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ADENOCARCINOMA OF THE COLON AND RECTUM

Definition and Epidemiology

Adenocarcinomas constitute 98% of the malignancies found in the large bowel. Most adenocarcinomas are believed to arise from adenomatous polyps that progress from severe dysplasia to invasive carcinoma. The peak incidence is from 60 to 79 years of age, with fewer than 10% of all cases arising before the age of 50. The geographic pattern of **colorectal cancer** worldwide is highly variable. The highest rates are found in industrialized countries, including the United States, Canada, New Zealand, and the countries of northwestern Europe. Most countries in Asia, Africa, and South America (with the exception of Argentina) have a relatively low rate. This geographic distribution is thought to be primarily due to environmental factors, since ethnic groups from low-incidence countries in Asia develop rates of disease equivalent to white Americans after they migrate to the West. African Americans in the United States also have a much higher risk for disease than black Africans. Population studies have found positive correlations between the risk for **colorectal cancer** and the dietary intake of red meat.

In the 2001, 135,000 new cases of **colorectal cancer** were detected in the United States and 57,000 deaths were caused by the disease, making **colorectal cancer** the second leading cause of cancer-related deaths after lung cancer. The 5-year survival rate for **colorectal cancer** is approximately 55%, but this varies greatly depending on the stage of disease at the time of diagnosis. Men and women have a similar incidence of adenocarcinoma of the colon, but rectal cancer is more common in men in most parts of the world. The overall rate of deaths due to **colorectal cancer** has declined in the last 20 years, perhaps owing to increased screening and improved treatment.

ENVIRONMENTAL FACTORS.

Recommendations for the primary prevention of **colorectal cancer** are based on risk factors that are associated with **colorectal cancer** ([Table 200-2](#)); it has been estimated that adoption of these diet and lifestyle changes could reduce the incidence of **colorectal cancer** by 50%. Total energy intake, irrespective of dietary content, is positively associated with the development of **colorectal cancer**. Colorectal adenomas are associated with tobacco use, and the increased consumption of ethanol, particularly beer, has been associated with a higher risk for **colorectal cancer**. The higher rates of **colorectal cancer** in countries that consume "Western-style" diets high in red meat suggests that high dietary fat and low fiber could promote **colorectal cancer**. However, recent data show no benefit of low-fat diets on **colorectal cancer** despite their other health advantages. The role of dietary fiber is controversial, and two major

TABLE 200-2 -- LIFESTYLE AND DIETARY RECOMMENDATIONS FOR THE PRIMARY PREVENTION OF COLORECTAL CANCER

DIETARY RECOMMENDATIONS	LIFESTYLE RECOMMENDATIONS
Limit total fat to below 20–30% total calorie intake	Maintain normal body weight
Increase quantity and variety of fruits and vegetables (at least five servings per day)	Exercise daily
Ingest 20–30 g of fiber per day	Avoid smoking
Consider supplementation with 3 g of calcium carbonate per day	Avoid excessive alcohol

prospective studies have found no correlation between the intake of dietary fiber and the development of colorectal adenomas.^{[2] [3]} Whether diets high in fruits and vegetables can prevent **colorectal cancer** is under investigation.

INHERITED PREDISPOSITION.

Individuals who have a first-degree relative with **colorectal cancer** face a two- to three-fold increase in risk for malignancy, and this risk rises to five- or six-fold if two first-degree relatives are involved. Various genetic studies suggest that a large percentage of the population (up to 50%) is susceptible to colorectal neoplasia on a familial basis.

INFLAMMATORY BOWEL DISEASE.

Adenocarcinoma of the colon is 10 to 20 times more common in persons with ulcerative colitis ([Chapter 142](#)) as compared with the general population. Between 2 and 4% of all patients with long-term ulcerative colitis develop this malignancy, and the cumulative incidence over a 25-year period is approximately 12%. The two most important predictors for eventual development of carcinoma are the duration of the inflammatory disease and the extent of colonic involvement. Identification of dysplasia in the setting of ulcerative colitis is the best indicator of early cancer, but it is difficult to distinguish true dysplastic lesions from areas of intense mucosal regeneration. Dysplasia in a plaque or elevated mass and high-grade dysplasia warrant consideration of colectomy. Most experts agree that colonoscopy every 2 years with multiple biopsies is warranted after 8 years of symptomatic ulcerative colitis with extensive colonic involvement. The recent evolution of surgical procedures, such as ileoanal pull-through, favors the use of prophylactic colectomy in high-risk patients. Individuals with Crohn's colitis have a four to seven times higher risk of **colorectal cancer** as compared with the general population. Although this risk is less than that seen with ulcerative colitis, routine surveillance is recommended in patients with extensive colonic disease.

OTHER HIGH-RISK FACTORS.

Persons diagnosed with endocarditis or septicemia from *Streptococcus bovis* have a high rate of occult colorectal neoplasias and other upper gastrointestinal malignancies; endoscopic or radiographic screening may be warranted in this setting. There is also a 5 to 10% increase in **colorectal cancer** rates 15 to 30 years after ureterosigmoidostomy to correct congenital extrophy of the bladder; the lesions are typically distal to the ureteral implant, where the mucosa is chronically exposed to urine and feces.

Pathobiology

PATHOLOGY.

The anatomic distribution of carcinoma of the colon ([Fig. 200-4](#)) is associated with distinct morphologic patterns. Right-sided tumors commonly grow as polypoid, exophytic masses that bleed, often occultly, and rarely cause obstruction, whereas carcinomas of the distal colon are generally annular, encircling lesions that both bleed and lead to constriction of the bowel ("napkin ring" or "apple core" constriction). Almost all **colorectal cancers** are adenocarcinomas that exhibit differing degrees of glandular differentiation; most tend to produce mucin that aids in extension of the lesion and worsens prognosis. Lesions spread by direct extension through the wall of the bowel into the pericolonic fat and mesentery, and they can also invade surrounding organs. Alternatively, tumors can enter the lymphatic system and spread to regional lymph nodes, or enter the venous system and drain to the liver via the portal vein. **Colorectal cancers** can spread throughout the peritoneal cavity and can also metastasize to the lung and bone marrow via the blood stream. Rectal cancers



Figure 200-4 Distribution of **colorectal cancers** in various regions of the large intestine.

can invade the perirectal fat and surrounding structures, including the vagina, prostate, bladder, ureters, and bony pelvis; they may also spread to the lungs and liver.

MOLECULAR GENETICS AND THE ADENOMA TO CARCINOMA SEQUENCE.

Colorectal cancer is caused by the accumulation of multiple genetic lesions in a specific sequence over time. Both the tissue architecture and the cellular genotype change as the disease progresses ([Fig. 200-5](#)).

Approximately 80 to 85% of sporadic **colorectal cancers** are aneuploid tumors that exhibit chromosomal instability. The initiating genetic event is often mutations in APC, the causative gene for familial adenomatous polyposis. APC is a multifunctional protein with an essential role in the regulation of the growth of intestinal epithelial cells. One of the important consequences of loss of normal APC is the accumulation of the β -catenin oncogene within the nucleus of cells, where it can participate in the regulation of gene expression that promotes malignancy. Other genomic abnormalities, including gain of function mutations in the *k-RAS* protooncogene and allelic

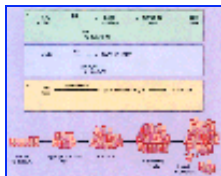


Figure 200-5 The molecular basis of **colorectal cancer**. Sequence-specific genetic lesions result in the transition from normal large bowel mucosa to invasive carcinoma. BAX = apoptosis-related protein; CRC = **colorectal cancer**; FAP = familial adenomatous polyposis; HNPCC = hereditary nonpolyposis colon cancer; IIR = Type II receptor; MMR = mutation mismatch repair; MSI = microsatellite instability; TGF β = transforming growth factor- β .

loss at 18q21 (where several putative tumor suppressor genes reside), hallmark the progression of the lesion from dysplastic epithelium to early and late adenomas. Loss-of-function mutations in the p53 tumor suppressor gene are commonly associated with progression to full-blown carcinoma and can occur even after transformation to cancer has developed. Other genetic and epigenetic alterations, including the expression of genes capable of cleaving extracellular matrix and a protein tyrosine phosphatase, lead to metastasis.

The remaining 15 to 20% of **colorectal cancers** without chromosomal instability exhibit the phenotype of genomic microsatellite instability characteristic of the hereditary syndrome HNPCC—mutations in mismatch repair genes and mutations in important growth regulatory genes such as transforming growth factor- β RII. Loss-of-function mutations in p53 commonly occur in carcinomas that arise in the setting of inflammatory bowel disease.

Clinical Manifestations

Colorectal adenocarcinomas can remain clinically silent for years. When present, symptoms often develop insidiously over a period of months and years. The major symptoms suggesting **colorectal cancer** are rectal bleeding, pain, and a change in bowel habits. Symptoms typically vary depending on where the lesion resides. Neoplasms in the proximal colon, where intestinal contents are relatively liquid, do not generally cause the abdominal pain or change in bowel habits characteristic of obstructive lesions. These lesions often ulcerate and cause chronic blood loss; patients commonly present with complaints of fatigue, palpitations, or even angina pectoris. Physician examination often reveals hemoccult positive stools ([Chapter 133](#)), and laboratory testing demonstrates hypochromic, microcytic anemia characteristic of iron deficiency ([Chapter 167](#)). Thus, the presence of unexplained iron deficiency anemia in any adult male or

postmenopausal female patient should prompt a rigorous evaluation for **colorectal cancer**, that is, endoscopic and/or radiographic visualization of the entire colon. In contrast to right-sided lesions, cancers in the distal colon may bleed, but they often cause constriction of the gut wall and can manifest with abdominal cramping, stool obstruction, or even perforation ([Fig. 200-6](#)). Tumors of the rectosigmoid region may manifest with hematochezia, tenesmus, and narrowing of the caliber

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of the stool. The differential diagnosis for rectal bleeding should include hemorrhoids, angiodysplasia, diverticulosis, and other benign and malignant tumors ([Chapter 133](#)).

Clinically apparent metastatic disease may present prior to or after resection of primary **colorectal cancer**. Symptoms may include pain related to distention of the liver capsule caused by massive hepatomegaly. If disease has spread to the abdomen, both ascites and bowel obstruction may occur. Metastatic spread to the pelvic region may present as bladder dysfunction, sacral or sciatic nerve pain, and vaginal discharge or bleeding. Lesions that have spread to the lung or bone marrow can remain silent until very advanced disease is present.

Diagnosis

The history, physical examination, and judicious use of both laboratory and radiologic tests are important in diagnosing **colorectal cancer**. Pertinent history should include a prior history of **colorectal cancer** or adenomatous polyps, inflammatory bowel disease, any inherited **colorectal cancer** syndromes, and whether the patient has any first-degree relative with **colorectal cancer**. On physical examination, extraintestinal lesions characteristic of Peutz-Jeghers or Gardner's



Figure 200-6 A barium enema radiograph in which a **colorectal cancer** in the distal segment of the large intestine has formed an annular, encircling lesion that leads to constriction of the bowel wall.

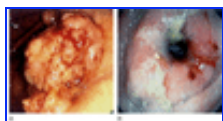


Figure 200-7 Two manifestations of **colorectal cancer**. A, Exophytic growth within the lumen. B, "Stricture" (apple core) lesion.

syndrome may be noticed. Metastatic disease is suggested by enlargement of the supraclavicular lymph nodes or liver or by the presence of an umbilical mass or ascites. The digital rectal examination may reveal a distal rectal cancer or the spread of tumor to the rectal shelf or pelvis. The stool shows evidence of frank or occult blood in 40 to 80% of advanced cases. Iron deficiency anemia or an elevation in liver enzymes may aid in diagnosis.

Methods for diagnosing **colorectal cancer** are similar to those used to detect adenomatous polyps. Colonoscopy is the procedure of choice for all patients who have occult blood in their stools or who present with signs and symptoms characteristic of **colorectal cancer** ([Fig. 200-7](#)). Colonoscopy is more accurate than radiographic studies for the detection of **colorectal neoplasms** of all sizes and has the advantage of being able to detect synchronous (simultaneously present, additional) cancers and obtain tissue for histologic analysis.

The staging of rectal cancers is helped by the use of endoscopic ultrasonography, by which the depth of lesion invasion can be accurately assessed. Patients with **colorectal cancers** who present with generalized abdominal pain or

symptoms characteristic of multiple diseases may be diagnosed initially by CT scanning of the abdomen. A CT scan may also play a role in determining the extent of tumor spread. Both a chest radiograph and a CT scan may detect lung or liver metastases.

TUMOR STAGING.

Accurate anatomic staging of **colorectal cancer** is essential, since the most important predictive factor for post-surgical outcome and the need for adjuvant chemotherapy is the stage of disease at the time surgery. **Colorectal cancers** are staged using both the Dukes method and the universal TNM classification system ([Table 200-3](#)). Stage A tumors (T1N0M0) are superficial lesions that do not

TABLE 200-3 -- CLASSIFICATION SYSTEMS USED TO STAGE COLON CANCER AND THEIR CORRELATION TO DISEASE OUTCOME

DUKES	TNM	STAGE	PATHOLOGY	PROGNOSIS (APPROXIMATE 5-YEAR SURVIVAL RATE, %)
A	T1N0M0	I	No invasion beyond submucosa	>90
B ₁	T2N0M0	I	Extension into muscularis	85
B ₂	T3N0M0	II	Extension into or through the serosa	70–80
C	TxN1M0	III	Involvement of regional lymph nodes	35–65
D	TxNxM1	IV	Distant metastases present	5

*T is the depth of tumor penetration, N is the presence of lymph node involvement, and M indicates the presence of distant metastases.

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penetrate the muscularis or involve regional lymph nodes. Neoplasms that are more invasive but have not yet spread to the lymph nodes are categorized as stage B. Stage C cancer involves regional lymph nodes, and stage D indicates distant metastases.



Treatment

SURGERY.

Total resection of all malignant tissue is the treatment of choice for most patients with **colorectal cancer** and is currently the only treatment option that offers a reasonable chance of cure or long-term survival. The primary goal is complete removal of the involved bowel and associated lymphatic drainage. Laparoscopic resection is the most common approach, but its long-term success compared with open resection is still being evaluated. A hemicolectomy is performed

when lesions are present in the left or right portions of the colon. Tumors located in the sigmoid region and upper rectum are resected anteriorly, with removal of normal colon both proximal and distal to the lesion; modern stapling techniques allow a sphincter-saving resection to be performed in a high percentage of cases. Lesions within 5 cm of the anal verge are treated by abdominoperineal resection and permanent colostomy; this approach is also used for large tumors that reside deep in the pelvis, for all neoplasms with high-grade histologic type, and when there is marked local spread of rectal lesions.

A palliative colostomy is often helpful in the presence of colonic obstruction caused by a tumor that is unresectable because it is widely metastatic or widely advanced into the peritoneum. Perforated lesions are generally managed by primary resection and colostomy followed by subsequent closure of the colostomy within a few months after the original surgery; in some patients, however, a permanent colostomy may be required. Focal surgical resection of a well-defined single liver metastasis or a wedge resection of a few lesions may be indicated depending on the medical condition of the patient; such procedures are associated with 5-year survival rates of 25 to 30% in patients who do not have advanced liver disease or other significant comorbidities.

RADIATION THERAPY.

For rectal cancer, radiation therapy can be combined with 5-fluorouracil (5-FU) and leucovorin preoperatively to minimize local recurrence and metastasis. Radiation therapy is also useful in reducing tumor size and enabling large, otherwise unresectable lesions to be resected. Postoperative radiation and chemotherapy reduce local recurrence and distant metastasis.^[4]

CHEMOTHERAPY.

The mainstay of adjuvant chemotherapy for **colorectal cancer** is 5-FU, a compound that targets the enzyme thymidylate synthase. The drug is well tolerated but produces response rates in only 10 to 20% of patients with advanced disease. Leucovorin acts as a biomodulator by enhancing the binding of 5-FU to its target. Regimens combining 5-FU with leucovorin can improve disease-free survival in patients with Dukes type C cancers.^[5] Direct infusion of the drug into the hepatic artery can improve response rates in patients with hepatic involvement, but the effect on survival is marginal and may not outweigh the cost and toxicity of this approach. The addition of either irinotecan, which is a topoisomerase inhibitor, or oxaliplatin to 5-FU and leucovorin improves response rates in cases of metastatic disease.^[6]

Prognosis

The 5-year survival rate of **colorectal cancer** directly correlates with the stage of disease at the time of diagnosis (see [Table 200-3](#)). Other predictors of poor outcome following surgical resection include poorly differentiated histologic type, perforation, adherence of tumor to adjacent organs, venous invasion, preoperative elevation of carcinoembryonic antigen (CEA) to levels greater than 5.0 ng/mL, aneuploidy, and specific chromosomal deletions.

Follow-up

A primary goal following curative resection for **colorectal cancer** is to detect curable recurrences or second primary tumors. Patients whose colon cancers have been cured face a 3 to 5% probability of developing an additional cancer of the large intestine during their lifetime and a more than 15% risk of developing an adenomatous polyp. It is also important to detect both synchronous (occurring at the same time) and metachronous (occurring at different times) cancers that may develop later. After curative resection, surveillance colonoscopy should be performed at 3 years and, if negative, at 5-year intervals thereafter. For patients who have had a low anterior resection of a stage B or C rectosigmoid cancer, flexible sigmoidoscopy should be performed to examine the lower bowel every 3 to 6 months for 2

years and a colonoscopy will be required to evaluate bowel beyond 60 cm. Additional follow-up measures include semiannual physical examinations and yearly blood chemistries. No clear consensus exists on the value of obtaining periodic chest radiographs or CT scans of the abdomen and pelvis in the absence of meaningful symptoms or signs. If the serum CEA level was normal after the initial resection, a rising CEA suggests recurrent **colorectal cancer**; some experts advocate periodic assays for blood CEA levels following curative resection.

Screening

Colorectal cancer is particularly amenable to widespread screening ([Chapter 11](#)). First, it is one of the most common and lethal malignancies in many countries, thereby justifying the public health cost associated with a population-wide screening. Second, the natural progression of the lesion from dysplastic mucosa to invasive disease takes on average 10 to 20 years, thereby allowing suitable time to detect the disease before it progresses to an incurable state. Finally, there is clear clinical evidence that early detection of **colorectal cancer** improves survival. The major approaches to screen for colon cancer are the fecal occult blood test (FOBT), flexible sigmoidoscopy, and colonoscopy.

Controlled prospective clinical trials performed in Minnesota, New York, Denmark, and the United Kingdom indicate that FOBT screening is relatively sensitive and reduces the rate of **colorectal cancer** mortality by 15 to 43%.^[7] However, the FOBT technique has a low sensitivity for detecting precancerous polyps and cancers of the rectosigmoid or distal rectum. Since many other conditions can cause blood in the stool, FOBT is relatively nonspecific. Although no randomized trials have demonstrated the efficacy of flexible sigmoidoscopy for screening of **colorectal cancer**, case-control and cohort studies have shown a 60 to 85% reduction in the rate of mortality from distal **colorectal cancers**. Flexible sigmoidoscopy is well tolerated, can be performed relatively quickly, and does not require sedation. It is also highly accurate, with a high positive predictive value. The major drawback of flexible sigmoidoscopy is its inability to detect the 40% or more of large bowel neoplasms that reside beyond its reach; as a result, a full colonoscopy is recommended if flexible sigmoidoscopy reveals a polyp or tumor. Future research will likely identify biomarkers for early detection of **colorectal cancer** based on the growing understanding of the molecular genetics of the disease using evaluation of stool DNA and other pertinent molecular markers. Other screening options that may be considered but for which supportive clinical evidence is limited include a barium enema plus flexible sigmoidoscopy every 5 years or a colonoscopy every 10 years.

Since colonoscopy is a required part of any screening strategy, an alternative is to screen only with colonoscopy every 10 years in persons over the age of 50 years. Because screening colonoscopy is now covered by Medicare, it is becoming a standard recommendation that is supported by several professional organizations and by formal quantitative analyses, despite the absence of a randomized trial. Screening recommendations for individuals at high risk due to the presence of inflammatory bowel disease or because of a familial disposition are summarized in [Table 200-4](#) .

Chemoprevention

Several chemicals, drugs, and nutraceuticals are being evaluated for either primary or secondary prevention of adenomatous polyps and **colorectal cancer**. In a randomized trial, calcium provided a moderate 15% reduction for colorectal adenomas as early as 1 year after dietary supplementation.^[8] The mechanism may be calcium's blockage of the tumor-promoting effects of bile acids. Chronic intake of aspirin and other nonsteroidal anti-inflammatory drugs is associated with a reduction in the relative risk for developing **colorectal cancer**, likely due to inhibition of the cyclooxygenase

RISK	TEST	INTERVAL	AGE TO BEGIN, yr
Average	FOBT <i>or</i> sigmoidoscopy <i>or</i> colonoscopy	Annually	50
		Every 5 years	
		Every 10 years	
FAP	Sigmoidoscopy	Every 6–12 months	10–12
HNPCC	Colonoscopy	Every 2 years until age 40 and annually thereafter	25
Low familial risk for sporadic cancer	FOBT <i>or</i> sigmoidoscopy <i>or</i> colonoscopy	Annually	40
		Every 5 years	
		Every 10 years	
High familial risk for cancer	Colonoscopy	Every 5 years	40
FAP = familial adenomatous polyposis; FOBT = fecal occult blood testing; HNPCC = hereditary nonpolyposis colorectal cancer .			

enzyme. Randomized trials of aspirin indicate a reduction in adenoma formation in the aspirin-treated group, but the preferred dose and duration of aspirin therapy remain uncertain.^[9] Patients with familial adenomatous polyposis have a reduced burden of polyps when placed on chronic nonsteroidal anti-inflammatory or cyclooxygenase-2 inhibitor therapy, and prospective trials are evaluating the efficacy of these drugs to prevent polyps. Several cohort and case-control studies indicate that folic acid may prevent colon cancer by unknown mechanisms. Hormone replacement therapy is associated with lower risk for **colorectal cancer**, but estrogen plus progestin supplementation has thrombogenic side effects that outweigh this benefit. There are no convincing clinical data that supplementation with vitamins or antioxidants reduces the risk for **colorectal cancer**.

