

Pathophysiology, Clinical Presentation, and Management of Colon Cancer

Mitchell S. Cappell, MD, PhD

Division of Gastroenterology, William Beaumont Hospital, MOB 233,
3601 West Thirteen Mile Road, Royal Oak, MI 48073, USA

Colorectal cancer afflicts approximately 150,000 Americans annually, approximately one third of whom die [1]. It afflicts approximately 250,000 annually in Europe [2] and approximately 1 million people worldwide [3]. A review of the pathophysiology, clinical presentation, and diagnosis of colon cancer is important and timely. This field is changing rapidly because of breakthroughs in the molecular basis of carcinogenesis and in the technology for colon cancer detection and therapy. This article provides an overview of the pathophysiology, clinical presentation, and management of colon cancer, with a focus on recent advances, to help clinicians and gastroenterologists appropriately screen, diagnose, and manage patients to reduce mortality from this cancer. The other articles in this issue focus on individual aspects of colon cancer in detail.

PATHOPHYSIOLOGY AND MOLECULAR GENETICS

Precursor Lesions

Colon cancer is the best understood complex (multistep) cancer in terms of molecular genetics. The first step in carcinogenesis is the development of specific types of neoplastic polyps in colonic mucosa. Polyp histology is critical for determining malignant potential. The two common histologic types are hyperplastic and adenomatous. Histologically, hyperplastic polyps contain an increased number of glandular cells with decreased cytoplasmic mucus but generally lack nuclear hyperchromatism, stratification, or atypia [4]. Adenomatous nuclei usually are hyperchromatic, enlarged, cigar-shaped, and crowded together in a palisade pattern. Adenomas are classified as tubular or villous. Histologically, tubular adenomas are composed of branched tubules, whereas villous adenomas contain digitiform villi arranged in a frond. Tubulovillous adenomas contain both elements.

Most colon cancers arise from adenomas (adenoma-to-carcinoma sequence) as demonstrated by epidemiologic, clinical, pathologic, and molecular genetic

E-mail address: mscappell@yahoo.com

findings. First, operative specimens containing colon cancer frequently contain one or more synchronous adenomas. Second, the risk for colon cancer increases markedly with increasing number of adenomatous polyps within the colon [5]. Third, adenomatous tissue frequently is found contiguous to frank carcinoma [6]. Fourth, patients who have familial adenomatous polyposis (FAP), who have hundreds or thousands of adenomatous colonic polyps, inevitably develop colon cancer if colectomy is not performed [7]. Fifth, patients who have adenomatous polyps larger than 1 cm diagnosed by barium enema who do not undergo colonoscopic polypectomy develop colon cancer at a rate of 1% to 1.5% per annum [8].

Although most hyperplastic polyps seem to have little or no association with colon cancer [9], some hyperplastic polyps are associated with colon cancer. Risk factors for malignancy in hyperplastic polyps include large polyp size (>1 cm diameter), location in the right colon, a focus of adenoma within the polyp (mixed hyperplastic-adenomatous polyp), more than 20 hyperplastic polyps in the colon, a family history of hyperplastic polyposis, and a family history of colon cancer [10]. Hyperplastic polyps seem to be linked to colon cancer via the recently reclassified (sessile) serrated adenoma, previously classified as a hyperplastic polyp [11]. A serrated adenoma arises within a hyperplastic polyp but differs from an ordinary hyperplastic polyp by abnormal proliferation of crypt epithelium and by nuclear atypia [12]. In one study, approximately 18% of removed polyp specimens originally classified as hyperplastic were reclassified as serrated adenomas using the revised classification [13].

The serrated adenoma seems to transform into colon cancer via a different pathway from that of conventional adenomas and to result in a recognizably different form of colon cancer (Table 1). Unlike conventional adenomas, serrated adenomas frequently have *BRAF* genetic mutations and exhibit extensive DNA methylation but lack adenomatous polyposis coli (*APC*) gene mutations [14]. The serrated adenoma is a precursor lesion of colorectal carcinoma with high microsatellite instability (MSI-H), which constitutes approximately 15% of sporadic colon cancer [15]. Like serrated adenomas, MSI-H colon cancers exhibit *BRAF* gene mutations and extensive DNA methylation but generally lack mutations of the *APC* gene or the *K-ras* oncogene [16]. DNA methylation at the promoter region can terminate and silence gene expression without DNA mutation [17]. For example, DNA methylation can inactivate DNA mismatch repair genes, such as the *hMLH1* gene, and thereby lead to microsatellite instability (MSI) [18,19]. The specific genetic defects responsible for the serrated adenoma are, however, unknown.

Considerable evidence supports that serrated adenomas can transform to cancer [10]. First, serrated adenomas share the same genetic mutations characteristic of sporadic MSI-H cancers (described previously), suggesting a common molecular pathway. Second, serrated adenomas sometimes are found contiguous to areas of severe dysplasia, suggesting that the dysplasia arose from this precursor lesion [20]. Third, patients who have hyperplastic polyposis and who have 30 or more hyperplastic polyps distributed throughout the colon

Table 1

Differences between the two pathways for sporadic colorectal cancer: adenoma-to-carcinoma sequence and serrated adenoma-to-carcinoma theory

| Characteristic | Conventional adenoma to carcinoma sequence | Serrated adenoma to carcinoma theory |
|--|--|--|
| Precursor lesion | Conventional adenoma | Serrated adenoma |
| Location of precursor lesion | Throughout colon | Predilection for right colon |
| Morphology of precursor lesion | Usually pedunculated (tubular adenoma) Occasionally sessile (eg, villous adenoma) | Often sessile, may be flat |
| Frequency of dysplasia in a moderate-sized polyp | Uncommon | Common |
| Likelihood of a small precursor adenoma transforming into cancer | Infrequent | Frequent?? |
| Progression from a medium sized polyp to cancer | Slow (7 or more years)? | Moderate (3–5 years)??? |
| Kudo pit pattern of adenoma | Types III or IV | Type II??? |
| Basic genetic defect | APC mutation | ??? |
| Frequently associated genetic mutation | p53 oncogene | BRAF mutation |
| DNA hypermethylation | Uncommon | Common |
| Mismatch repair gene malfunction/ inactivation | Uncommon | Common (<i>hMLH1</i> inactivation) |
| MSI-H | Rare | Typical |
| Genetic syndrome exhibiting same pathway | Familial polyposis coli | Hyperplastic polyposis??? |
| Estimated relative frequency in sporadic colon cancer | 85% ^a | 15% ^a |
| Evidence for pathway | Well established and well documented | Theory supported by significant evidence |
| Pathway first proposed | More than 50 years ago | Last 5–7 years |

? denotes uncertain data and ??-??-??-?? denotes increasing uncertainty.

^aThe molecular mechanism of colon cancer in inflammatory bowel disease is unknown and may be distinct from either of these molecular pathways.

(or at least five hyperplastic polyps proximal to the sigmoid colon, at least two of which are greater than 1 cm in diameter) [21] frequently have serrated adenomas and frequently develop colon cancer. Fourth, in a retrospective pathologic study, 91 MSI-H colorectal cancers developed in the same area of the proximal colon where hyperplastic polyps previously were identified by colonoscopy with pathologic examination of polyp tissue; all the previously removed polyps on re-review were reclassified as serrated adenomas [22].

With separation of the high-risk serrated adenomas from hyperplastic polyps in the reclassified nomenclature, the remaining conventional hyperplastic polyps are believed to harbor a negligible risk for developing colon cancer.

Syndromic Colon Cancer

Discoveries in the pathogenesis of the uncommon genetic cancer syndrome of FAP led to breakthroughs in understanding the molecular basis of the transformation of sporadic adenomas to colon cancer. Patients who have FAP develop hundreds or thousands of adenomatous polyps throughout the colon beginning after puberty and inevitably develop colon cancer [7]. This syndrome is inherited as a classic Mendelian single autosomal dominant gene. During the past 2 decades, FAP was shown to be the result of germline mutation of the *APC* gene located on chromosome 5q. Patients who have FAP carry this germline mutation in one allele in all somatic cells, including colonocytes (Table 2) [23–26]. This mutation underlies the development of hundreds of adenomatous polyps throughout the colon; colonic adenomas form when the second *APC* allele is lost or undergoes mutation in an individual colonocyte.

In hereditary nonpolyposis colon cancer (HNPCC), multiple kindred develop colon cancer. Affected patients typically have only a few colonic polyps. Colon cancer typically occurs in the right colon beginning as sessile polyps in middle age. The Amsterdam II criteria, used to clinically diagnose HNPCC, include all the following: three or more relations with colon cancer, one of whom is a first-degree relative of the other two; colon cancer involving at least two generations in the family; and at least one colon cancer diagnosed before age 50 [27]. During the past 15 years, HNPCC was shown to be the result of

Table 2
Milestones in the molecular genetics of syndromic colon cancer

| First author (reference) | Discovery/finding |
|---------------------------------------|---|
| A. APC | |
| Veale [23] | Determined by pedigree analysis that FAP resulting from a single dominant mutation |
| Herrera [24] | Reported a de novo <i>APC</i> mutation associated with a large deletion in chromosome 5 |
| Bodmer [25] | Applied restriction length polymorphism to localize the <i>APC</i> mutation to the long arm of chromosome 5 |
| Kinzler [26] | Identified the <i>APC</i> gene on chromosome 5 by positional cloning |
| B. HNPCC | |
| Peltomaki [28] | Described MSI in HNPCC |
| Fishel [29] | Identified and cloned the first human mismatch repair gene <i>hMSH2</i> (<i>hMLH2</i>) |
| Bronner [30] and Papadopoulos [31] | Identified the second mismatch repair gene, <i>hMLH1</i> , and localized it to chromosome 3p |
| Kolodner [32] | Showed patients who have Muir-Torre syndrome (HNPCC associated with sebaceous gland and skin tumors) have <i>hMSH2</i> mutations or other mutations that cause MSI. |

mutations of one of the mismatch repair genes, such as *hMLH1*, *hMSH2*, and *hMSH6* (see Table 2) [28–33]. Germline mutations of the *hMLH1* or *hMSH2* gene account for most cases. Mismatch repair enzymes, encoded by the mismatch repair genes, normally recognize errors in nucleotide matching of complementary chromosome strands and initiate segmental excision of the newly synthesized strand to ensure faithful strand replication [27]. Cells with mismatch repair gene mutations cannot repair spontaneous DNA errors and progressively accumulate mutations with succeeding DNA replications throughout the genome, resulting in genetic hypermutability and chaos. Accumulation of mutations in oncogenes and tumor suppressor genes can result in colon cancer. Mismatch repair gene mutation is detected as MSI, in which errors occur in simple DNA repetitive sequences, such as poly-A (ie, AAAAA. . .) or CA-tandem repeating (ie, CACACACA. . .) nucleotide sequences [27]. The molecular genetics of variants of FAP and HNPCC are described in Table 3. The history of

Table 3
Molecular genetics of syndromic colon cancer

| Gene mutations | Clinical syndromes | Manifestations |
|-----------------|--------------------|---|
| APC | FAP | Development of hundreds of colonic adenomas and inevitably of colon cancer, without colon resection |
| | Attenuated FAP | Mutations at specific sites (both terminals or exon 9) of APC gene can cause attenuated polyposis syndrome with development of dozens of colonic adenomas |
| | Gardner's syndrome | Variant of FAP with prominent extracolonic growths, such as osteomas |
| | Turcot syndrome | Variant of FAP with typical colonic manifestations and medulloblastomas or other tumors of the central nervous system, often the result of mutations of the APC gene |
| MYH | | Mutation of the MYH gene causes an attenuated adenomatous polyposis syndrome phenotypically resembling attenuated adenomatous polyposis from APC mutation. It is characterized by the presence of 10 or more adenomatous polyps in the colon and a high risk for developing colon cancer. |
| Mismatch repair | HNPCC | Develop several adenomatous colonic neoplasms, primarily in the right colon, with rapid malignant transformation |
| | Turcot syndrome | Variant of HNPCC with typical colonic findings of few colonic neoplasms and glioblastoma multiforme tumors of the central nervous system, sometimes due to mutations of mismatch repair genes |

molecular genetic discoveries in other intestinal polyposis syndromes is described in Table 4 [34–37]. Genetic factors in the pathogenesis of syndromic colon cancer are reviewed in the article by Desai and Barkel elsewhere in this issue.

Sporadic Cancer

These breakthroughs not only provided the molecular basis of syndromic hereditary colon cancer but also contributed to understanding sporadic colon cancer. Colon cancer is believed the result of a cascade of genetic mutations leading to progressively disordered local DNA replication and accelerated colonocyte mitosis. Progressive accumulation of multiple genetic mutations results in the transition from normal mucosa to benign adenoma to severe dysplasia to frank carcinoma (Table 5). Malfunction of the mismatch repair genes may account for approximately 15% of sporadic colon cancers [38]. In the HNPCC syndrome, the mismatch repair genes malfunction because of genetic mutation. In sporadic serrated adenomas, the mismatch repair gene *hMLH1* often malfunctions because of DNA hypermethylation. *APC* mutation is believed to account for approximately 80% to 85% of sporadic colon cancers [38]. Colon cancer may arise in inflammatory bowel disease from a different but so far uncharacterized pathway. Spontaneous somatic *APC* mutation in colonocytes is believed to underlie the development of sporadic adenomatous polyps. *APC* gene mutations occur early in adenoma development and often are found in aberrant crypt foci, the earliest identifiable dysplastic crypts [39]. *APC* mutations are found in approximately 50% of sporadic adenomas [40]. Adenomas usually remain benign. Malignant transformation requires further genetic alterations.

The *k-ras* gene encodes for a protein involved in signal transduction from the cell membrane to the nucleus. Specific mutations of this gene activate this signal

Table 4
History of molecular genetics of other intestinal polyposis syndromes

| First author (reference) | Discovery/finding |
|--------------------------|---|
| Zigman [34] | Showed the Ruvalcaba-Myhre-Smith syndrome (hamartomatous, lipomatous hemangiomas, and lymphangiomatous gastrointestinal polyps) results from an autosomal dominant mutation of the <i>PTEN</i> gene on chromosome 10q |
| Nelen [35] | Showed Cowden's disease (gastric and colonic hamartomatous polyps) results from an autosomal dominant mutation of the <i>PTEN</i> gene on chromosome 10q |
| Howe [36] | Showed familial juvenile polyposis (more than 10 juvenile intestinal polyps) results from an autosomal dominant mutation in the <i>SMAD4</i> (<i>DRC4</i>) gene on chromosome 10q |
| Jenne [37] | Showed Peutz-Jeghers syndrome (small number of intestinal polyps associated with mucocutaneous pigmentation) results from an autosomal dominant mutation in the <i>STK11</i> gene on chromosome 19p |

Table 5
Molecular genetics of sporadic colon cancer

| Gene | Chromosome location | Normal physiologic function of encoded protein | Clinical manifestations of mutation |
|-----------------------|--------------------------------|--|--|
| APC gene | 5q | Regulates cell growth and apoptosis | Homozygous somatic mutation associated with colonic adenomas. |
| K-ras gene family | Various chromosomes | Encodes a small guanosine triphosphate binding protein on cell membrane involved in transduction of mitogenic signals across cell membrane | Mutated in approximately 50% of colon cancers. May act in an intermediate stage of carcinogenesis. Mutation common in hyperplastic polyps. |
| P53 gene | 17p | Regulates G1 cell cycle and apoptosis | Critical in transition from late adenoma to early cancer. |
| DCC gene | 18q | Encodes a neural cell adhesion molecule; facilitates apoptosis, tumor suppressor | Believed to promote progression to frank carcinoma. |
| Mismatch repair genes | Located on several chromosomes | Recognize errors in nucleotide matching on complementary chromosome strand and initiate excision of erroneous strand | Progressive accumulation of mutations throughout the genome in affected cells leading to hypermutability and genetic chaos. Mutations of oncogenes or tumor suppressor genes can lead to colon cancer. |

pathway and promote colonocyte replication. These mutations are associated with exophytic growth of adenomas in the transition to carcinoma [27]. Approximately 50% of colon cancers have *k-ras* mutations [41].

The normal p53 gene product arrests the cell cycle after DNA injury to permit DNA repair, if the damage is mild and correctable, or apoptosis, if the damage is severe and irreversible. The wild-type p53 protein product is upregulated after cell stress from radiation exposure, or other noxious events, to prevent new DNA synthesis and halt cell division. Loss of p53 function can promote genomic instability as genetic errors are replicated without check, resulting in loss of heterozygosity (LOH). Mutation of the p53 gene is believed important in the transition from advanced adenoma to frank carcinoma. Approximately 50% of colonic lesions with high-grade dysplasia and approximately 75% of frank cancers exhibit p53 mutations [27].

Accumulation of genetic mutations leads to genetic instability, manifested by LOH [42]. LOH accelerates carcinogenesis. Cells with LOH have one, instead of the normal two, alleles of some genes because of chromosomal loss. A tumor suppressor gene is more likely to lose normal function when only one allele is present after LOH. Only one, rather than two, allelic mutations then are required for loss of its function.

This molecular mechanism is important in loss of function of the deleted in colon cancer (*DCC*) gene. The *DCC* gene encodes for a neural cell adhesion molecule receptor that normally promotes apoptosis and suppresses tumors. Loss of the normal *DCC* gene is believed important in the transition from an intermediate to an advanced adenoma [41].

DNA methylation can inactivate suppressor genes, thereby promoting cancer (described previously for *hMLH1*) [43]. Approximately 25% of colon cancers are associated with methylation and inactivation of p14, normally an upstream inducer of the p53 tumor suppressor pathway [44]. The inactivation produces the same cancer phenotype as *p53* mutation [43]. Methylation of the tumor suppressor gene p16, designated *CDKN2A*, occurs in approximately 35% of colon cancers [45].

PATHOLOGY OF COLON CANCER

Histology

Colon cancers are classified as well differentiated, moderately well differentiated, or poorly differentiated based on the degree of preservation of normal glandular architecture and cytologic features. Poor differentiation presumably is a histologic marker of severe underlying genetic mutations, but the mutations associated with poor differentiation currently are unknown. Approximately 20% of colon cancers are poorly differentiated. They have a poor prognosis [46]. Approximately 15% of colon cancers are classified as mucinous, or colloid, because of prominent intracellular accumulation of mucin. In the signet-ring variety of mucinous colon cancer, cancerous cells contain so much mucin that the nuclei are displaced peripherally. This cancer variant is very aggressive and has a poor prognosis [47]. This biologic behavior may be the result of extracellular mucin dissecting beyond the tumor wall, thereby promoting local extension [48].

Colon cancer associated with HNPCC has unusual histopathologic features, such as mucinous differentiation, prominent lymphocytic reaction, and a medullary growth pattern [49]. The medullary form of colon cancer, previously classified as an undifferentiated carcinoma, is characterized by sheets of eosinophilic and polygonal cells heavily infiltrated with small lymphocytes and devoid of glandular elements. This form of cancer also is associated with high MSI [50].

Other cancers of the colon are rare. Kaposi's sarcoma can involve the colon as part of disseminated disease with the acquired immunodeficiency syndrome [51]. Lymphoma of the colon is rare. It is a non-Hodgkin's lymphoma. It may be associated with the acquired immunodeficiency syndrome [52]. Carcinoid usually occurs in the lower gastrointestinal tract in the rectum or appendix but rarely can present in the rest of the colon.

Gross Pathology

Colon cancer can occur in a pedunculated polyp, sessile polyp, mass, or stricture. Small polyps rarely contain cancer. Only approximately 1% of diminutive

polyps contain cancer [53]. Cancer in a sessile polyp may metastasize earlier than cancer in a pedunculated polyp because of closer proximity to the lymphatic drainage [54]. Also, a flat lesion may be biologically more aggressive than a pedunculated polyp because of cellular growth into the colonic wall rather than the colonic lumen. The relative frequency of right-sided colon cancer has increased gradually during the past several decades, and now approximately one half of colon cancers are right sided [55]. This effect is attributed to a decreased frequency of left-sided cancer resulting from polypectomy of pre-malignant left-sided polyps at flexible sigmoidoscopy [56]. Flexible sigmoidoscopy results in substantial reduction of the incidence of left-sided colon cancer but negligibly reduces the incidence of right-sided colon cancer [57].

Stage

Colon cancer spreads by local invasion to contiguous organs or by lymphatic or hematogenous invasion. Carcinoma in situ, or high-grade dysplasia, denotes cancer that is confined to the mucosa without penetration of the muscularis mucosa. This cancer is highly unlikely to produce metastases because the lymphatic and vascular channels are below the muscularis mucosa. Invasive colon cancer most commonly is staged from A through D according to the Dukes' classification, with stage A penetrating beyond the muscularis mucosa into the submucosa. Stage B1 extends beyond the submucosa into the muscularis propria; stage B2 extends through the muscularis propria into the serosa; stage C has regional lymph node metastases; and stage D has distant metastases.

Colon cancer recently is staged according to the tumor, node, metastases (TNM) classification by mural depth of the primary tumor (T), by presence of local lymph node metastases (N), and by presence of distant metastases (M). This classification is helpful particularly in endosonographic staging of colon cancer (described later) [58]. In the TNM classification, invasive colon cancer is classified from stage I to IV. Stage I in the TNM classification corresponds to Dukes' A or B1 lesions, stage II corresponds to Dukes' B2 lesion, stage III corresponds to Dukes' C lesion, and stage IV corresponds to Dukes' D lesion. Pathologic stage, as classified by either scheme, correlates highly with cancer prognosis [59].

Approximately 20% of patients initially present with Dukes' D colon cancer, with identified metastases [60]. Perhaps another 30% of patients have no metastases detected preoperatively or intraoperatively but eventually succumb to colon cancer after apparently curative surgery because of gross cancer recurrence presumably from initially undetected micrometastases. The most common sites of gross metastases are the regional lymph nodes and liver. Colon cancer metastasizes early to the liver because of venous drainage of the colon via the portal system. Other sites, including the lungs, peritoneum, pelvis, and adrenals, typically become involved only after hepatic or lymphatic metastases occur. Rectal cancers, which are below the peritoneal reflection, lack a serosa and, therefore, penetrate early into adjacent pelvic structures.

EPIDEMIOLOGY

The incidence of colon cancer exhibits a striking geographic variation: the age-adjusted incidence varies by up to 12-fold among different countries [54]. Industrialized nations have the highest incidence, whereas South American countries and China have a low incidence. The wide international variation is attributed largely to national differences in diet and other environmental factors [61]. The rate in Japan used to be much lower than that in America but recently has increased with industrialization and adaptation of a Western diet. Moreover, descendants of Japanese immigrants to America, like other Americans, have a high incidence of colon cancer attributed to dietary and other environmental adaptations [61].

The lifetime risk for colon cancer in America is approximately 1 in 17 [54]. It is responsible for approximately 10% of all cancer mortality in the United States [1]. The incidence of colon cancer has decreased by approximately 20% in the United States, whereas the mortality has decreased by approximately 30% in the past 25 years [62]. American blacks have a small increased risk for colon cancer compared with whites [63]. American Indians have a significantly lower risk [64]. The incidence is slightly higher in American men than women [54]. The incidence of colon cancer rises sharply with age, beginning at age 50, attributed to accumulation of random somatic mutations with age. Ninety percent of cases occur after age 50, and only 4% of cases occur before age 40 [65].

CLINICAL PRESENTATION

Symptoms

Symptoms are common and prominent late in colon cancer when the prognosis is poor but are less common and less obvious early in the disease. Common symptoms are listed in Table 6 [54,66–68]. Less common symptoms include nausea and vomiting, malaise, anorexia, and abdominal distention [66]. Although colon cancer can present with diarrhea or constipation, a recent change in bowel habits more likely is from colon cancer than chronically abnormal bowel habits.

Symptoms depend on cancer location, cancer size, and presence of metastases. Left colon cancers are more likely than right colon cancers to cause partial

Table 6
Symptoms associated with colon cancer

| Symptom | Frequency |
|-------------------------|-----------|
| Abdominal pain | 44% |
| Change in bowel habits | 43% |
| Hematochezia or melena | 40% |
| Weakness or malaise | 20% |
| Involuntary weight loss | 6% |

Data from Refs. [66–68].

or complete intestinal obstruction because the left colonic lumen is narrower and tends to contain better formed stool due to reabsorption of water in the proximal colon [6]. Large exophytic cancers also are more likely to obstruct the colonic lumen. Partial obstruction produces constipation, nausea, abdominal distention, and abdominal pain. Partial obstruction occasionally and paradoxically produces intermittent diarrhea as stool moves beyond the obstruction.

Distal cancers sometimes cause gross rectal bleeding, but proximal cancers rarely produce this symptom because the blood becomes mixed with stool and chemically degraded during colonic transit. Bleeding from proximal cancers tends to be occult, and patients may present with iron deficiency anemia without gross rectal bleeding. The anemia may produce weakness, fatigue, dyspnea, or palpitations. Advanced cancer, particularly when metastatic, can cause cancer cachexia [6], characterized by a symptomatic tetrad of involuntary weight loss, anorexia, muscle weakness, and a feeling of poor health.

Signs

Colon cancer also tends not to produce signs until advanced [66]. Anemia from gastrointestinal bleeding may produce pallor. Iron deficiency anemia can cause koilonychia manifested by brittle, longitudinally furrowed, and spooned nails; glossitis manifested by lingual erythema and papillae loss; and cheilitis manifested by scaling or fissuring of the lips. Hypoalbuminemia may manifest clinically as peripheral edema, ascites, or anasarca. Hypoactive or high-pitched bowel sounds suggest gastrointestinal obstruction. A palpable abdominal mass is a rare finding that suggests advanced disease. Rectal cancer may be palpable by digital rectal examination. Although colon cancer previously was believed to frequently cause fecal occult blood as detected by guaiac tests [69], a recent prospective trial reported that only a minority of patients who had colon cancer had fecal occult blood detected by a single guaiac test [70]. Fecal immunochemical testing for occult blood seems to have a much higher sensitivity for detecting occult blood from colon cancer. For example, in a colonoscopic study of 2512 patients, the fecal immunochemical test detected 87.5% of colon cancers [71]. Other physical findings, although rare, should be searched for systematically, including a palpable Virchow's lymph node in the left supraclavicular space, hepatomegaly from hepatic metastases, and temporal or intercostal muscle wasting from cancer cachexia [54].

Laboratory Abnormalities

Patients who have suspected colon cancer should have routine blood tests, including a hemogram with platelet count determination, serum electrolytes and glucose determination, evaluation of routine serum biochemical parameters of liver function, and a routine coagulation profile. Approximately half of patients who have colon cancer are anemic [66]. Anemia, however, is common, so only a small minority of patients who have anemia have colon cancer. Iron deficiency anemia of undetermined cause, however, warrants evaluation for colon cancer, particularly in the elderly [72]. Advanced colon cancer may result in hypoalbuminemia from malnutrition [6]. Routine serum biochemical

parameters of liver function usually are within normal limits in patients who have colon cancer. The serum alkaline phosphatase and the serum lactate dehydrogenase levels may increase, however, with hepatic metastases [6].

The serum carcinoembryonic antigen level is not useful to screen for colon cancer because of insufficient sensitivity, especially for patients who have early and highly curable colon cancer [73]. Preoperative testing, however, is useful for cancer prognosis and as a baseline for comparison with postoperative levels. An elevated serum level preoperatively is a poor prognostic indicator: the higher the serum level the more likely the cancer is extensive and will recur postoperatively [73]. After apparently complete colon cancer resection, the serum level almost always normalizes; failure to normalize postoperatively suggests incomplete resection. A sustained and progressive rise after postoperative normalization strongly suggests cancer recurrence [54]. Patients who have this finding require prompt surveillance colonoscopy to exclude colonic recurrence and abdominal imaging to exclude metastases.

Unusual Clinical Presentations

Colon cancer can cause acute colonic obstruction, most commonly from exophytic intraluminal growth and uncommonly from intussusception or volvulus. Patients present with abdominal pain, nausea and vomiting, obstipation, abdominal tenderness, abdominal distention, and hypoactive bowel sounds. Colon cancer rarely causes ischemic colitis due to colonic dilatation proximal to malignant obstruction or malignant infiltration of blood vessels. Colon cancer rarely can perforate acutely through the colonic wall and cause acute generalized peritonitis and rarely can perforate slowly to form a walled-off inflammatory mass or abscess with localized peritoneal signs. Colon cancer also can penetrate and create fistulas into adjacent organs, such as the bladder or small bowel. Factors promoting colonic perforation include disruption of mucosal integrity resulting from transmural malignant extension or colonic ischemia and increased intraluminal pressure resulting from colonic obstruction. Colonic obstruction or perforation is a poor prognostic indicator. Colon cancer occasionally causes gross rectal bleeding because of cancerous mucosal ulceration. Approximately 6% of metastatic adenocarcinomas with an unknown primary eventually are shown to arise from the colon [74].

COLONOSCOPY

Colonoscopy is a highly specific test for colon cancer. At colonoscopy, polyps are removed and masses are biopsied for a pathologic diagnosis. Early colon cancer may occur in an adenomatous polyp and, therefore, may be difficult to distinguish by colonoscopy from a nonmalignant adenomatous polyp. For example, a 2-cm-wide villous adenoma has an approximately 40% chance of harboring cancer [72]. Polyp risk factors for malignancy include villous rather than tubular histology, large size, sessile morphology, and increasing number of colonic polyps [72]. Advanced colon cancer typically appears as a large, exophytic mass because of intraluminal growth or as a colonic stricture because of circumferential growth.

A colonic stricture, however, may be benign. Malignancy is suggested when a colonic stricture is ulcerated, indurated, asymmetric, and friable and has irregular or overhanging margins. The colonoscopic appearance is suggestive but not definitive. Pathologic examination of multiple colonic biopsies and cytologic analysis of stricture brushings usually are diagnostic.

TESTS FOR INTRAMURAL PENETRATION AND EXTRACOLONIC SPREAD OF COLON CANCER

CT

CT has been the standard modality to image the abdomen in patients who have colorectal cancer. CT is relatively accurate at detecting liver metastases, with an accuracy of approximately 85% [75]. CT is much more sensitive at detecting large than small hepatic lesions. CT is only moderately accurate at T staging. For example, the accuracy for T staging was only 74% in a large multicenter study [75]. CT errors typically occur from underestimating the T stage. CT is approximately only 50% to 70% accurate in N staging of rectal cancer [75].

MRI

MRI is more accurate than CT in detecting focal liver metastases, particularly small metastases, from colon cancer because of the typically sharp contrast between metastatic lesions and the normal liver on MRI [76]. Administration of contrast agents, such as superparamagnetic iron oxide, improves test sensitivity further. MRI also is more specific for hepatic metastases than CT. Hepatic metastases have a much shorter T2 sequence than hepatic hemangiomas or cysts. Hepatic metastases typically demonstrate rapid and strong enhancement with intravascular contrast due to enhanced vascularity but may enhance inhomogeneously due to hypovascular areas within metastases. Despite these advantages, CT is the standard test because of lower cost, greater machine availability, and more widely available expertise in image interpretation [6]. MRI traditionally is reserved for characterizing ambiguous hepatic lesions detected by abdominal ultrasound or CT.

Transrectal and Colonic Ultrasonography

Endosonography has been used for T and N staging of rectal cancer because of the relative inaccuracy of CT for this staging. Preoperative evaluation of the T stage and the N stage has a great impact on the therapy for rectal cancer. Patients who have superficial cancer (T1N0) can be treated by local endoscopic or transanal resection without wide excision. Patients who have T2N0 lesions are treated surgically without preoperative adjuvant therapy. Patients who have deep intramural involvement (T3 or T4) or who have nodal involvement (N1 or N2) receive radiation and possibly chemotherapy before surgery. Patients who do not have rectal sphincter involvement may avoid a colostomy.

Endoscopic ultrasound (EUS) is more accurate than CT or MRI for T staging. In a study of 80 patients who had rectal cancer, the accuracy of T staging by endosonography was 91% compared with 71% for CT ($P = .02$) [77]. Other

studies report that rectal endosonography has an approximately 85% accuracy for T staging [78,79]. This accuracy compares favorably to that of MRI for T staging, which ranges from 70% to 80% [80]. Tumors generally appear as homogeneous hypoechoic masses that disrupt the normal five-layer ultrasonographic structure of the rectal wall [81]. Errors in endosonographic T staging may be the result of distortion of the ultrasound image by inflammation in tissue adjacent to cancer. Endosonography is more accurate for staging T1, T3, and T4 lesions than T2 lesions because of difficulty in assessing cancer invasion through the muscularis propria [58]. Endosonography has an approximately 75% accuracy for N staging [58,77]. This accuracy is greater than the reported accuracy of 55% to 65% for CT and 60% to 65% for MRI [80]. At endosonography, malignant lymph nodes tend to be large (>1 cm), to be hypoechoic, to have sharply demarcated borders, and to be round rather than ovoid or flat [81]. Inflamed lymph nodes, however, occasionally mimic these sonographic features.

Rectal ultrasound has become the standard preoperative imaging modality for local T and N staging of rectal cancer because of relatively high accuracy but has not yet been shown to prolong survival. The rectum easily is accessible via an ultrasound probe using a rigid probe inserted blindly or an echoendoscope inserted under endoscopic guidance. The procedure is safe. Endosonographic findings frequently modify a treatment plan. For example, in a study of 80 patients, endosonographic findings resulted in the addition of preoperative neoadjuvant therapy in 25 patients [77]. The accuracy of endoscopic ultrasound is operator dependent. Other factors affecting accuracy include the ultrasound frequency, with higher frequency improving the resolution but decreasing the depth of penetration; the tumor location, with reduced accuracy for tumors low in the rectum; and prior radiotherapy because of increased wall echogenicity after radiation.

There is scant data on the impact of EUS-guided fine needle aspiration (FNA) in rectal cancer staging [58]. In one study of 41 patients, EUS-guided FNA of a lymph node upgraded the N stage in one patient and downgraded the N stage in eight patients [77]. Unfortunately, these changes were incorrect in three of the nine cases. Although a FNA diagnosis of cancer in a lymph node is secure, a finding of benignity may be erroneous because of sampling error. A recent prospective study, so far published only in abstract form, reported that EUS with FNA demonstrated malignant lymph nodes in 15 patients who had rectal cancer as compared with a yield of only eight patients who had suspicious nodes on CT [82]. Current data are insufficient to recommend standard use of FNA in N staging of rectal cancer [58].

Locally recurrent rectal cancer potentially is important to detect early so that patients can undergo salvage surgery for possible cure. EUS currently is the most reliable imaging study for detecting recurrence. In a study of 62 patients undergoing surveillance after rectal cancer surgery, EUS detected all 11 recurrent cancers [83]. The clinical benefit of early detection of rectal cancer recurrence, however, is limited by the low cure rate of salvage surgery.

Data on endosonography for colon cancer beyond the rectum are limited. Colonic endosonography technically is more demanding and time consuming than rectal endosonography. Most patients who have colon cancer without distant metastases undergo colonic resection, regardless of T or N stage. In a study of 50 small colon cancers, endosonography was 92% accurate in T staging compared with 63% for magnifying colonoscopy [84]. This difference was statistically significant. Endosonography, however, was only 24% accurate for N staging in this study. In a study of 86 patients who had colon cancer, endosonography, using a balloon-sheathed miniprobe inserted during colonoscopy, was 85% accurate for T staging and 73% accurate for N staging [85].

Conventional endosonography produces a 2-D image. The recently developed 3-D endosonography may provide better spatial information that improves diagnostic accuracy. For example, in a study of 86 patients who had rectal cancer, the accuracy of 2-D endosonography was 69%, whereas the accuracy of 3-D endosonography was 78% [86]. 3-D endosonography also was superior to conventional 2-D endosonography in a study of 35 patients who had rectal cancer [87].

PROGNOSTIC FACTORS

Clinicopathologic characteristics and molecular markers of colon cancer greatly help to determine prognosis. Many adverse warning signs and risk factors have been identified (Table 7) [88–98]. Currently, these sometimes are helpful in guiding treatment, including use of neoadjuvant therapy before cancer surgery, as discussed in the article by Robertson elsewhere in this issue. It is hoped that the currently identified molecular risk factors may be a prelude to therapy targeted according to molecular markers. In particular, targeted therapy could block the abnormal molecular pathways involved in specific molecular forms of colon cancer.

Table 7

Prognostic factors associated with a poor outcome from colon cancer

| Prognostic factor | First author (reference) |
|---|--------------------------|
| Intramural depth of colon cancer | Tominaga [88] |
| Regional nodal involvement | Greene [89] |
| Nodal micrometastases | Yasuda [90] |
| Vascular invasion | Newland [91] |
| Residual cancer after definitive therapy | Compton [92] |
| Elevated serum carcinoembryonic antigen level | Slentz [93] |
| Histologic grade (degree of differentiation) | Wiggers [94] |
| Cancer involvement at surgical margins | de Haas-Kock [95] |
| Liver metastases at clinical presentation | Tsai [96] |
| 18q genetic deletions (especially of <i>DCC</i> gene) | Watanabe [97] |
| Aneuploidy | Bazan [98] |

PREVENTION

Dietary Modifications

Despite the importance of genetic mutations in colon cancer pathogenesis, environmental factors also play an important etiologic role in colon cancer. Colon cancer has many proven environmental and demographic risk factors (Table 8) [99,100]. Other risk factors are suspected but unproven (Table 9). The most prominent of these risk factors for colon cancer are obesity, physical inactivity, alcoholism, smoking, and a diet that is high in fats or low in fruits and vegetables [101]. Environmental factors presumably modulate the risk for genetic mutations responsible for colon cancer, although the precise molecular mechanisms currently are unknown.

Dietary fiber may reduce the risk for colon cancer [99], but this effect is somewhat controversial [102]. Proposed mechanisms include decreased mucosal exposure to intraluminal carcinogens resulting from stimulated intestinal transit, decreased concentration of carcinogens in stool due to increased stool bulk, increased concentrations of anticarcinogenic short-chain fatty acids, and stabilization of insulin levels due to delayed starch absorption that otherwise might promote colonic carcinogenesis [100].

The identification of environmental risk factors is potentially important clinically because modification or elimination of an identified risk factor could lower the cancer risk. Environmental risk factors, however, are believed to exert their effects after long-term (chronic) exposure for decades. This may explain the weak protective effects of most reported experimental environmental interventions, such as dietary modifications, that last only several years. This topic is considered in detail in the article by Marshall elsewhere in this issue.

Chemoprevention

Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce cellular proliferation, slow cell cycle progression, and stimulate apoptosis [100]. NSAIDs are believed to reduce adenoma formation and inhibit colon cancer development by inhibiting the cyclooxygenase enzymes required for the synthesis of prostaglandin E₂; prostaglandin E₂ promotes tissue inflammation, cellular proliferation, and tumor growth [103]. NSAIDs also may retard carcinogenesis by effects on cell adhesion and apoptosis. Various NSAIDs prevent carcinogen-induced colon cancer in rodents and inhibit adenoma formation in the Min mouse model of human FAP. Case-control and cohort epidemiologic studies also provide evidence of decreased adenoma incidence or decreased colon cancer mortality with chronic NSAID use, particularly use of aspirin. In a prospective study of more than 600,000 adults over a 6-year period, the relative mortality from colon cancer was approximately 0.6 in men and 0.58 in women who used aspirin 16 or more times per month compared with nonusers of the same gender [104]. In the Nurses' Health Study, women who took aspirin for at least 20 years had a relative risk of 0.56 for developing colon cancer compared with nonusers [105]. In a double-blind, placebo-controlled, prospective trial of 635 patients who had prior colon cancer, chronic aspirin use was associated with

Table 8
Recognized risk factors for colon cancer

| Parameters | Proposed mechanism |
|---|---|
| Epidemiology | |
| Old age | Acquired colonocyte mutations accumulate with age |
| Living in United States and other highly industrialized nations | Dietary and environmental carcinogens |
| Diet | |
| Low fruit and vegetable consumption | Anticarcinogenic substances in fruits and vegetables (eg, folic acid) |
| Obesity | Carcinogens in an unhealthy diet or role of abnormal insulin levels in carcinogenesis? |
| Social habits | |
| Smoking cigarettes | Carcinogens present in tobacco |
| Alcohol | May promote cell proliferation and inhibit DNA repair |
| Genetics/family history | |
| FAP | Develops hundreds of adenomatous colonic polyps. Inevitably develops colon cancer resulting from small but significant risk for malignant transformation in each adenoma. |
| Gardner's syndrome | Variant of FAP |
| HNPCC (Lynch syndrome) | Mutant mismatch repair gene leads to accumulation of genetic mutations, including mutations of tumor suppressor genes |
| Peutz-Jeghers syndrome | Syndromic hamartomatous polyps occasionally may transform to adenomas |
| Juvenile polyposis | Syndromic juvenile polyps can transform to adenomas and then cancers over time |
| Family history of nonsyndromic colon cancer | Postulated shared genetic factors leading to mild susceptibility to colon cancer and possibly shared environmental factors |
| Hyperplastic polyposis | Genetic mutation in hyperplastic polyposis seems to predispose to colon cancer |
| Inflammatory bowel disease | |
| Chronic ulcerative colitis | Dysplasia and genetic mutations associated with mucosal injury and repair |
| Chronic Crohn's colitis | Dysplasia and genetic mutations associated with cell injury and repair |
| History of prior neoplasia | |
| Colonic adenomatous polyps | Precursor lesions of colon cancer |
| Prior colon cancer | Genetic predisposition or environmental factors |
| Other | |
| Pelvic radiation | Carcinogenic effects resulting from radiation-induced mutations |
| <i>Streptococcus bovis</i> bacteremia | May promote colonocyte proliferation |
| Ureterosigmoidostomy | Carcinogens excreted in urine or colonic mucosal proliferation during repair after urine-induced mucosal injury |
| Acromegaly | Growth hormone promotes proliferation of preexisting colonic adenomas and cancers |

Table 9

Questionable or controversial risk factors for colon cancer

| Parameter | Proposed mechanism |
|-----------------------|--|
| Physical inactivity | Physical activity may stimulate immunosurveillance and stimulate intestinal peristalsis to decrease mucosal contact with fecal carcinogens |
| Low calcium | Calcium binds to bile acids that otherwise are potentially colonotoxic |
| High fat | Various theories (eg, increased bile secretion) |
| High red meat | Animal fat in red meat or carcinogens (eg, nitrosamines) in cooked meat |
| Low selenium | Selenium can help neutralize toxic free radicals due to antioxidant effects |
| Low folate | Folate needed for DNA synthesis and repair |
| Low carotenoid diet | Carotenoids can help neutralize free radicals resulting from antioxidant effects |
| Low fiber diet | Dilution of carcinogens in stool due to increased stool bulk and stool water with a high fiber diet |
| Breast cancer | Shared reproductive hormonal or environmental factors |
| Diabetes mellitus | Insulin may modulate colonocyte proliferation |
| Prior cholecystectomy | Continuous colonic exposure to potentially carcinogenic bile acids after cholecystectomy |

a one-third reduction of the risk for adenomas compared with controls detected at follow-up colonoscopy at a mean of 12.8 months [106]. In a large, double-blind, placebo-controlled prospective trial of patients who had prior adenomas, chronic low-dose aspirin therapy was associated with a smaller, but still statistically significant, reduction in the incidence of recurrent adenomas at colonoscopy performed 1 or more years later compared with the controls [107]. Other NSAIDs, such as sulindac, seem to cause similar reductions in colon cancer or colon polyp incidence [108], although the effects are less well analyzed.

Cyclooxygenase has two isoforms, COX-1 and COX-2. Although nonselective NSAIDs inhibit both isoforms, several COX-2 selective inhibitors recently have been developed. COX-2 is believed to mediate cell proliferation and tumor growth. Hence, selective COX-2 inhibitors may block adenoma formation and cancer development. Celecoxib, a selective COX-2 inhibitor, was effective in preventing and treating adenomas in the Min mouse model of FAP [109]. Celecoxib shows some promise in causing regression of colonic adenomas in patients who have FAP. In a study of 77 patients who had FAP, patients receiving celecoxib (400 mg twice daily) had a 28% reduction in the mean number of rectal polyps compared with a 4.5% reduction in the placebo-treated group [110].

The effects of NSAIDs on sporadic adenomas generally are less dramatic. Although data support that NSAIDs inhibit colonic carcinogenesis, the optimal specific NSAID, NSAID dosage, and duration of treatment are unknown. The role of COX-2 selective inhibitors versus nonselective COX inhibitors needs to be analyzed and defined better.

NEW AND EVOLVING TECHNOLOGY

Colon cancer incidence and survival has improved only moderately during the past 2 decades despite the manifest efficacy of colonoscopic polypectomy at cancer prevention [56]. This failure is caused by insufficient implementation of colonoscopy screening partly because of the expense, invasiveness, discomfort, and risks for colonoscopy. New simpler, less invasive, and safer tests are being designed to overcome these barriers to universal screening for colon cancer. Potentially exciting screening or diagnostic tests still in the experimental stage include stool genetic markers [111] and videocapsule endoscopy of the colon [112]. The role of CT colonography (virtual colonoscopy) in the screening of colon cancer currently is unclear and may be clarified by further studies as the technology matures [113].

SUMMARY

With improved education of physicians resulting in effective and appropriate implementation of screening colonoscopy guidelines, and with improved technology, equipment, and training, this preventable, lethal disease should be virtually eradicated, as were cholera and other infectious scourges of yore.

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