age, especially after 60 years of age. The lifetime probability (magnitude of absolute risk) for the development of colorectal cancer in the United States is about 6%. In the United States, the overall mortality declined by 1.8% a year from 1992 through 1998, although the mortality for African Americans remains higher than that for other ethnic and racial groups.[2]

Pathogenesis

Adenomatous Polyps (Adenomas)

It is thought that most colorectal cancers arise from preexisting adenomas. Such potentially premalignant lesions should be distinguished from juvenile polyps, hamartomas, and inflammatory polyps, which are not thought to progress to colorectal cancer. Recent evidence suggests that serrated adenomas, hyperplastic polyps, and admixed polyps may arise through a pathway different from that of conventional adenomatous polyps -- that is, through abnormalities in mismatch repair.[3]

Adenomatous polyps are grossly visible, gland-forming mucosal protrusions that may be pedunculated (attached by a narrow base and a long stalk) or sessile (attached across a broad, flat base with no stalk)[4] (see Figure 1). Histologically, adenomatous polyps may be tubular (composed of tubular glands extending downward from the outer surface of the polyp), villous (composed of fingerlike epithelial projections extending outward from the surface of the bowel mucosa), or both (tubulovillous).[4] The larger the adenoma, the greater the likelihood that a villous component will be present. Villous polyps are more likely to contain invasive carcinoma than are tubular polyps of the same size.[5,6] Regardless of histologic class, large polyps -- especially those larger than 1.0 cm in diameter -- are more likely to contain invasive carcinoma.[5,7]



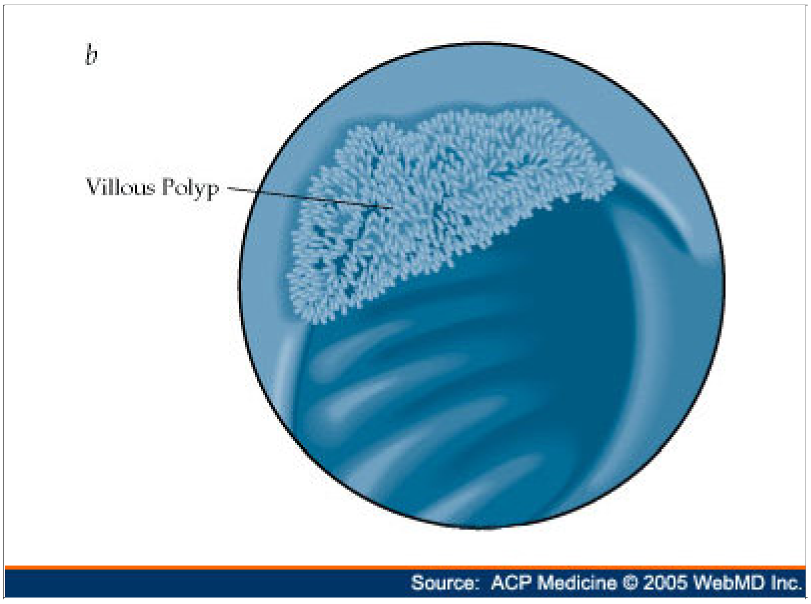


Figure 1. Adenomatous polyps. It is thought that most colorectal cancers arise from adenomatous polyps, which may be tubular (pedunculated or sessile [a]), villous (b), or tubulovillous.

Five lines of evidence suggest that colon cancers develop from premalignant adenomatous polyps:

1. Countries in which colon cancer is prevalent also have a high prevalence of colonic adenomatous polyps; conversely, a low prevalence of colon cancer correlates with a low prevalence of such adenomas.
2. Patients who have undergone resection of adenomatous polyps are at increased risk for the subsequent development of colorectal cancer.[8]
3. Adenomatous polyps occur in younger persons than do carcinomas,[9] a finding that is consistent with the suggestion that adenomas are precursor lesions.
4. Susceptibility to the development of adenomatous polyps and colorectal cancer is commonly inherited.
5. Colonoscopic polypectomy reduces the expected incidence of colorectal cancer.[10]

Adenomatous polyps are common: autopsy studies have demonstrated that such lesions are present in more than 30% of persons older than 50 years and that their prevalence increases with age.[11] However, fewer than 1% of adenomatous polyps ever become malignant.[9] After an adenomatous polyp is detected, the entire large bowel should be visualized endoscopically because synchronous lesions are found in approximately 33% of cases. Thereafter, colonoscopy should be repeated periodically, even in the absence of a documented cancer, because patients in whom one adenomatous polyp is detected have a 30% to 50% risk of developing another adenoma and are at higher than average risk for colorectal cancer.[12] The risk of subsequent colon cancer appears to depend on the histologic type, size, and number of adenomas found at the time of initial examination.[13,14] It is thought that adenomatous polyps require more than 5 years of growth before they become clinically significant.

Genetic Alterations

Colorectal cancer is a heterogeneous disease arising from a complex series of molecular changes.[15] The successive evolution of normal colonic mucosa to a benign adenoma, then to an adenomatous polyp containing cancer, and then to a potentially life-threatening invasive cancer is associated with a series of genetic events occurring over a long period. The original model that was proposed over a decade ago involves key derangements in several genes, including *APC* (in patients with familial adenomatous polyposis [FAP]), K- *ras, DCC,* and *p53. APC* gene mutations alter cell adhesion by affecting the binding of ß-catenin; they also affect the WnT signaling pathway. C-myc, a transcription factor, is activated by abnormal WnT signaling, skewing the balance between proliferation and apoptosis. Loss of APC influences tumor initiation, whereas inactivation of E-cadherin, which complexes with ß-catenin, plays a role in tumor progression.

K- *ras* gene mutations induce proliferation via the EGFR-RAS-RAF-ERK-JUN/FOS pathway and inhibit apoptosis by phosphorylating procaspase. Other genes may be affected, including *SMAD4* and *SMAD2,* which in turn may interfere with transforming growth factor-ß signaling. Additional genetic changes (e.g., DNA aneuploidy, *p53* overexpression), as well as other abnormalities, have been described in subsequent malignant transformation. Cancers arising through these mechanisms are termed microsatellite stable.

A different pathway involves deficiency of mismatch repair, as exemplified by hereditary nonpolyposis colorectal cancer. Dominant inheritance of a germline mutation involving either *hMLH1* or *hMLH2* coupled with somatic loss of the second allele results in a deficiency of mismatch repair. This mutator phenotype is characterized by the presence of multiple somatic mutations involving microsatellite repeats, termed microsatellite instability (MSI). MSI is also found in about 15% of sporadic colorectal cancers and is usually the result of acquired loss of *hMLH1* through hypermethylation of the gene promoter. Dense aggregates of the cytosine-guanine dinucleotide sequence (CpG dinucleotides) may occur in the promoter regions of several genes; these aggregates are termed CpG islands. Extensive methylation of cytosine bases is associated with promoter silencing. Cancers demonstrating methylation of multiple genes are described as CIMP (CpG island methylation phenotype) positive.

Etiology

As with many other cancers, the development of colorectal cancer typically results from a complex interaction between genetic and environmental influences.

Hereditary Syndromes and Predisposing Conditions

As many as 25% of patients with colorectal cancer have a family history of the disease, which suggests the involvement of a genetic factor. Such inherited colon cancers can be divided into two main types: the well-studied but rare FAP syndrome, which accounts for approximately 1% of cases of colon cancer annually, and the increasingly well-characterized, more common hereditary nonpolyposis colorectal cancer (HNPCC), which accounts for 5% to 10% of cases.[16]

Familial Adenomatous Polyposis

FAP is an autosomal dominant disorder characterized by the appearance of thousands of adenomatous polyps, each typically smaller than 1 cm in diameter, throughout the entire large bowel. Such polyps may occasionally be accompanied by extracolonic findings, such as osteomas, desmoid tumors, epidermoid and sebaceous cysts, pigmented retinal lesions, upper gastrointestinal tract polyps, and periampullary cancers (Gardner syndrome) or brain tumors (Turcot syndrome).[16] Persons with FAP are born with normal-appearing colonic mucosa; polyps develop during the second and third decades of life. If surgical treatment is not performed, colorectal cancer is almost certain to develop by 40 years of age.

FAP is associated with a deletion of chromosome 5q21 (known as the *APC* gene)[17] in neoplastic cells (somatic mutation) and normal cells (germline mutation); this deletion apparently leads to abnormal proliferative patterns in the colonic mucosa.[18] Mutations at the far 5' end and the far 3' end and occasional specific mutations in other areas of the *APC* gene result in an attenuated form of FAP characterized by fewer adenomas, a proximal colonic distribution of polyps, a somewhat delayed development of adenomas and cancer, and a decreased colon cancer risk.[19]

Genetic testing is now the standard of care for FAP. Despite the detailed genetic knowledge of FAP that is now available, genetic testing is often poorly interpreted. Consequently, genetic counseling is an integral part of management and should precede genetic testing.[20] Testing for FAP in a family is most informative when it begins with the affected family member, to identify the mutation responsible for FAP within that family. Once a causal mutation has been identified in an affected person, predictive testing can be done to identify other family members at risk.[21] DNA testing for *APC* gene mutations has a sensitivity of 70% to 90% and a specificity of 100%. If the test result is positive or the test is not available, flexible sigmoidoscopy is performed at 10 to 12 years of age. During the procedure, mucosal biopsy specimens are taken to identify subtle adenomatous changes. Colonoscopy with mucosal biopsies is advisable at 18 to 20 years of age. If adenomas are detected, surgical prophylaxis should be considered. Routine gastroduodenoscopic surveillance is also recommended for patients with FAP, because these patients are at high risk for potentially precancerous gastric and duodenal adenomas.[22]

Surgical prophylaxis in FAP consists of resection of the entire large bowel, to prevent malignant transformation. In the past, surgical alternatives included total colectomy with a permanent ileostomy and subtotal colectomy with an ileorectal anastomosis; the latter procedure is complicated by the frequent appearance of rectal polyps, which often necessitates a subsequent proctectomy. Currently, total proctocolectomy with J-pouch ileoanal anastomosis is advocated as surgical prophylaxis.

In a prospective, randomized trial of 83 FAP patients, a 6-month regimen of celecoxib was shown to reduce the number of colorectal adenomas by an average of 28%, compared to a 5% reduction with placebo ($P = 0.003$).[23] On the basis of this study, the Food and Drug Administration approved celecoxib as oral adjunctive therapy for adults with FAP. Nevertheless, endoscopic surveillance and colectomy as indicated remain the standard of care.

Hereditary Nonpolyposis Colorectal Cancer

HNPCC, like FAP, is an autosomal dominant disorder. The median age at which adenocarcinomas appear in HNPCC is less than 50 years, which is 10 to 15 years younger than the median age at which they appear in the general population.[24,25] In contrast to FAP, HNPCC is associated with an unusually high frequency of cancers in the proximal large bowel. Also, families with HNPCC often include persons with multiple primary cancers; in women, an association between colorectal cancer and either endometrial or ovarian carcinoma is especially prominent.

Several sets of selection criteria have been developed for identifying patients with this syndrome. The Amsterdam-2 criteria comprise the following: histologically documented colorectal cancer (or other HNPCC-related tumor) in at least three relatives, one of whom is a first-degree relative of the other two; a family history of one or more cases of colorectal cancer diagnosed before 50 years of age; and cases of colorectal cancer in at least two successive generations of the family. Affected relatives should be on the same side of the family (maternal or paternal), FAP must be excluded in colorectal cancer cases, and tumors must be pathologically verified. Another selection set, the Bethesda criteria, is more sensitive than the Amsterdam criteria but is less specific. These selection criteria were developed to identify patients whose tumors should be tested for features consistent with HNPCC, such as MSI.[26,27]

In addition to testing for MSI, genetic testing is available for two mismatch repair genes, *hMSH2* and *hMLH1,* which account for about 60% of all HNPCC cases. Unfortunately, tests for mutations of *hMSH2* and *hMLH1* are not perfectly sensitive, and genetic sequencing is expensive. The discovery of a mutation in a family provides a rationale for predictive testing for at-risk family members, although such testing may cause the unaffected individuals unnecessary concern and lead to unnecessary screening procedures.[28]

If HNPCC is confirmed, affected family members should undergo colonoscopy between the ages of 20 and 25 or at the age of 10 years younger than the youngest age at diagnosis in the family, whichever is earlier. This procedure should be repeated every 1 to 2 years. Recommended screening for women includes an annual transvaginal ultrasound or endometrial aspiration, beginning at age 25 to 35 years.[29]

If an adenoma or adenocarcinoma of the colon is identified, total abdominal colectomy with an ileorectal anastomosis is recommended. In women, total abdominal hysterectomy and bilateral salpingo-oophorectomy are often considered, particularly if the patient has no intention of having children in the future, because of the increased risk of ovarian and endometrial carcinoma.

Inflammatory Bowel Disease

Long-standing, extensive inflammatory bowel disease, including both ulcerative colitis and Crohn colitis, increases the risk of colon cancer. Surveillance colonoscopy with multiple biopsies of the entire colon should be considered every 1 to 2 years after 8 years of disease in patients with pancolitis or after 15 years in those with left-sided colitis. Colectomy must be carefully considered in each case, depending on the biopsy results.[29]

Environmental Factors

Specific factors that increase the risk of colorectal cancer have been identified, as have factors that reduce risk (see Table 1).

Diet

Diet plays a complex role in the etiology of colorectal cancer (see Table 2).[30] Both the total energy intake and individual components of the diet have been implicated.

The relationship between total energy intake and colorectal cancer risk is not simple; possible biologic mechanisms include increased levels of endogenous hormones (e.g., sex steroids, insulin, and insulin growth factor).[30] Nevertheless, a prospective study of a large United States cohort suggested that obesity (i.e., high body mass index [BMI]) is a significant risk factor for the development of colorectal cancer.[31] The relative risks for BMIs of 25 to 29.9, 30 to 34.9, and 35 to 35.9 were 1.20, 1.47, and 1.84, respectively. These data are consistent with previous case-control and cohort studies.

Dietary Fat. Many experimental studies have shown that intestinal tumorigenesis is enhanced as the fat content of the diet is increased. Dietary fat is thought to increase the concentration of bile acid in the bowel or to promote the formation of excess intraluminal diacylglycerol as the result of the interaction of fat, bile acids, and bacteria.[32] The effect of diacylglycerol may be to amplify cell-replication signals.[33] Early studies supported the relationship of dietary fat to colorectal cancer; these studies showed that colon cancer rates were high in populations with high total fat intake, with odds ratios of 1.3 to 2.2, and were lower in those consuming less fat.[34] However, many of these early studies failed to adjust for total energy intake. Cohort studies and a meta-analysis of 13 case-control studies of colorectal cancer failed to find clear evidence for the association of colorectal cancer with dietary fat intake.[32] In the aggregate, the epidemiologic and experimental evidence suggests that diets high in total fat may increase the risk of colorectal cancer.[30] A review of the data concerning saturated fat concluded that diets high in fat possibly increased the risk of colorectal cancer but that the evidence relating risk to intake of monounsaturated fat and polyunsaturated fat was inconsistent.[30] High fat intake has also been found to increase the risk of adenoma recurrence after polypectomy.[35]

Meat. An authoritative review concluded that red meat intake is associated with increased risk of colorectal cancer and that processed meat possibly increases the risk.[30] However, the data concerning red meat are not entirely consistent. The Nurses' Health Study reported that persons who consumed red meat frequently had an increased risk of colon cancer (relative risk, 2.5), compared with those who rarely consumed red meat.[36] No increase in risk with meat or fat consumption was seen, however, in two other large prospective studies: the American Cancer Society's Cancer Prevention Study II and the Iowa Women's Health Study.[37,38] It has been hypothesized that heterocyclic amines that are formed when fish or meat is cooked at high temperature may contribute to increased risk, but not all of the mechanisms are well understood.

Dietary Fiber. The term fiber is used to describe a complex mixture of compounds that include insoluble fiber (typified by wheat bran) and soluble fiber (oat bran). Ingestion of fiber could modify carcinogenesis in the large bowel by a number of potential mechanisms.[39] A meta-analysis of 13 case-control studies from nine countries concluded that intake of fiber-rich foods is inversely related to cancers of both the colon and the rectum.[40] Despite the evidence of a protective effect from case-control studies, results from a large prospective trial in women (the Nurses' Health Study) found no difference in risk of colorectal cancer between the highest and the lowest quintile groups with respect to dietary fiber.[41] In a multicenter, randomized, controlled trial, a diet low in fat (20% of total calories) and high in fiber, fruits, and vegetables did not reduce the risk of recurrence of colorectal adenomas.[42] High-fiber cereal supplements also failed to influence the rate of recurrence of colorectal adenomas.[43]

Vegetables and Fruit. Many epidemiologic studies have examined the relationship between fruit and vegetable intake and the incidence of colon or rectal cancer, with considerable variation in the findings. A prospective study utilized food-frequency questionnaires to study dietary intake in 88,764 women and 47,325 men; no association was found in men or women between overall fruit and vegetable consumption and risk of colon or rectal cancer.[44]

Calcium. Calcium may indirectly inhibit colorectal cancer by binding bile acids into insoluble soaps, thereby blocking contact with the luminal epithelium. It may also modulate protein kinase C and fatty acid-induced destabilization of cellular membranes. Experimental studies and epidemiologic studies[45] have reported an inverse relationship between calcium intake and cancer risk. A randomized, placebo-controlled trial tested the effect of calcium supplementation (3 g of calcium carbonate daily, which is equivalent to 1,200 mg of elemental calcium) on the risk of recurrent adenoma.[46] The effect was modest; supplemental calcium reduced the risk of recurrence by 19%. The effect may be dependent on dose. It is possible to safely administer up to 2,000 mg of calcium daily.

Antioxidants. It has been postulated that antioxidants such as retinoids, carotenoids, ascorbic acid, α-tocopherol, and selenium prevent carcinogen formation by neutralizing free radicals. Epidemiologic evidence of their benefit is difficult to confirm, however, because antioxidants and other putative cancer-prevention agents are comingled in common foods such as fruits and vegetables. ß-Carotene may reduce the risk of adenoma recurrence in nonsmokers but increases the risk in those who both smoke and drink.

Folate and Methionine. Fresh fruit and leafy green vegetables are rich in folate, whereas red meat, chicken, and fish have relatively high concentrations of methionine. Both folate and methionine supply the methyl groups necessary for essential cellular processes such as nucleotide synthesis and gene regulation. Retrospective and prospective studies support an inverse association between dietary folate or methionine intake and the risk of colorectal adenomas and carcinomas.[47] Both the level and duration of intake are important. For persons in the highest folate and methionine quintiles, the risk of distal colorectal adenomas was approximately 35% lower in participants in the Health Professionals Follow-Up Study and 25% lower in the Nurses' Health Study.[48] In women, the long-term (? 15 years) use of folate-containing multivitamins had a striking preventive benefit (75% risk reduction), whereas use of such multivitamins for 4 years had no preventive benefit.[49] Prospective studies of folate in patients who underwent resection of adenomas are in progress.

Medications

The ability of specific chemical compounds to reduce the incidence of colorectal cancer has been demonstrated in epidemiologic studies and is currently undergoing clinical testing (see Table 3). Technological advances, including genomics and proteomics, will facilitate the identification of new molecular targets for chemoprevention.

Postmenopausal Hormone Replacement Therapy. Many epidemiologic studies have examined the possible associations between exogenous estrogens and colorectal neoplasia risk. In a meta-analysis of 18 epidemiologic studies, postmenopausal hormone replacement therapy (HRT) was associated with a 33% reduction in the risk of colon cancer in recent users; the relative risk was 0.67, compared with a relative risk of 0.92 in women who had used HRT more than 1 year ago.[50] Similarly, HRT may protect against adenoma formation.[51] Data from the Women's Health Initiative trial will be helpful in clarifying the influence of hormone supplements over a long period.

Nonsteroidal Anti-Inflammatory Drugs. Most epidemiologic studies have reported reductions in the incidence of colorectal adenomas, colorectal cancer, and colon cancer mortality associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin. For example, a prospective study in over 660,000 adults found that mortality from cancers of the colon and rectum was about 40% lower in regular users of aspirin.[52] The Health Professionals Follow-Up Study of 47,000 men found that regular use of aspirin (at least twice a week) was associated with a 30% overall reduction in colorectal cancer.[53] However, in the Physicians' Health Study, there was no reduction in invasive cancers or adenomas at a median follow-up of 4.5 years when aspirin was taken at a dosage of 325 mg every other day.[54] A study of patients with prior colorectal cancer who had undergone curative resection found that compared with placebo, 325 mg of aspirin a day over 13 months was associated with a 35% reduction in risk of recurrent adenoma, as well as a prolongation in the time to detection of a first adenoma.[55] In a study of patients with a recent history of adenomas who had undergone resection by colonoscopic polypectomy, ingestion of 81 mg of aspirin a day for an average of nearly 3 years reduced the risk of recurrence of any adenoma by 19%.[56] For advanced neoplasms (i.e., adenomas measuring at least 1 cm in diameter or with tubulovillous or villous features, severe dysplasia, or invasive cancer), the reduction was about 41%. Interestingly, 325 mg of aspirin appeared to have minimal effect. The reason for this discrepancy in the dose-effect relationship is unknown. Side effects of treatment included upper gastrointestinal hemorrhage and hemorrhagic stroke. The potential value of other NSAIDs for primary prevention of colorectal neoplasia is being studied.

Drugs in Familial Adenomatous Polyposis. Several medications may reduce colorectal cancer risk in FAP. Sulindac reduces the size and number of adenomas.[57] A randomized, double-blind, placebo-controlled study of 83 patients with FAP found that patients who received 400 mg of celecoxib twice a day had a 28% reduction in the mean number of colorectal adenomas and a 30.7% reduction in polyp burden (i.e., the sum of polyp diameters), as compared with a group receiving placebo; a lower dose (100 mg twice daily) was associated with a non-statistically significant reduction.[23]

Lifestyle Factors

Physical Activity. Most studies have shown an inverse relationship between physical activity and colon cancer incidence.[58] The average relative risk reduction provided by regular physical activity is 40%. In men, physical activity for 2 hours or more a week was more strongly associated with a reduction in risk of advanced adenomas than in a reduction in risk of nonadvanced adenomas.[59] The mechanism of protection by physical activity is unknown but may be linked to effects on colonic mucosal prostaglandins.

Cigarette Smoking. Most case-control studies of cigarette exposure and adenomas have found an elevated risk for smokers.[60] In addition, a significantly increased risk of adenoma recurrence after polypectomy has been associated with smoking in both men and women.[61] In the Nurses' Health Study, the minimum induction period for cancer appears to be at least 35 years.[62] In the Cancer Prevention Study II, a large national cohort study, mortality was highest in current smokers, intermediate in former smokers, and lowest in persons who never smoked; an increased risk was observed in both men and women after 20 or more years of smoking.[61]

Screening

Screening and early detection (secondary prevention) are important in influencing the outcome in patients with colorectal neoplasia. Many deaths from colorectal cancers could probably be averted by appropriate use of screening.[63] Despite the acknowledged benefits of screening, most average-risk persons in the United States do not undergo screening for colorectal cancer. Data from the 1999 Behavioral Risk Factor Surveillance System Survey indicate that only 21% of respondents had undergone a fecal occult blood test (FOBT) within the previous year, and approximately 34% had undergone sigmoidoscopy or colonoscopy within the previous 5 years.[64] Improving screening rates for these persons remains a significant challenge.

A screening test is intended to distinguish those most likely to have a neoplastic lesion from those least likely. Those with abnormal results are advised to undergo diagnostic tests to confirm the presence or absence of cancer. The rationale for screening for colorectal neoplasia is twofold: first, detection of adenomas and their removal will prevent subsequent development of colorectal cancer; second, detection of localized, superficial tumors in asymptomatic individuals will increase the surgical cure rate.

Of the four screening tests currently in routine use, FOBT is supported by the strongest evidence. Intermediate-level evidence is available for flexible sigmoidoscopy. Only indirect evidence supports the use of colonoscopy and double-contrast barium enema (DCBE) (see Table 4).

Fecal Occult Blood Testing

The rationale for screening for the presence of blood in the stool is that large adenomas and most cancers bleed intermittently. Small adenomas rarely bleed. Annual testing is recommended with FOBTs because randomized trials have demonstrated that testing every 2 years is less effective. Annual testing may allow detection of disease that, although undetected on previous occasions, has not yet reached an advanced and perhaps incurable stage. Meta-analysis of mortality results from randomized, controlled trials shows that patients screened with FOBTs had a decrease in colorectal cancer mortality of 16% (relative risk, 0.84). When adjusted for screening attendance in the individual studies, the mortality reduction is 23% (relative risk, 0.77).[65]

Estimates of the sensitivity of FOBT have ranged from 25% to over 90%. In studies that show a higher sensitivity, the figure usually refers to so-called program sensitivity, which is the effectiveness of repeated FOBTs over several years. The major concern over low sensitivity is that patients who have a falsely negative test may be falsely reassured. A high false positive rate has also been a concern, because it results in persons who are free of colorectal neoplasia undergoing follow-up screening colonoscopy, with its associated risks and costs. It is estimated that if 10,000 people were included in a biennial FOBT screening program and two thirds underwent at least one test, there would be 8.5 deaths from colorectal cancer prevented over 10 years. Data from the Minnesota trial suggest that the screening process would also result in 2,800 participants having at least one colonoscopy, with 3.4 colonoscopy complications (perforation or hemorrhage).[65] Compared with endoscopic tests, FOBT detects relatively few adenomas; the principal benefit of an FOBT program is to increase detection of early-stage cancers.

Two types of FOBTs are used: chemical (guaiac-based) and immunochemical (see Table 5 and Table 6). Guaiac-based tests, which detect peroxidase activity, have been the most commonly used in population screening; typically, patients take test cards home and collect two samples from three consecutive specimens. These tests are subject to false positive results caused by dietary substances or drugs. Newer fecal occult blood tests have enhanced guaiac reagents, which improve sensitivity with little loss of specificity if recommended dietary measures are followed. The sensitivity of immunochemical FOBTs is better than that of guaiac-based tests, without an unacceptable decline in specificity.[66] Newer immunochemical FOBTs are more user friendly and can be read by automated techniques.[67] Immunochemical tests do not require any alteration in diet or medication intake.

Endoscopic Screening Tests

Examination of the large bowel by flexible sigmoidoscopy or colonoscopy permits direct visualization of the mucosa and allows photodocumentation, biopsy of suspicious lesions, and endoscopic polypectomy.

Flexible Sigmoidoscopy

A case-control study demonstrated a risk reduction of 70% for death from cancers within reach of the sigmoidoscope; the data suggested that the benefit may last as long as 10 years.[68] A prospective study showed that screening (primarily with flexible sigmoidoscopy) was associated with a 60% reduction in the incidence of distal colorectal cancer.[69] In a prospective, randomized trial in Norway, 400 patients underwent screening with flexible sigmoidoscopy screening; those patients in whom polyps were detected underwent colonoscopy. This protocol led to an 80% reduction in the incidence of colorectal cancer, compared with results in unscreened control subjects. [70] Two large-scale, prospective, randomized, controlled studies are examining the efficacy of flexible sigmoidoscopy. In the United States, the Prostate, Lung, Colorectal, Ovary (PLCO) trial has enrolled 154,000 patients 55 to 74 years of age. The final results will not be available for several years.[71] In the United Kingdom, the baseline findings of a multicenter trial showed that of approximately 40,000 patients screened, distal adenomas were detected in 12%, and distal cancers were detected in 0.3%.[72] Proximal adenomas were detected in 19% of those undergoing colonoscopy, and proximal cancer was detected in 0.4%; 62% of cancers were of early stage (Dukes stage A). There was one perforation after flexible sigmoidoscopy, and four perforations after colonoscopy.[73]

Sigmoidoscopy detects 70% to 85% of advanced lesions in the entire colon.[74] Patients with an advanced distal adenoma have a 6% to 10% chance of having an advanced proximal adenoma. When a nonadvanced adenoma is found during sigmoidoscopy, the chance of a proximal advanced lesion is lower -- 4.7%. Studies of screening colonoscopy have suggested that patients with an apparently normal sigmoidoscopy have a 1% to 2% risk of having an advanced proximal lesion.[75] In contrast, in patients with advanced distal polyps, the prevalence of advanced proximal neoplasia was 11.5%.

Obstacles to more widespread use of flexible sigmoidoscopy include lack of training and relatively low reimbursement rates. Training of nonphysicians to perform flexible sigmoidoscopy may facilitate more widespread use of this technique, especially in high-volume centers.

Combining FOBT with flexible sigmoidoscopy is a recognized approach to screening, but the data regarding the impact on mortality are limited. In a study of 2,885 veterans (97% men; mean age, 63 years), the prevalence of advanced adenoma at colonoscopy was 10.6%. Using examination of the rectum and sigmoid during colonoscopy as a surrogate for sigmoidoscopy, these researchers estimated that combined screening with one-time FOBT and sigmoidoscopy would detect 75.8% of advanced neoplasms. This represented a statistically insignificant increase in detection rate of advanced neoplasia when compared with flexible sigmoidoscopy alone (70.3%).[75] In assessing this study, it is important to note that in calculating the detection rate, the researchers assumed that all patients with an adenoma in the distal colon would undergo colonoscopy; it is also important to note that the use of one-time FOBT in this study differs significantly from the annual or biennial method used in large-scale trials.

Colonoscopy

The effectiveness of colonoscopy has been demonstrated by several studies. Observational, case-control, and prospective, randomized trials have shown that colonoscopic polypectomy lowers the incidence of colorectal cancers by 50% to 90%.[75-79]

Three nonrandomized studies have reported the baseline results of screening colonoscopy. In a study of 3,212 United States veterans (almost all men) with a mean age of 63 years, an adenoma incidence rate of 37% was reported.[74] The incidence of advanced adenoma (defined as adenomas with a diameter at least 10 mm, villous features, and high-grade dysplasia or cancer) was 10.5%. A study in 1,322 women reported an adenoma incidence of 21% and an advanced adenoma incidence of 3%.[79] A randomized, controlled trial of screening colonoscopy to examine efficacy has not been performed, although a pilot study is in progress.[80]

The American Cancer Society currently recommends colonoscopy every 10 years, starting at age 50, for asymptomatic adults at average risk for colorectal cancer. Repeat examinations at more frequent intervals are indicated for patients at increased or high risk (see Implementation of Screening, below).

Double-Contrast Barium Enema

There has not been a formal trial of DCBE as a screening test for colorectal neoplasia in a general population. A comparison study in patients who have undergone colonoscopic polypectomy found colonoscopy to be a more effective method of surveillance than DCBE.[81] The proportion of examinations in which adenomatous polyps were detected by DCBE, compared with colonoscopy, was significantly related to the size of the adenomas: the rate for DCBE was 53% for detection of lesions from 0.6 to 1.0 cm in size and 48% for lesions exceeding 1.0 cm. Although screening recommendations for colorectal cancer include DCBE, the steady decrease in training of new radiologists in this technique is likely to limit its use in the future.

Emerging Technologies for Screening

Molecular Detection Methods

Detection of gene mutations in the stool has been possible for over a decade.[82] It is technically feasible to detect *APC* and *p53* mutations, long DNA, and K- *ras* mutations.[83-85] In addition, right-sided lesions can be detected by the identification of *BAT-26* mutations. Systematic, large-scale, population-based studies are in progress to compare DNA mutation techniques with colonoscopy. At present, the cost of such techniques is high, and it remains to be seen whether their use will be cost-effective relative to other techniques, including newer immunochemical tests.

Virtual Colonoscopy (Computed Tomography Colonography)

CT colonography relies on sophisticated graphic software to assemble, from a fast CT scan, an endoluminal image that includes surface and volume characteristics.[86] Recent data from research centers in patients at increased risk suggest a sensitivity of 90% for lesions larger than 1 cm. However, it remains to be seen whether similar results can be attained in general screening use. Advances in this technique are occurring rapidly and include the possibility that patients will not need extensive bowel preparation. The effectiveness of the technique in screening remains to be established. One cost analysis has suggested that CT colonography is unlikely to be cost-effective relative to colonoscopy or other screening modalities.[87]

Implementation of Screening

The process of screening starts with targeting patients at risk for colorectal cancer. Adults 50 years of age and older who have no other risk factors are considered at average risk, and published screening recommendations endorse regular screening in this population (see Table 7).[28,88,89] Screening schedules and methods vary for patients at increased or higher risk (see Table 8). Follow-up is an important part of the screening process (see Table 9).

Cost-Effectiveness of Colorectal Cancer Screening

Analyses of cost-effectiveness of colorectal cancer screening programs have been carried out to provide a basis for legislative decision making and to construct health plans. The cost-effectiveness of colorectal cancer screening is estimated to be approximately $20,000 to $40,000 per year of life gained. This compares favorably with the cost of other usually accepted preventive services, such as end-stage renal dialysis or mammography.[90]

Diagnosis

Clinical Manifestations

The presenting symptoms that lead patients with colorectal cancer to seek medical attention vary with the anatomic location of the lesion. Because stool is relatively liquid as it passes into the right side of the colon through the ileocecal valve, tumors in the cecum and ascending colon can become large and can markedly narrow the bowel lumen without causing any obstructive symptoms or noticeably altering bowel habits. Lesions in the ascending colon frequently ulcerate, which leads to chronic blood loss in the stool; however, the stool retains a grossly normal color. Therefore, patients experience symptoms related to anemia, such as fatigue, palpitations, and even angina pectoris, and are found to have a hypochromic, microcytic anemia indicative of iron deficiency. Because the tumor may bleed only intermittently, a test for fecal occult blood (see above) may not always reveal the presence of occult blood in the stool. For that reason, colonoscopy should be performed in any adult who develops iron deficiency anemia, perhaps with the exception of a young menstruating woman.

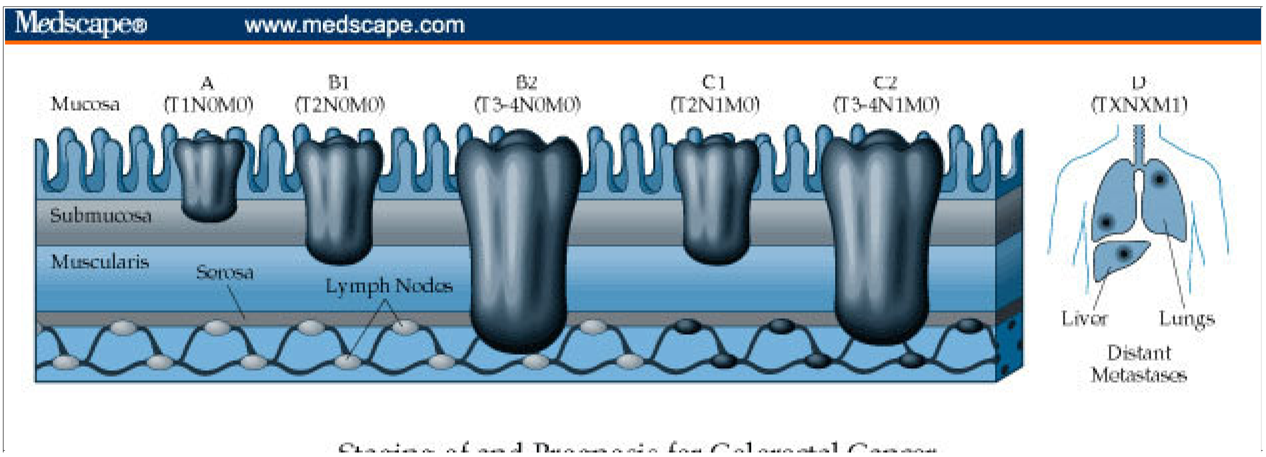
Stool becomes more concentrated as it passes into the transverse colon. Cancers arising in this section of the large bowel cause abdominal cramping, occasional obstruction, and even perforation. Tumors that markedly narrow the bowel lumen (so-called napkin-ring lesions) in the transverse colon are often smaller than those in the more proximal bowel because the short duration and localized pattern of the symptoms lead to a somewhat earlier diagnosis.

Cancers developing in the rectosigmoid are associated with tenesmus, narrowing of the stool, and hematochezia. Anemia is unusual, despite the passage of what appears to the patient to be copious quantities of bright-red blood from the rectum. Patients and physicians may attribute these symptoms to hemorrhoids. Development of altered bowel habits, rectal bleeding, or both mandate a digital rectal examination and colonoscopy.

Staging and Prognosis

The prognosis for patients with adenocarcinoma of the colorectum is closely associated with the depth of tumor penetration into the bowel wall and the presence or absence of regional lymph node involvement and distant metastases. The most frequently used staging system, which incorporates these prognostic variables, was introduced by Dukes and later modified by Kirklin, Astler, and Coller, as well as others. More recently, the Dukes system has been applied to the TNM classification method, in which T represents the depth of tumor penetration; N, the presence or absence of lymph node involvement; and M, the presence or absence of distant metastases (see Figure 2). These parallel staging systems subdivide colorectal cancer into the following categories[91]:

1. Stage A (T1N0M0). These are superficial lesions that do not penetrate the muscularis and do not involve regional lymph nodes.
2. Stage B. These are tumors that penetrate more deeply into the bowel wall without lymph node involvement; stage B is subdivided into stage B1 (T2N0M0), in which the tumor is re stricted to the muscularis, and stage B2 (T3-4N0M0), in which the tumor penetrates into or through the serosa.
3. Stage C. These are tumors that involve regional nodes; they are sub divided, in an analogous manner to stage B lesions, into stage C1 (T2N1M0) and stage C2 (T3-4N1M0).
4. Stage D. These are tumors that have metastasized to liver, lung, bone, or other anatomically distant sites (TXNXM1).



Staging of and Prognosis for Colorectal Cancer

Stage			Five-Year Survival (%)	
Dukes	TNM	Description	1940s and 1950s	1960s to Present
A	T1N0M0	Infiltration no deeper than submucosa	80	> 90
B1	T2N0M0	Infiltration of muscularis; no penetration through colonic wall; no lymph node involvement	60	85
B2	T3-4N0M0	Extension through colonic wall; no lymph node involvement	45	70–75
C1	T2N1M0	Infiltration of muscularis; no penetration through colonic wall; lymph node involvement	15–30	35–65
C2	T3-4N1M0	Extension through colonic wall; lymph node involvement		
D	TXNXM1	Distant metastases	< 5	< 5

Note: see reference 91.

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Figure 2. Staging of colorectal cancer. One staging classification that incorporates several modifications of the system devised by Dukes is useful for evaluating colorectal cancer. A tumor is classified according to the extent of infiltration of the bowel wall and whether it has spread to lymph nodes or to distant organs such as the liver or lungs. Staging is significant for determining prognosis.

In the absence of obvious evidence of metastatic disease, the stage of the disease can be accurately determined only after resection and histopathologic analysis of the specimen.

Because most recurrences after resection occur within 3 to 4 years, the cure rate is reasonably estimated by 5-year survival rates. Five-year survival is closely linked to the stage of the disease (see Figure 2). For uncertain reasons, 5-year survival rates have improved for patients at almost every stage during the past several decades. This seeming improvement has been reported from single institutions[91] and multi-institutional groups[92] and represents the experience of community and university-affiliated hospitals.[93] It seems unlikely that changes in surgical technique or in the etiologic factors that lead to tumor development can explain this improvement. Rather, this change may best be understood as resulting from more thorough staging procedures, which involve careful intraoperative inspection of the liver and peritoneal cavity and more meticulous dissection of the resected specimen, including identification and examination of each of the lymph nodes surrounding the tumor. Improvements in adjuvant therapy may also account for the improvement in survival.

More exacting attention to pathologic detail has revealed that prognosis after resection not only is related to regional lymph node involvement but also may be more precisely defined by the number of involved nodes. The prognosis for patients with colorectal cancer is more favorable when tumor specimens reveal involvement of one to four lymph nodes than when they reveal five or more involved nodes. Other poor prognostic indicators in patients who have undergone a complete resection include poorly differentiated histologic type, tumor adherence to adjacent organs, bowel perforation, colonic obstruction at the time of diagnosis, and venous invasion by the tumor. Preoperative elevation of the carcinoembryonic antigen (CEA) level (see below) suggests that the tumor will recur, regardless of the clinicopathologic stage of the resected specimen.[94,95] The prognosis is also less favorable, particularly for patients who have undergone resection of stage B2 tumors, when the DNA content of the malignant cells (i.e., ploidy) and the percentage of proliferating cells are increased[96] or when there is allelic loss of chromo some 18q.[97] In contrast to the prognosis for patients with most other solid tumors, the prognosis for patients with colorectal cancer is not influenced by the size of the primary lesion when corrected for nodal involvement and histologic differentiation.[98]

Colorectal cancer initially spreads to regional lymph nodes and then through the portal venous circulation to the liver, which represents the most common visceral site of metastasis: the liver is the initial site of distant spread in one third of patients with recurrences, and liver involvement is seen in more than two thirds of patients by the time of death. As a rule, colorectal cancer rarely spreads to supra diaphragmatic sites, such as the lungs or supraclavicular nodes, or to less common areas, such as bone or the brain, without previous involvement of the liver. The main exception to this generalization occurs in patients whose primary tumor is in the distal rectum: tumor cells that are shed from these lesions may escape the portal venous system and spread through the paravertebral venous plexus to the lungs or supraclavicular nodes.[99] The median survival time for patients after the detection of distant metastases (stage D) is 6 to 9 months.

Carcinoembryonic Antigen

Although CEA is an imperfect tumor marker, it can provide useful information for the management of colorectal cancer patients if its limitations and attributes are understood[100] (see Table 10). CEA is a glycoprotein that was initially found in association only with colorectal cancer and embryonic and fetal gut tissues. Plasma levels of CEA, which can be measured by radioimmunoassay, have subsequently been shown to be elevated in patients with many other malignant diseases (e.g., cancers of the stomach, pancreas, breast, and lung) and with various nonmalignant conditions (e.g., alcoholic liver disease, inflammatory bowel disease, heavy cigarette smoking, chronic bronchitis, and pancreatitis). Plasma CEA levels generally rise only when colorectal tumor cells have penetrated through the bowel wall (i.e., with cancer of at least stage B2). Therefore, the CEA assay is not useful as a screening test, even when applied to patients with gastrointestinal signs or symptoms. The CEA test is erratic as a quantitative measure of tumor bulk because the CEA level is highest when the liver is involved, even to only a minor degree, and may be barely elevated in patients with a bulky intra-abdominal recurrence (see Table 11).

Despite these shortcomings, there are several defined roles for the CEA assay:

1. Preoperatively, the CEA level is related to the stage of disease and may serve as a predictor of surgical incur ability: preoperative CEA values greater than 5 ng/ml have been associated with a poor prognosis, in dependent of surgical stage.[94,95]
2. Postoperatively, the CEA level may serve as a measure of the completeness of tumor resection. If a preoperatively elevated CEA value does not fall to normal levels within 4 weeks (a period that is twice the plasma half-life of CEA) after surgery, the resection was probably incomplete or occult metastases are present.
3. The CEA level may serve as a useful monitor of tumor recurrence.
4. The CEA assay may serve as a monitor of response to treatment of metastatic disease. Serial CEA values parallel either tumor regression or tumor progression.[101] A rising CEA level is incompatible with tumor regression, whereas CEA values decrease in most patients who have responded to treatment.

Until better reagents become clinically available, the CEA assay will remain a source of information about tumor status that is unavailable through other means. Thus, this assay continues to merit a role in the management of selected colorectal cancer patients.

Treatment

Surgical Management

Curative resection offers the greatest potential for cure in patients with invasive colorectal cancer. Patients considered for such surgery are often elderly and should be evaluated preoperatively for metastatic disease by thorough physical examination, biochemical studies, and imaging of the chest and pelvis (when appropriate). These studies are particularly appropriate for patients with significant comorbid disease who might represent poor operative candidates and for patients who have symptoms suggestive of hepatic spread, such as weight loss, anorexia, and fever. The identification of metastases does not constitute an absolute contraindication to surgery in patients experiencing tumor-induced gastrointestinal bleeding or obstruction, but it frequently results in a more conservative operative procedure designed primarily to relieve symptoms. Beforesurgery, the CEA titer should be determined and, if possible, the entire bowel mucosa should be visualized by colonoscopy to detect synchronous polyps or neoplasms.

The most useful adjunct for the preoperative assessment of rectal lesions (in addition to a digital rectal examination) is endorectal ultrasonography. Endorectal ultrasound allows clear visualization of the layers of the rectal wall and thus enables the depth of invasion to be precisely determined. Endorectal ultrasound has an accuracy of 82% to 93% with respect to depth of invasion. Assessment of lymph node involvement is less reliable, with reported accuracy of 65% to 81%.

Surgery for colorectal cancer is based on the pattern of local disease spread and on the vascular anatomy of the bowel. Limited, or wedge, resections are inadequate; the regional lymph nodes draining a given segment of large bowel should be removed, along with associated blood vessels, and surgical margins of at least 5 cm should be obtained. During laparotomy, the surgeon should thoroughly examine the entire abdomen -- including the liver, hemidiaphragms, and pelvis -- and carefully palpate the full length of the large bowel.

The surgical management of cancers that arise in the distal rectum presents a particular problem because the traditional operative procedure for these lesions -- abdominal-perineal resection -- requires that patients receive a permanent sigmoid colostomy. Although such an operation remains unavoidable in most cases in which the cancer occurs within 5 to 6 cm of the anal verge, staple devices permit the construction of end-to-end anastomoses by experienced surgical oncologists for many patients with midrectal lesions. These anastomoses, which do not increase the risk of complications or tumor recurrence, allow the anal sphincter to be preserved. Preservation of the anal sphincter has also been achieved by the use of transanal or transcoccygeal resection in selected patients who have superficial, nonulcerated tumors that are too close to the anal verge for a stapled anastomosis. [102] The ideal margin for rectal cancer resection is 2 cm or more distally and 5 cm or more proximally. Lymphovascular resection of the rectum should include a wide anatomic resection of the mesorectum.[103]

Laparoscopic Colectomy

Minimally invasive (laparoscopic) colectomy is still under study in the United States and Europe. The primary end points include safety, effectiveness, and quality of life. An interim report that focused on the frequency of such symptoms as nausea, fatigue, and pain indicated that patients treated with laparoscopic colectomy had only slightly better postoperative in-hospital analgesia requirements and length of stay (shorter by 0.8 days). However, these differences did not translate into statistically significant improvement in symptoms or quality of life in the immediate postoperative period or over 2 months of follow-up.[104] It is important to await the results of randomized trials in both the United States and Europe before advising patients to undergo this procedure.[105] Laparoscopic resection of rectal cancer is even more challenging and is being perfected in specialized centers.

Postoperative Surveillance

Colonoscopy. Before a planned curative resection of a colorectal cancer, patients should undergo a preoperative colonoscopy to exclude the presence of synchronous neoplasia. If the colon is obstructed preoperatively, colonoscopy can be performed approximately 3 to 6 months after surgery. If this or a complete preoperative examination is normal, subsequent colonoscopy should be offered 3 years later; if the results of that colonoscopy are normal, colonoscopies should then be performed every 5 years. The intent is to detect recurrent adenomatous polyps and new primary cancers.[28] Although colonoscopy can detect recurrent colon cancer, anastomotic recurrences occur in only about 2% of colon cancers. Commonly, these are associated with intra-abdominal recurrence that cannot be surgically resected. Recurrent tumors may be missed, as demonstrated by a study in which the incidence of secondary colorectal cancers was increased despite intensive surveillance, with a cumulative incidence of 1.5% at 5 years in patients treated for localized colon cancer.[106]

History and Physical Examination. There are no data that directly address the contribution of the history and physical examination to outcomes of colorectal cancer surveillance. However, a clinical history and pertinent physical examination should be performed every 3 to 6 months for the first 3 years, and annually thereafter.[107]

Complete Blood Count. Routine complete blood counts are not recommended.

Carcinoembryonic Antigen. If resection of liver metastases is clinically indicated, it is recommended that postoperative serum CEA testing be performed every 3 months in patients with stage II or III disease for 2 years after diagnosis. An elevated CEA level, if confirmed by retesting, warrants further evaluation for metastatic disease but does not justify the institution of systemic therapy for presumed metastatic disease.

Liver Enzymes. Regular monitoring of liver enzymes after primary therapy for colon and rectal cancer is not recommended.

Fecal Occult Blood Test. Periodic fecal occult blood tests are not recommended.

Chest X-Ray. Routine yearly chest x-rays are not recommended. Chest x-rays may be ordered for patients with elevated CEA levels or symptoms suggestive of a pulmonary metastasis.

Computed Tomography. Routine CT scans are not recommended in the follow-up of patients with colorectal cancer.

Positron Emission Tomography. Although the sensitivity and specificity of positron emission tomography (PET) is still being defined, PET may be particularly useful in a patient with suspected recurrence (e.g., a patient with rising CEA levels). PET may be helpful in identifying patients who may have resectable recurrences, thereby warranting laparotomy.[108]

Flexible Proctosigmoidoscopy. Surveillance with flexible proctosigmoidoscopy is appropriate for selected patients with rectal cancer. Combined chemotherapy and pelvic radiation represent the standard treatment for stages II and III rectal cancer (see below). For patients who have not received pelvic radiation, direct visualization of the rectum at periodic intervals is suggested. For patients who have received pelvic radiation, direct visualization of the rectum (except for colonoscopy at 3 to 5 years) is not usually suggested. However, it is the custom of some surgeons to inspect the rectum in all patients who have undergone low anterior resection by performing proctosigmoidoscopy 6 and 12 months after resection.

Radiation Therapy

Radiation therapy plays an important role in the treatment of patients with stage B2 or stage C rectal tumors. Cancer recurs locally or regionally in 20% to 40% of these patients after complete resection.[109] This unusually high frequency of recurrence is presumably the result of two factors: the loss of integrity of the serosa of the large bowel as it enters the pelvis facilitates the infiltration of tumor, and the rich lymphatic supply of the pelvic side wall immediately adjacent to the rectum enhances the early spread of malignant cells into surgically inaccessible tissue. There fore, adjuvant radiation therapy was introduced to remove tumor cells from perirectal tissue and to increase the chance of cure.

The rationale for using adjuvant radiation therapy to decrease pelvic recurrence appears sound, but it is uncertain whether such treatment should be administered before or after surgery. Patients with large, potentially unresectable rectal cancers may require preoperative irradiation to shrink the tumor sufficiently to allow its resection.

Prospective, randomized trials have demonstrated that neither preoperative[110] nor postoperative[111] irradiation alone significantly affects overall survival, although both forms significantly reduce the local recurrence rate. Survival is prolonged, however, when such adjuvant radiation therapy is combined with concomitant chemotherapy (see below).

Postoperative radiation therapy, when administered in doses of 4,500 to 5,000 cGy, causes transient diarrhea, cystitis, and perianal skin irritation; chronic damage to the small bowel or bladder is uncommon.[110] Preoperative chemoradiation therapy (usually with intravenous fluorouracil [5-FU] or oral capecitabine) is increasingly being used; the long-term complications of this regimen are still being defined.

Chemotherapy

After decades of use of 5-FU as chemotherapy, the arrival of new and more effective agents has changed the approach to chemotherapy for the treatment of colorectal cancer. Although 5-FU remains the backbone of most regimens, the new agents -- irinotecan, capecitabine, and oxaliplatin -- are being incorporated into frontline therapies for advanced colorectal cancer.

Fluorouracil

Synthesized in 1952, 5-FU remains an important drug in the treatment of advanced colon cancer. 5-FU may be administered as a bolus injection either weekly or daily for 5 days every 4 weeks. Partial response rates with these regimens have been approximately 10% to 15%. The development of permanent venous access devices and portable infusion pumps now permits the continuous infusion of 5-FU on an outpatient basis. The use of continuous infusion enhances the likelihood that 5-FU will be present during the S phase of the tumor cell cycle, when this agent is most effective.

5-FU is modulated by leucovorin, which raises the level of 5,10-methylenetetrahydrofolate and results in the formation of a stable ternary complex of the folate coenzyme thymidylate synthase with 5-FU in the form of its principal metabolite, fluorodeoxyuridine. The use of 5-FU with leucovorin results in a higher response rate than with 5-FU alone.

Irinotecan

Irinotecan is a novel topoisomerase inhibitor that has significant therapeutic activity in metastatic colorectal cancer. It is used when the tumor has recurred or spread after standard chemotherapy. In two phase III trials, irinotecan with leucovorin and fluorouracil increased median survival by 27% and 41%, compared with treatment with leucovorin and 5-FU.[112,113] The primary toxicities are diarrhea and neutropenia, which can be life threatening if not treated promptly and aggressively.

Capecitabine

Capecitabine is a fluoropyrimidine -- specifically, a prodrug of 5-FU -- that mimics continuous-infusion 5-FU. It has the advantage of oral administration. In two studies that compared capecitabine with 5-FU in patients with advanced disease, capecitabine therapy was associated with an improved response rate (26% versus 17%), but there was not a significant benefit in survival.[114]

Oxaliplatin

Oxaliplatin differs in its preclinical activity profile from cisplatin and also has a distinct toxicity profile. It causes no renal toxicity and minimal hematologic toxicity, but it is associated with both a reversible, acute, cold-related dysesthesia and a dose-limiting, cumulative, peripheral sensory neuropathy.

Comparative Trials

To establish the best first-line regimen in advanced colorectal cancer, the National Cancer Institute designed a six-arm study comparing various combinations of 5-FU, leucovorin, irinotecan, and oxaliplatin that are used throughout Europe and the United States.[115] Early results suggested that the combination of oxaliplatin and 5-FU infusion was superior to the combination of irinotecan and bolus 5-FU (response rate, 38% versus 29%; time to disease progression, 8.8 months versus 6.9 months; and overall survival, 18.6 months versus 14.1 months).[116]

Molecular Targeted Therapy

Molecular targets for therapy are becoming more widely known and include epidermal growth factors, tyrosine kinases, vascular endothelial growth factor, and intracellular signaling pathways. Many trials of compounds targeting these pathways in tumor cells and the surrounding stroma are in progress.

Adjuvant Chemotherapy

A 6-month regimen of 5-FU plus leucovorin is used as adjuvant chemotherapy for patients with stage III (node positive) colon cancer.[117] Adjuvant chemotherapy is not considered standard for stage II disease. New regimens containing oxaliplatin and irinotecan or capecitabine may be instituted in the future.

Chemoradiotherapy for Rectal Cancer

Concomitant radiotherapy and chemotherapy decrease the probability of local or regional recurrences after complete resection of stage B2 or stage C rectal cancer and prolong survival.[118-120] In this setting, the chemotherapy is thought to make the radiation therapy more effective (i.e., radiosensitization). This approach produced its most successful outcome when a continuous intravenous infusion of 5-FU was administered through a portable pump for the entire 4- to 5-week period of radiation therapy.[120] Capecitabine is now being tested in combination with postoperative radiation therapy.

Palliation

Laser photoablation or stenting of obstructing rectosigmoid or rectal cancers should be considered if surgical decompression is not possible or advisable because of extensive metastatic disease or comorbidity.

Table 1. Risk Factors for Colorectal Cancer

Average risk	Age 50 years and older
Decreased risk	High vegetable consumption
	Oral contraceptive use
	Estrogen replacement
	Multivitamins containing folic acid
	Long-term use of aspirin and other NSAIDs
Increased risk	Family history Colorectal cancerColorectal adenomas
	Personal history Colorectal adenomasOvarian, uterine cancer
	Familial adenomatous polyposis
	Hereditary nonpolyposis colorectal cancer
	Peutz-Jegher syndrome
	Juvenile polyposis
	Inflammatory bowel disease of long standing
	Physical inactivity (< 3 hr of exercise a week)
	Obesity
	Smoking
	Alcohol (> 1 drink/day)

NSAIDs = nonsteroidal anti-inflammatory drugs

Table 2. Food and Nutrition and the Risk of Colorectal Cancer

Strength of Evidence	Decreases Risk	No Relationship	Increases Risk
Convincing	Vegetables (not fruit)	--	--
Probable	--	--	Red meat
			Alcohol
Possible	Fiber	Calcium	High body mass*
	Starch	Selenium	Greater adult height
	Carotenoids	Fish	Frequent eating
			Sugar
			Total fat
			Saturated/animal fat
			Processed meat
			Eggs
			Heavily cooked meat
Insufficient	Resistant starch	--	Iron
	Vitamin C		
	Vitamin D		
	Vitamin E		
	Folate		
	Methionine		
	Cereals		
	Coffee		

*Colon cancer only.

Table 3. Selected Agents under Study for Prevention of Colorectal Cancer in Humans[121]

Nonspecific NSAIDs AspirinPiroxicamSulindac	Miscellaneous Folic acidSulindac sulfoneUrsodeoxycholic acidDFMO
Cyclooxygenase-2-selective NSAIDsCelecoxibRofecoxib	Combinations Sulindac + DFMOAspirin + folic acidPiroxicam + calciumCelecoxib + DFMOCelecoxib + selenium

DFMO = difluoromethylornithine; NSAIDs = nonsteroidal anti-inflammatory drugs

Table 4. Evidence Supporting the Effectiveness of Colorectal Cancer Screening Tests[122]

Test	Quality of Evidence*	Comments
Fecal occult blood test (FOBT)	I	33% reduction in colorectal cancer mortality with annual rehydrated FOBT; 15%-18% reduction in colorectal cancer mortality with biennial, unrehydrated FOBT
Sigmoidoscopy	I	80% reduction in colorectal cancer incidence with flexible sigmoidoscopy
	II	60%-95% reduction in mortality for cases of distal colorectal cancer
Colonoscopy	III	Sensitivity 27%-47% greater than that of 60-cm flexible sigmoidoscopy for advanced adenomas
Double-contrast barium enema	III	Sensitivity for adenomatous polyps lower than that of colonoscopy but higher than that of FOBT

*I = randomized controlled trial; II = controlled observational study (case-control or cohort); III = descriptive study.

Table 5. Main Features of Different Types of Fecal Occult Blood Tests (FOBTs)[63]

Type of FOBT	Basis	Stool-Sampling Method	End Point
Chemical	Guaiac; detects peroxidase	Wooden spatula and fecal smear for most	Blue color on paper card
Immunochemical	Antihemoglobin antibody	Wooden spatula, spoon, or brush	Latex or red cell agglutination
			Solid-phase immunochromatography
			Enzyme-linked immunosorbent assay

Table 6. Usage Issues with Different Types of Fecal Occult Blood Tests[63]

Type of FOBT	Diet Restrictions	Drug Interference	Site of Bleeding Detectable	End Point for Test Result
Chemical	Must avoid red meats; possibly avoid certain raw plant foods*	Vitamin C; possibly NSAIDs†	Rectum > colon > stomach (in decreasing order of sensitivity)	Subjective and transient‡
Immunochemical	None required	None required	Colon and rectum	Agglutination tests‡ -- can be difficult to read
				Immunochromatography -- easy to read
				ELISA -- machine-read

*Delaying development for 72 hr minimizes interference from plant foods and avoids the need for their restriction.

†Low-dose aspirin is not a problem, but therapeutic doses for rheumatic disorders may be so.

‡The tests generally provide a qualitative result, but newer immunochromatographic tests may be quantifiable.

ELISA = enzyme-linked immunosorbent assay; FOBT = fecal occult blood test; NSAIDs = nonsteroidal anti-inflammatory drugs

Table 7. American Cancer Society Recommendations for the Early Detection of Colorectal Cancer in Average-Risk, Asymptomatic Men and Women123

Annual fecal occult blood test (FOBT), starting at age 50 or
Flexible sigmoidoscopy every 5 yr, starting at age 50
or
Annual FOBT* and flexible sigmoidoscopy every 5 yr, starting at age 50
or
Double-contrast barium enema every 5 yr, starting at age 50
and
Colonoscopy every 10 yr, starting at age 50

*FOBT, as it is sometimes done in physicians' offices, with the single stool sample collected on the fingertip during a digital rectal examination, is not an adequate substitute for the recommended at-home procedure of collecting two samples from three consecutive specimens. Toilet-bowl FOBT tests also are not recommended. In comparison with guaiac-based tests for detection of occult blood, immunochemical tests are more patient-friendly and are likely to have equal or better sensitivity or specificity. There is no justification for repeating FOBT in response to an initial positive finding. Flexible sigmoidoscopy together with FOBT is preferable to FOBT or flexible sigmoidoscopy alone.

Table 8. American Cancer Society Guidelines on Screening and Surveillance for the Early Detection of Colorectal Adenomas and Cancer for Women and Men at Increased Risk or High Risk

Risk Category	Description	Age to Begin Screening	Recommended Screening Method	Comments
Increased risk	Persons with a single, small (< 1 cm) adenoma	3-6 yr after the initial polypectomy	Colonoscopy*	If examination is normal, the patient can thereafter be screened as per average-risk guidelines
	Persons with a large (>/= 1 cm) adenoma, multiple adenomas, or adenomas with high-grade dysplasia or villous change	Within 3 yr after the initial polypectomy	Colonoscopy*	If normal, repeat examination in 3 yr; if normal then, the patient can thereafter be screened as per average-risk guidelines
	Personal history of curative-intent resection of colorectal cancer	Within 1 yr after cancer resection	Colonoscopy*	If normal, repeat examination in 3 yr; if normal then, repeat examination every 5 yr
	Colorectal cancer or polyps in any-degree relative before age 60 or in two or more first-degree relatives at any age (if not a hereditary syndrome)	Age 40, or 10 yr before the age of the youngest patient in the immediate family	Colonoscopy*	Every 5-10 yr; colorectal cancer in relatives more distant than first-degree does not increase risk substantially above the average-risk group
High risk	Family history of familial adenomatous polyposis (FAP)	Puberty	Early surveillance with endoscopy, and counselling to consider genetic testing	If the genetic test is positive, colectomy is indicated; these patients are best referred to a center with experience in the management of FAP
	Family history of hereditary nonpolyposis colon cancer (HNPCC)	Age 21	Colonoscopy and counseling to consider genetic testing	If the genetic test is positive or if the patient has not had genetic testing, every 1-2 yr until age 40, then annually; these patients are best referred to a center with experience in the management of HNPCC
	Inflammatory bowel disease (chronic ulcerative colitis, Crohn disease)	Cancer risk begins to be significant 8 yr after the onset of pancolitis, or 12-15 yr after the onset of left-sided colitis	Colonoscopy with biopsies for dysplasia	Every 1-2 yr; these patients are best referred to a center with experience in the surveillance and management of inflammatory bowel disease

*If colonoscopy is unavailable, not feasible, or not desired by the patient, double-contrast barlum enema (DCBE) alone or the combination of flexible sigmoidoscopy and DCBE are acceptable alternatives. Adding flexible sigmoidoscopy to DCBE may provide a more comprehensive diagnostic evaluation than DCBE alone in finding significant lesions. A supplementary DCBE may be needed if a colonoscopic examination fails to reach the cecum, and a supplementary colonoscopy may be needed if a DCBE identifies a possible lesion or does not adequately visualize the entire colorectum.

Table 9. Screening Process for Colorectal Cancer[63]

Target patients at risk for colorectal cancer
Invite participation in screening program

Identify special circumtances (e.g., symptoms, family history) early in the process, so that appropriate measures can be advised
Perform the screening test
Use the result to identify patients who should undertake the diagnostic process (colonoscopy preferred)
Ensure compliance with the appropriate diagnostic follow-up
Provide adequate subsequent treatment
Offer rescreening at appropriate intervals
Monitor the outcomes of the program

Table 10. Indicators of Poor Prognosis for Colorectal Cancer

Regional lymph node involvement
More than 4 involved regional lymph nodes
Tumor penetration through the bowel wall
Poorly differentiated histologic findings
Tumor adherence to adjacent organs
Bowel perforation
Obstruction
Venous invasion
Preoperative elevation of carcinoembryonic antigen level to > 5.0 ng/ml
Increased DNA content (aneuploidy) of malignant cells
Allelic loss of chromosome 18q

Table 11. Carcinoembryonic Antigen Level as a Marker for Colorectal Cancer

Uses Preoperative prognostic indicatorPostoperative measure of completeness of tumor resectionMonitor of response of metastatic disease to treatmentMost sensitive monitor of recurrence
Limitations Nonspecific: elevated levels in many malignant and benign diseasesUnsatisfactory screening testErratic monitor of tumor bulkNot produced by poorly differentiated tumors

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The author has received grants for clinical research from Pfizer/Pharmacia in the past 12 months.