The pathophysiology, clinical presentation, and diagnosis of colon cancer and adenomatous polyps

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Colon cancer afflicts more than 135,000 patients per year in America. It kills more than 55,000 patients per year [1] and many more patients suffer morbidity from curative colon cancer surgery or chemotherapy. Recently promulgated screening and surveillance colonoscopy regimens, as recommended by medical professional societies (including the American Gastroenterological Association [2], the American Society for Gastrointestinal Endoscopy [3], the American College of Gastroenterology [4], and the American Cancer Society [5,6]), and as approved by Medicare [7] and most private medical insurance companies [8] for reimbursement, can largely avoid this morbidity by colonoscopic removal of premalignant polyps [9], and can largely prevent this mortality by early detection of colon cancer at a curable stage [9–11].

Yet only about one quarter of eligible patients currently undergo any form of colon cancer screening [12]. This failure tragically results in tens of thousands of preventable deaths and even greater morbidity per annum in America. Aside from patient reluctance to undergo colonoscopy because of the invasiveness, risks, and discomfort of the test [13], a major factor in this breakdown is the failure by primary care physicians and internists to educate their patients and refer them for screening colonoscopy [14]. Contrariwise, primary care physicians and internists occasionally refer patients who are inappropriate candidates for screening colonoscopy because of age less than 50 years, a negative screening colonoscopy within the past decade, or severe medical comorbidity and a poor prognosis. Education of primary care physicians and internists, who can in turn educate their patients, should
eliminate these barriers to mass screening and optimize referral for colonoscopy [14].

A review of the pathophysiology, clinical presentation, and diagnosis of colon cancer and colonic polyps is important and timely for the internist and primary care physician. This field is rapidly changing because of breakthroughs in the molecular basis of carcinogenesis and in the technology for colon cancer detection and treatment. This article reviews colon cancer and colonic polyps, with a focus on recent dramatic advances, to help the primary care physician and internist appropriately refer patients for screening colonoscopy and intelligently evaluate colonoscopic findings to reduce the mortality from this cancer. Companion articles elsewhere in this issue focus on screening for colon cancer in average-risk patients, surveillance of colon cancer in high-risk patients, and chemoprevention and therapy for colon cancer.

Pathophysiology

Histopathogenesis

Colon cancer arises from mucosal colonic polyps. The critical parameter of polyps in terms of natural history, particularly malignant potential, is histology. The two most common histologic types are hyperplastic and adenomatous. Histologically, hyperplastic polyps contain an increased number of glandular cells with decreased cytoplasmic mucus, but lack nuclear hyperchromatism, stratification, or atypia [15]. Adenomatous nuclei are usually hyperchromatic, enlarged, cigar-shaped, and crowded together in a palisade pattern [16]. 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.

Virtually all colon cancers arise from adenomas as demonstrated by multiple epidemiologic, clinical, and pathologic findings. First, about one third of operative specimens containing colon cancer contain one or more synchronous adenomas, a significantly higher rate than in age-matched controls without colon cancer [17]. Second, the risk of colon cancer markedly increases with increasing number of adenomatous polyps [18]. Third, adenomatous tissue is frequently found contiguous to frank carcinoma [19]. Fourth, patients with familial adenomatous polyposis (FAP), who have hundreds or thousands of adenomatous colonic polyps, inevitably develop colon cancer if colectomy is not performed [20]. Fifth, patients who refuse polypectomy for adenomas develop colon cancer at a rate of about 4% after 5 years and 14% after 10 years [21]. This adenoma-to-cancer sequence is supported by recent findings about the molecular basis of colon cancer, as described later.
A relationship between hyperplastic polyps and colon cancer is controversial. Hyperplastic polyps may increase slightly the risk of colon cancer, but the effect is small [22,23]. 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); occurrence of more than 20 hyperplastic polyps in the colon; a family history of hyperplastic polyposis; and a family history of colon cancer [24]. Serrated polyps sometimes previously classified as a type of hyperplastic polyp may, like adenomas, be a significant risk factor for colon cancer [25]. Serrated polyps, unlike ordinary hyperplastic polyps, tend to be large and to occur in the right colon [26]. The colonocytes in these polyps frequently have BRAF genetic mutations and DNA methylation [27].

Molecular pathogenesis

History of recent molecular advances

Colon cancer is probably the best understood complex (multistep) cancer in terms of molecular genetics. A brief history helps summarize and place in perspective the recent, revolutionary advances in the molecular basis of colon cancer. Investigation of the pathogenesis of two uncommon familial colon cancer syndromes, FAP and hereditary nonpolyposis colon cancer (HNPCC), led to dramatic breakthroughs in understanding the molecular basis of the more common sporadic (nonsyndromic) form of colon cancer. The clinical genetics and clinical phenotype of FAP was described during the last two centuries: patients with FAP develop hundreds or thousands of adenomatous polyps throughout the colon beginning after puberty and inevitably develop colon cancer (Table 1) [20,28–37]. This syndrome is inherited as a classic mendelian autosomal-dominant single gene. During the past two decades FAP was shown to be caused by germline mutation of the adenomatous polyposis coli (APC) gene located on chromosome 5q. A patient with FAP carries this germline mutation in one allele in all somatic cells, including colonocytes (Table 2) [38–44]. This mutation underlies the development of hundreds of adenomatous polyps throughout the colon; colonic adenomas form when the second APC allele is damaged or lost in a colonocyte.

The clinical genetics and clinical phenotype of HNPCC were characterized during the twentieth century (Table 3) [45–53]. In HNPCC multiple cases of colon cancer, without gastrointestinal polyposis, occur within a family. Colon cancer typically occurs in the right colon beginning as sessile polyps in middle age. The Amsterdam Criteria, as recently modified by the Amsterdam II Criteria, are used clinically to diagnose HNPCC. These criteria 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 years [54]. During the past 15 years, HNPCC was shown to be caused by mutations of one of the mismatch repair genes, including hMSH2,
hMSH6, hMLH1, hMLH3, hPMS1, and hPMS2 [55]. Germline mutations of the hMLH1 and hMSH2 genes account for most of the cases. Mismatch repair enzymes, encoded for by 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 [56]. Cells with mismatch repair gene mutations cannot repair spontaneous DNA errors and progressively accumulate mutations throughout the genome with succeeding DNA replications. This progressive

Table 1
Milestones in the clinical genetics of familial adenomatous polyposis

<table>
<thead>
<tr>
<th>Author, year of discovery [Ref.]</th>
<th>Discovery and finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menzelio, 1721 [28]</td>
<td>Report of a patient with many colonic polyps of undetermined histology</td>
</tr>
<tr>
<td>Corvisart, 1847 [29]</td>
<td>Possible first case report of FAP</td>
</tr>
<tr>
<td>Chargelaigue, 1859 [30]</td>
<td>Possible second case report of FAP</td>
</tr>
<tr>
<td>Cripps, 1882 [31]</td>
<td>First confirmed case report of FAP; noted syndrome was possibly familial</td>
</tr>
<tr>
<td>Bickersteth, 1890 [32]</td>
<td>Confirmed familial nature of the syndrome</td>
</tr>
<tr>
<td>Smith, 1887 [33]</td>
<td>Described colon cancer arising in the polyps of FAP</td>
</tr>
<tr>
<td>Handford, 1890 [34]</td>
<td>Second report of colon cancer arising in polyps of FAP</td>
</tr>
<tr>
<td>Lockhart-Mummery, 1925 and 1934 [35]</td>
<td>Reported numerous cases of FAP</td>
</tr>
<tr>
<td>Dukes, 1930 [36]</td>
<td>Recognized clinical variability in the expression of adenomatous polyps, and developed clinical diagnostic criteria for FAP</td>
</tr>
<tr>
<td>Gardner and Richards, 1953 [37]</td>
<td>Described extracolonic tumors and other abnormalities associated with FAP (Gardner’s syndrome)</td>
</tr>
<tr>
<td>Bussey, 1975 [20]</td>
<td>Described the natural history of FAP in a large clinical series</td>
</tr>
</tbody>
</table>

Table 2
Milestones in the molecular genetics of familial adenomatous polyposis

<table>
<thead>
<tr>
<th>Author, year of discovery [Ref.]</th>
<th>Discovery and finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veale, 1965 [38]</td>
<td>Determined by pedigree analysis that FAP is caused by a single dominant mutation</td>
</tr>
<tr>
<td>Cockyne, 1967 [39]</td>
<td>Confirmed Veale’s discovery</td>
</tr>
<tr>
<td>Herrera et al, 1986 [40]</td>
<td>Reported a de novo APC mutation associated with a large deletion in chromosome 5</td>
</tr>
<tr>
<td>Bodmer et al, 1987 [41]</td>
<td>Applied restriction length polymorphism to localize the APC mutation to the long arm of chromosome 5</td>
</tr>
<tr>
<td>Leppert et al, 1990 [42]</td>
<td>Confirmed Bodmer’s findings</td>
</tr>
<tr>
<td>Kinzler et al, 1991 [43]</td>
<td>Identified the APC gene on chromosome 5 by positional cloning</td>
</tr>
<tr>
<td>Olschwang et al, 1993 [44]</td>
<td>Confirmed the identification of the APC gene</td>
</tr>
</tbody>
</table>
accumulation leads to genetic hypermutability and chaos; mutations accumulate in oncogenes and tumor suppressor genes that can result in colon cancer [57]. Mismatch repair gene mutation is detected as microsatellite instability, in which errors occur in simple DNA repetitive sequences, such as in poly-A or CA-tandem repeating sequences [56]. The molecular genetics of variants of FAP and HNPCC are described in Table 4. The molecular genetics of other intestinal polyposis syndromes are described in Table 5 [58–63].

Molecular biology

These breakthroughs provided not only the molecular basis of syndromic hereditary colon cancer but also of sporadic colon cancer. Colon cancer is believed caused by a cascade of genetic mutations leading to progressively disordered local DNA replication and accelerated colonocyte replication. The progressive accumulation of multiple genetic mutations results in the transition from normal mucosa to benign adenoma to severe dysplasia to frank carcinoma (Table 6). Mutations of the mismatch repair genes are believed to account for about 15% of sporadic colon cancers [64]. APC mutation is believed to account for about 80% of sporadic colon cancers [64]. 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 are often found in aberrant crypt foci, the earliest identifiable dysplastic crypts [65]. APC mutations are found in about 50% of sporadic adenomas [66]. Adenomas usually remain benign. Malignant transformation requires further genetic alterations.

The DCC (deleted in colon cancer) gene encodes for a neural cell adhesion molecule receptor and normally promotes apoptosis and suppresses tumors. Loss of the normal DCC gene is believed to be important in the transition from an intermediate to a late adenoma. Its role in this transition is supported by its frequent allelic deletion during this transformation [67].

The normal p53 gene product arrests the cell cycle following DNA injury to permit either DNA repair if the damage is correctable, or apoptosis if the damage is too severe. The wild-type p53 protein product is up-regulated after cell stress from radiation exposure, DNA injury, or other noxious events to prevent new DNA synthesis and halt cell division. Loss of p53

<table>
<thead>
<tr>
<th>Gene mutation</th>
<th>Clinical syndromes</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>Familial adenomatous polyposis</td>
<td>Development of hundreds of colonic adenomas and inevitably of colon cancer without colon resection</td>
</tr>
<tr>
<td>Attenuated familial adenomatous polyposis</td>
<td>Mutations at specific sites (both terminals or exon 9) of APC gene can cause attenuated familial polyposis syndrome with development of dozens of colonic adenomas</td>
<td></td>
</tr>
<tr>
<td>Gardner’s syndrome</td>
<td>Variant of familial adenomatous polyposis with prominent extracolonic growths, such as osteomas</td>
<td></td>
</tr>
<tr>
<td>Turcot’s syndrome</td>
<td>Variant of familial adenomatous polyposis with typical colonic manifestations and medulloblastomas or other tumors of CNS often caused by mutations of the APC gene</td>
<td></td>
</tr>
<tr>
<td>Mismatch repair</td>
<td>HNPCC</td>
<td>Develop several adenomatous colonic neoplasms, primarily in the right colon, with rapid malignant transformation</td>
</tr>
<tr>
<td>Turcot’s syndrome</td>
<td>Variant of HNPCC with typical colonic findings of few colonic neoplasms and glioblastoma multiforme tumors of CNS sometimes caused by mutations of mismatch repair genes</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: CNS, central nervous system.
function can promote genomic instability as genetic errors are replicated without check, resulting in loss of heterozygosity. Mutation of the \( p53 \) gene is believed to be important in the transition from late adenoma to frank carcinoma. About 50% of lesions with high-grade dysplasia and about 75% of frank cancers exhibit loss of normal \( p53 \) function, usually from a missense point mutation of one allele and deletion of the other, wild-type, allele [56,68].

The \( K-ras \) gene encodes for a protein involved in signal transduction from the cell membrane to the nucleus [69]. Specific mutations of this gene result in constitutive activation of this signal pathway and increased colonocyte replication. These mutations are associated with exophytic growth of adenomas in the transition to carcinoma [70]. About 50% of colon cancers have \( K-ras \) mutations [67].

The accumulation of genetic mutations leads to genetic instability, manifested by loss of heterozygosity [71]. Loss of heterozygosity accelerates carcinogenesis. Cells with loss of heterozygosity have one, instead of the normal two, alleles of some genes because of loss of individual chromosomes during mitosis. A tumor suppressor gene is more likely to lose normal function when only one allele is present after loss of heterozygosity. Only one, rather than two, allelic mutations are then required for loss of its function.

DNA methylation at the promoter region can terminate and silence gene expression without DNA mutation [72]. In particular, DNA methylation can inactivate suppressor genes, thereby promoting cancer [73]. Colon cancer is sometimes associated with methylation and inactivation of p14,

<table>
<thead>
<tr>
<th>Author, year of discovery [Ref.]</th>
<th>Discovery and finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zigman et al, 1997 [58]</td>
<td>Showed the Ruvalcaba-Myhre-Smith syndrome (hamartomatous, lipomatous hemangiomatous, and lymphangiomatous gastrointestinal polyps) is caused by an autosomal-dominant mutation of the ( PTEN ) gene on chromosome 10q</td>
</tr>
<tr>
<td>Nelen et al, 1996 [59] and 1997 [60]</td>
<td>Showed Cowden’s disease (gastric and colonic hamartomatous polyps) is caused by an autosomal-dominant mutation of the ( PTEN ) gene on chromosome 10q</td>
</tr>
<tr>
<td>Houlston et al, 1998 [61]; Howe et al, 1998 [62]</td>
<td>Showed familial juvenile polyposis (more than 10 juvenile intestinal polyps) is caused by an autosomal-dominant mutation in the ( SMAD4 (DRC4) ) gene on chromosome 10q</td>
</tr>
<tr>
<td>Jenne et al, 1998 [63]</td>
<td>Showed Peutz-Jeghers syndrome (small number of intestinal polyps associated with mucocutaneous pigmentation) is caused by an autosomal-dominant mutation in the ( STK11 ) gene on chromosome 19p</td>
</tr>
</tbody>
</table>
Table 6
Molecular genetics of sporadic colon cancer

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome location</th>
<th>Normal physiologic function of encoded protein</th>
<th>Clinical manifestations of mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>5q</td>
<td>Regulates cell growth and apoptosis</td>
<td>Homozygous somatic mutation associated with colonic adenomas</td>
</tr>
<tr>
<td>K-ras family</td>
<td>Various chromosomes</td>
<td>Encodes a small GTP binding protein on cell membrane involved in transduction of mitogenic signals across cell membrane</td>
<td>Mutated in about one half of colon cancers; may act in an intermediate stage of carcinogenesis; mutation common in hyperplastic polyps</td>
</tr>
<tr>
<td>p53</td>
<td>17p</td>
<td>Regulates G1 cell cycle and apoptosis</td>
<td>Critical in transition from late adenoma to early cancer</td>
</tr>
<tr>
<td>DCC</td>
<td>18q</td>
<td>Encodes a neural cell adhesion molecule, facilitates apoptosis, tumor suppressor</td>
<td>Believed to promote progression to frank carcinoma</td>
</tr>
<tr>
<td>Mismatch repair genes</td>
<td>Located on several chromosomes</td>
<td>Recognize errors in nucleotide matching of complementary chromosome strand and initiate excision of erroneous strand</td>
<td>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</td>
</tr>
</tbody>
</table>
normally an upstream inducer of the $p53$ tumor suppressor pathway. This occurs in about 25% of colon cancers [74]. The inactivation produces the same cancer phenotype as mutation of the tumor suppressor gene $p53$ [72]. Methylation of the tumor suppressor gene $p16$, designated $CDKN2A$, occurs in about 35% of colon cancers [75].

Pathology

Histology

Colon cancers are classified as well-differentiated, moderately well differentiated, or poorly differentiated on the degree of preservation of normal glandular architecture and cytologic features. Progressively more poor differentiation is presumably a histologic marker of further underlying genetic mutations, but the mutations associated with poor differentiation are currently unknown. About 20% of cancers are poorly differentiated. They have a poor prognosis [76]. About 15% of colon cancers are classified as mucinous or colloid because of prominent intracellular accumulation of mucin. These cancers are more aggressive [77].

Gross pathology

About 65% of colon cancers are distal to the splenic flexure and potentially detectable by sigmoidoscopy [78]. Contrariwise, about 35% of colon cancers are proximal to the sigmoid and not detectable by flexible sigmoidoscopy. Colon cancer can occur in a pedunculated polyp, sessile polyp, mass, or stricture. Small polyps rarely contain cancer. Only about 1% of diminutive polyps contain cancer [79]. Cancer in a sessile polyp may metastasize faster than cancer in a pedunculated polyp because of the closer proximity of the lymphatic drainage [80].

Stage

Carcinoma in situ, or high-grade dysplasia, is histologically cancer but is pathologically confined to the mucosa without penetration of the muscularis mucosa. Invasive colon cancer is most commonly staged from A through D according to the Dukes classification, with stage A penetrating beyond the colonic 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 is recently 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) [81]. This classification is particularly helpful in endosonographic staging of colon cancer [82]. 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 a Dukes B2 lesion, stage III corresponds to a Dukes C lesion, and stage IV corresponds to a Dukes D lesion. Pathologic stage, as classified by either scheme, is highly correlated with cancer prognosis [83]. Diagnostic delays result in a more advanced pathologic stage at diagnosis.

Metastases

About 20% to 25% of patients initially present with Dukes D colon cancer with identifiable metastases [84]. Perhaps another 30% of patients have no detectable metastases 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 [85]. The lungs, peritoneum, pelvis, and adrenals are less common sites [85]. These sites typically become involved only after hepatic or lymphatic metastases occur.

Epidemiology

Colon cancer is the second most common cause of mortality from cancer [1]. The lifetime risk of colon cancer is about 1 in 17 [1]. Colon cancer incidence declined by about 2% per annum in America from 1985 through 1995, but has increased recently [86]. This probably reflects increased (earlier) detection through screening programs [10,86]. If so, the incidence should begin to decline again in several years as the benefits of aggressive screening colonoscopy become manifest. Colon cancer has numerous environmental and demographic risk factors (Table 7) [1,37,62,87–117]. Environmental factors play a major etiologic role in colon cancer despite the importance of genetic mutations in colon cancer pathogenesis. Environmental factors presumably modulate the risk of the genetic mutations responsible for colon cancer, although the precise molecular mechanisms are currently unknown.

The incidence of colon cancer exhibits a striking geographic variation: the age-adjusted incidence varies by up to 15-fold among different countries [118]. Industrialized nations, except Japan, have the highest incidence, whereas South American countries and China have a relatively low incidence [1]. The wide variation in incidence is largely attributed to national differences in diet and other environmental factors [119]. In contrast to native Japanese, descendants of Japanese immigrants to America have, like other Americans, a high incidence of colon cancer attributed to dietary and other environmental adaptations [120]. Indeed, the incidence of colon cancer has recently increased in native Japanese attributed to their adopting a Westernized diet and other environmental changes with industrialization [119].

American blacks have an increased risk of colon cancer compared with whites, but the difference is small [121]. Native American Indians have
a significantly lower risk [122]. The incidence is slightly higher in American men than women [123]. The incidence of colon cancer rises sharply with age, beginning at age 50 years [124]. This phenomenon is attributed to accumulation of chance somatic mutations with age.

Clinical presentation of colon cancer

Symptoms

Symptoms are common and prominent late in colon cancer when the prognosis is poor but are less common and less obvious early in the disease. Common symptoms include abdominal pain, rectal bleeding, altered bowel habits, and involuntary weight loss [125]. Although colon cancer can present with either diarrhea or constipation, a recent change in bowel habits is much more likely to be from colon cancer than chronically abnormal bowel habits. Less common symptoms include nausea and vomiting, malaise, anorexia, and abdominal distention [10].

Symptoms depend on cancer location, cancer size, and presence of metastases. Left colonic cancers are more likely than right colon cancers to cause partial or complete intestinal obstruction because the left colonic lumen is narrower and the stool in the left colon tends to be better formed because of reabsorption of water in the proximal colon [126]. Large exophytic cancers are also more likely to obstruct the colonic lumen. Partial obstruction produces constipation, nausea, abdominal distention, and abdominal pain. Partial obstruction occasionally paradoxically produces intermittent diarrhea as stool moves beyond the obstruction.

Distal cancers sometimes cause gross rectal bleeding, but proximal cancers rarely produce this symptom because the blood becomes mixed with stool and chemically degraded during colonic transit [127]. Bleeding from proximal cancers tends to be occult, and the patient may present with iron deficiency anemia without gross rectal bleeding [128]. The anemia may produce weakness, fatigue, dyspnea, or palpitations. Advanced cancer, particularly with metastasis, can cause cancer cachexia [129], characterized by a symptomatic tetrad of involuntary weight loss, anorexia, muscle weakness, and a feeling of poor health.

Signs

Just as with symptoms, colon cancer tends not to produce signs until advanced [10]. 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 [130]. Hypoalbuminemia may clinically manifest as peripheral edema, ascites, or anasarca. Hypoactive or high-pitched bowel sounds suggest
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Proposed mechanism</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Old age</td>
<td>Acquired colonocyte mutations accumulate with age</td>
<td>[87]</td>
</tr>
<tr>
<td>Living in United States and other highly industrialized nations, possibly excluding Japan</td>
<td>Dietary and environmental carcinogens</td>
<td>[1]</td>
</tr>
<tr>
<td>Physical inactivity?</td>
<td>Physical activity may stimulate immunosurveillance, and stimulate intestinal peristalsis to decrease mucosal contact with fecal carcinogens</td>
<td>[88]</td>
</tr>
<tr>
<td><strong>Diet</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High fat?</td>
<td>Various theories (eg, increased bile secretion)</td>
<td>[89]</td>
</tr>
<tr>
<td>Low fruit and vegetable consumption</td>
<td>Anticarcinogenic substances in fruits and vegetables (eg, folate acid)</td>
<td>[90,91]</td>
</tr>
<tr>
<td>Low calcium?</td>
<td>Calcium binds to bile acids that are otherwise potentially colonotoxic</td>
<td>[92]</td>
</tr>
<tr>
<td>High red meat?</td>
<td>Animal fat in red meat or carcinogens (eg, nitrosamines) in cooked meat</td>
<td>[93]</td>
</tr>
<tr>
<td>Low selenium?</td>
<td>Selenium can help neutralize toxic free radicals because of antioxidant effects</td>
<td>[94]</td>
</tr>
<tr>
<td>Low folate?</td>
<td>Folate needed for DNA synthesis and repair</td>
<td>[95]</td>
</tr>
<tr>
<td>Low carotenoid diet?</td>
<td>Carotenoids can help neutralize free radicals because of antioxidant effects</td>
<td>[96]</td>
</tr>
<tr>
<td>Low-fiber diet?</td>
<td>Dilution of carcinogens in stool cause by increased stool bulk and stool water with a high-fiber diet</td>
<td>[89,97]</td>
</tr>
<tr>
<td>Obesity</td>
<td>Carcinogens in an unhealthy diet, or role of abnormal insulin levels in carcinogenesis?</td>
<td>[98,99]</td>
</tr>
<tr>
<td><strong>Social habits</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking cigarettes</td>
<td>Carcinogens present in tobacco</td>
<td>[100]</td>
</tr>
<tr>
<td>Alcohol</td>
<td>May promote cell proliferation and inhibit DNA repair</td>
<td>[101]</td>
</tr>
<tr>
<td><strong>Genetics and family history</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAP</td>
<td>Develops hundreds of adenomatous colonic polyps. Inevitably develops colon cancer because of small but significant risk of malignant transformation in each adenoma</td>
<td>See text</td>
</tr>
<tr>
<td>Parameters</td>
<td>Proposed mechanism</td>
<td>References</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Gardner’s syndrome</td>
<td>Variant of FAP</td>
<td>[37]</td>
</tr>
<tr>
<td>HNPCC (Lynch syndrome)</td>
<td>Mutant mismatch repair gene leads to accumulation of genetic mutations, including mutations of tumor suppressor genes</td>
<td>See text</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>Syndromic hamartomatous polyps may occasionally transform to adenomas</td>
<td>[102]</td>
</tr>
<tr>
<td>Juvenile polyposis</td>
<td>Syndromic juvenile polyps can transform to adenomas and then cancers over time</td>
<td>[62]</td>
</tr>
<tr>
<td>Family history of nonsyndromic colon cancer</td>
<td>Postulated shared genetic factors leading to mild susceptibility to colon cancer and possibly shared environmental factors</td>
<td>[103]</td>
</tr>
<tr>
<td>Hyperplastic polyposis</td>
<td>Genetic mutation in hyperplastic polyposis may predispose to cancer</td>
<td>[104]</td>
</tr>
<tr>
<td><strong>Inflammatory bowel disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic ulcerative colitis</td>
<td>Dysplasia and genetic mutations associated with mucosal injury and repair</td>
<td>[105]</td>
</tr>
<tr>
<td>Chronic Crohn’s colitis</td>
<td>Dysplasia and genetic mutations associated with cell injury and repair</td>
<td>[106]</td>
</tr>
<tr>
<td><strong>History of prior neoplasia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colonic adenomatous polyps</td>
<td>Precursor lesions to colon cancer</td>
<td>[107]</td>
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<td>Prior cholecystectomy?</td>
<td>Continuous colonic exposure to potentially carcinogenic bile acids after cholecystectomy</td>
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**Abbreviation:** ?, questionable, controversial, or weak risk factor for colon cancer.
gastrointestinal obstruction. A palpable abdominal mass is a rare finding that suggests advanced disease. Rectal examination, including fecal occult blood testing (FOBT), is important in the evaluation of possible colon cancer, as discussed later in the section on colon cancer screening. Rectal cancer may be palpable by digital rectal examination. Other physical findings, although rare, should be systematically searched for, including peripheral lymphadenopathy, especially a Virchow’s node in the left supraclavicular space; hepatomegaly from hepatic metastases; and temporal or intercostal muscle wasting from cancer cachexia. Very rare findings with colon cancer include a Sister Mary Joseph node caused by metastases to a periumbilical node, and a Blumer’s shelf caused by perirectal extension of the primary tumor [127].

**Laboratory abnormalities**

Patients with suspected colon cancer should have routine blood tests including a hemogram with platelet count determination, serum electrolytes and glucose determination, evaluation of routine serum biochemical parameters of liver function, and a routine coagulation profile. About half of patients with colon cancer are anemic [10]. Anemia, however, is very common, so that only a small minority of patients with anemia have colon cancer. Iron deficiency anemia of undetermined etiology, however, warrants evaluation for colon cancer, particularly in the elderly [131]. Hypoalbuminemia is uncommon, but not rare, in colon cancer. It usually indicates poor nutritional status from advanced cancer [132].

Routine serum biochemical parameters of liver function are usually within normal limits in patients with colon cancer. Abnormalities, particularly elevation of the alkaline phosphatase level, often indicate hepatic metastases [133]. The serum lactate dehydrogenase level may increase with colon cancer. Diarrhea associated with colon cancer can rarely produce electrolyte derangements or dehydration. Nausea and vomiting from colon cancer can rarely produce metabolic derangements of hypovolemia, hypokalemia, or alkalosis.

The serum carcinoembryonic antigen level is not useful to screen for colon cancer [134]. It is only moderately sensitive. Although patients with very advanced cancer tend to have highly elevated levels, patients with early and highly curable colon cancer tend to have only minimally elevated levels, with considerable overlap with the levels of patients without colon cancer [135]. It is poorly specific. Other colonic diseases or systemic disorders can cause a carcinoembryonic antigen elevation. Preoperative testing is, however, useful to determine cancer prognosis and to provide a baseline for comparison with postoperative levels. An elevated serum level preoperatively is a poor prognostic indicator: the higher the serum level the more likely the cancer is extensive and will recur postoperatively [135]. After apparently complete colon cancer resection the serum level almost always normalizes; failure to normalize postoperatively suggests incomplete resection [136]. A sustained
and progressive rise after postoperative normalization strongly suggests cancer recurrence [137]. Patients with this finding require prompt surveillance colonoscopy to exclude colonic recurrence and abdominal imaging to exclude metastases.

Unusual clinical syndromes caused by colon cancer

Colon cancer can cause acute colonic obstruction, most commonly from exophytic intraluminal growth, and most uncommonly from intussusception or volvulus. Obstruction typically occurs in the sigmoid colon because of the narrow lumen and hard stool in this region. Patients present with abdominal pain, nausea and vomiting, obstipation, abdominal tenderness, abdominal distention, and hypoactive bowel sounds. Colon cancer can rarely perforate acutely through the colonic wall and cause acute generalized peritonitis, and can rarely perforate slowly to form a walled-off inflammatory mass or abscess with localized peritoneal signs. Factors promoting colonic perforation include disruption of mucosal integrity because of transmural malignant extension or colonic ischemia, and increased intraluminal pressure because of colonic obstruction. Presentation with colonic obstruction or perforation indicates a poor prognosis. Colon cancer rarely causes ischemic colitis because of colonic dilatation proximal to malignant obstruction or malignant infiltration of blood vessels [138]. Colon cancer occasionally causes gross rectal bleeding because of cancerous mucosal ulceration.

Clinical presentation of colonic adenomas

Adenomatous polyps are most commonly asymptomatic. In a review of 800 patients with colorectal polyps about two thirds were asymptomatic [139]. Moreover, these symptoms are often coincidental and not caused by the polyps. For example, rectal bleeding in a patient with a small colonic polyp is more often caused by other conditions, particularly hemorrhoids. Hemorrhoidal bleeding characteristically is postdefecatory, coats the stools, and produces very bright red blood [140]. Polyps more than 1 cm in diameter are more likely to produce symptoms, and polyps less than 0.5 cm rarely produce symptoms [141,142]. The most common symptoms attributable to polyps are rectal bleeding, abdominal pain, and change in bowel habits. A rectal polyp can rarely cause rectal prolapse. A large polyp rarely forms the leading edge of a colonic intussusception [143]. Large villous adenomas, especially in the distal colon, can rarely cause profuse watery diarrhea [144].

Physical findings and laboratory abnormalities are uncommon with adenomatous colonic polyps. A rectal polyp may be palpable by digital rectal examination. Only about half of adenomas cause fecal occult blood [145]. Large adenomas are more likely to cause occult bleeding and small adenomas rarely cause occult bleeding [141,142]. A benign colonic polyp rarely causes
iron deficiency anemia; iron deficiency anemia is much more common with a malignant polyp because of quantitatively greater chronic blood loss.

Symptoms and signs are common when colon cancer is advanced and likely to be incurable, are less common when colon cancer is early and highly curable, and are relatively uncommon with adenomatous polyps. This phenomenon renders adenomas or early cancer difficult to detect by clinical presentation and provides the rationale for mass screening of the general asymptomatic population for early detection and prevention of colon cancer.

Screening and diagnostic tests for colonic lesions

 Screening of average-risk patients

 Fecal occult blood testing

  FOBT was the traditional mainstay of screening for colon cancer and colonic polyps. It is most commonly tested by a colorimetric assay of a reaction on guaiac catalyzed by the pseudoperoxidase present in blood. It has advantages as a screening test of low cost, test simplicity, noninvasiveness, and safety. It has a disadvantage as a screening test because of low specificity. FOBT is based on increased microscopic rectal bleeding in patients with colon cancer compared with patients without colonic disease. Patients with and without colon cancer, however, have a wide range of microscopic bleeding with considerable overlap [145]. This overlap results in low test specificity [146]. Specificity is increased by avoiding ingestion of broccoli, cauliflower, or red meats and by avoiding therapy with aspirin for 3 days before the test. Whether iron causes a false-positive FOBT is controversial [147], but withholding iron therapy for several days before the test is prudent because of possible test interference. Even in ideal research studies, only 5% to 10% of patients with fecal occult blood have colon cancer, and another 20% to 30% have colonic adenomatous polyps [148–150]. Although true-positive tests can lead to early colon cancer detection and cure, false-positive FOBT results in a large number of expensive and nondiagnostic colonoscopies.

  FOBT is, moreover, only moderately sensitive. Sensitivity is improved by performing stool tests on three different occasions because colon cancer typically only intermittently bleeds, and by avoiding ascorbic acid for several days before the test because ascorbic acid inhibits the guaiac reaction [151]. Test sensitivity is also improved by performing the test on fresh stool or by rehydrating the stool specimen, but rehydration decreases the test specificity. Nevertheless, the sensitivity of FOBT for colon cancer using ideal techniques under the ideal circumstances of a research study is only about 85% [152]. The sensitivity for detecting adenomas is considerably lower because colonic adenomas bleed less frequently than colon cancer. The sensitivity for adenomas is only about 50% [145]. The sensitivity is particularly low for adenomas that are small or located in the proximal colon [145].
Despite these flaws, FOBT is an important element in the armamentarium of colon cancer screening because of test safety and convenience. Mandel et al [153] demonstrated in a large, prospective, randomized, controlled study that annual screening by FOBT results in reduced mortality from colon cancer. Unexplained fecal occult blood mandates further evaluation of the colon to exclude colon cancer or polyps in any patient more than 40 years old [154].

Barium enema

Barium enema was touted as a cheaper, less invasive, and safer alternative to colonoscopy. Barium enema entails a risk of colonic perforation of only about 1 per 25,000 examinations [155]. Patients are exposed to about 0.03 Gy of radiation during a barium examination. Indeed, Medicare approved barium enema for reimbursement for screening for colon cancer. Barium enema, however, is only moderately sensitive at detecting colon cancer. For example, in a review of 2193 consecutive colorectal cancers, barium enema was much less sensitive (82.9% sensitivity) than colonoscopy (95% sensitivity) in detecting colon cancer [156]. Barium enema is even less sensitive at detecting colonic polyps. For example, in a study of 580 patients undergoing both barium enema and colonoscopy, barium enema detected only 32% of colonic polyps less than 6 mm in diameter, 53% of colonic polyps between 6 and 10 mm, and 48% of polyps larger than 10 mm [157]. Diverticulosis, colonic spasm, poor colonic preparation, and redundant overlapping colonic loops interfere with barium enema interpretation and accuracy. Rectal lesions may be missed because of interference by the intrarectal occluding balloon. Barium enema does not permit histologic characterization of an identified lesion because of an inability to perform biopsies, and does not permit therapeutic removal of polyps. Detection of a polyp at barium enema necessitates colonoscopy as a second examination for biopsy or polypectomy.

Flexible sigmoidoscopy

Flexible sigmoidoscopy every 3 to 5 years has been recommended in conjunction with annual FOBT for screening for colon cancer [5,158,159]. Sigmoidoscopy decreases mortality from rectosigmoid colon cancer. For example, Selby et al [160] reported a 59% reduction of rectosigmoid cancer in patients undergoing one or more rigid sigmoidoscopies in the prior decade compared with unscreened controls matched for age and sex.

The role of flexible sigmoidoscopy is becoming increasingly limited in the screening and diagnosis of colon cancer. Sigmoidoscopy is relatively insensitive at colon cancer or colon polyp detection because the proximal half of the colon is not endoscopically visualized. From one third to one half of lesions are proximal to the sigmoid colon [161,162]. This effect has become quantitatively larger with the recent shift of colonic polyps and cancers to the right side of the colon [163]. Even a screening strategy that calls for
colonoscopy when a patient has a distal colonic polyp detected by sigmoidoscopy misses most proximal lesions because most proximal lesions do not have synchronous distal lesions [164,165]. Sigmoidoscopy is also an inadequate test for patients with distal colon cancer. About 3% to 5% of patients with an index colon cancer have a synchronous cancer [166,167]. The presence of proximal synchronous lesions affects distal cancer management. If a synchronous proximal lesion is malignant, the patient requires larger colonic resection to extirpate both lesions. If the proximal lesion is a benign adenoma, the patient should undergo colonoscopic polypectomy before undergoing sigmoid colectomy. Finding an adenomatous polyp or cancer at sigmoidoscopy mandates a full colonoscopy to diagnose synchronous lesions.

**Diagnostic colonoscopy**

Colonoscopy is recommended for screening of patients more than 50 years old at average risk for colon cancer or colonic polyps [5,159]. Colonoscopy is highly sensitive at detecting large (> 1 cm) colonic polyps, with a miss rate of only 6%, and is moderately sensitive at detecting diminutive (<0.6 cm) polyps with a miss rate of about 27% [168]. Colonic polyps may be missed around sharp turns, especially the hepatic and sigmoid flexures; at areas of colonic spasm, especially in the sigmoid or with severe diverticulosis; and areas covered by stool because of poor colonic preparation. Colon cancers are rarely missed at colonoscopy because they tend to be larger than adenomatous polyps. Colonoscopy is a highly specific test. At colonoscopy polyps are removed and masses biopsied for a pathologic diagnosis.

Colonoscopy, however, has disadvantages as a screening test because it is resource intensive; expensive; somewhat invasive; uncomfortable; and entails a small, but significant, risk of serious complications. It requires a team including a technician, nurse, and highly trained colonoscopist. Colonoscopy is not readily available with long waiting times because of a shortage of highly trained colonoscopists [169,170]. The test requires patient preparation for 24 hours before the procedure. The test is uncomfortable and generally requires sedation and analgesia. The patient requires postprocedure monitoring until the effects of the sedatives and analgesics wear off. The complication rate of diagnostic colonoscopy is about 0.4% [171,172]. The most common major complications are gastrointestinal bleeding and colonic perforation. Most colonic perforations require colonic surgery, but conservative management with parenteral fluids, antibiotics, and surgical back-up occasionally suffices [173].

At colonoscopy, polyps are characterized according to size; color; number; segmental location; intramural location (mucosal versus submucosal); presence or absence of a stalk (pedunculated versus sessile); and superficial appearance. Polyp characteristics at colonoscopy provide important clues concerning polyp histology and malignant potential, which can influence the colonoscopic management. Hyperplastic polyps are usually small, pale,
unilobular, and located in the rectum [174]. Adenomas are larger, redder, more multilobular, and distributed throughout the colon. Villous adenomas tend to be large, bulky, sessile, shaggy, soft, velvety, and friable [140]. Colonoscopic appearance is, however, only moderately correlated with polyp histology. Pathologic examination of a colonoscopic biopsy provides an indication of polyp histology, but is subject to sampling error. A polyp is definitively classified by pathologic examination of the entire polyp after polypectomy. Colonoscopic polypectomy is diagnostic and therapeutic for noncancerous adenomatous polyps.

Flat adenomas tend to be small, discoid, and erythematous plaques. Flat adenomas are important because of a significant risk of high-grade dysplasia and occasionally of cancer. Flat adenomas are difficult to detect and are often missed at colonoscopy. These lesions are identified by chromoendoscopy with colonoscopic instillation of methylene blue or indigo carmine [175,176].

The differential diagnosis of numerous polypoid colonic masses detected at colonoscopy includes FAP, attenuated FAP, hyperplastic polyposis, juvenile polyposis, Peutz-Jeghers syndrome, pseudopolyposis, diffuse colonic hemangiomatosis, and pneumatosis coli. These conditions are differentiated by clinical, radiologic, colonoscopic, and histologic findings. In patients with FAP, the colonic mucosa is carpeted by hundreds or thousands of adenomatous polyps. In patients with attenuated FAP, only about 30 adenomatous polyps are present. These polyps are usually located in the proximal colon and tend to be flat growths because of intramural, rather than intraluminal, growth [42]. Classic and attenuated FAP are both caused by APC mutations. In attenuated FAP, APC mutations occur at certain sites, particularly the extreme proximal or distal ends of the $APC$ gene [177]. Patients with FAP must undergo prophylactic colectomy after puberty to prevent colon cancer [178]. Hyperplastic polyposis is characterized by 20 or more polyps in the colon, a predominantly right colonic polyp distribution, and a positive family history [104]. Juvenile polyposis is characterized by a family history of juvenile polyposis, more than five juvenile polyps in the colon, multiple juvenile polyps throughout the rest of the gastrointestinal tract, and polyp development at a young age [179]. In Peutz-Jeghers syndrome multiple hamartomatous polyps, which characteristically contain abundant branching smooth muscle, occur throughout the gastrointestinal tract. Patients characteristically have perioral and oral hyperpigmentation because of melanin deposition [180]. Pseudopolyps represent islands of variably inflamed residual mucosa surrounded by a background of previously sloughed off mucosa. It is most commonly associated with ulcerative colitis. Other colonoscopic findings of ulcerative colitis, including mucosal erythema, granularity, blunting of the normal vascular pattern, friability, mucopus, mucosal hemorrhage, and superficial ulcerations, may be present. At colonoscopy, hemangiomas often appear as multiple violet-blue, sessile, polypoid lesions [181]. They are associated with characteristic dermatologic
lesions in the blue rubber bleb nevus syndrome. In pneumatosis coli multiple air-filled cysts are present in the colonic submucosa. Colonoscopy reveals multiple, pale, cystic, round polypoid masses with overlying intact mucosa [182].

Early colon cancer may occur in an adenomatous polyp and 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 [183]. Polyp risk factors for malignancy include villous rather than tubular histology, large size, sessile morphology, and increasing number of colonic polyps [17]. 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 may, however, 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 not definitive. Pathologic examination of multiple colonic biopsies and cytologic analysis of stricture brushings are usually diagnostic.

Surveillance of high-risk patients and diagnostic testing of patients with strong clinical indications

Patients at average risk for colonic adenomatous polyps or cancer undergo screening colonoscopy every 10 years, or alternative screening tests at periodic intervals, as outlined previously and described in detail elsewhere in this issue. Patients who are members of high-risk groups, as listed in Box 1,
undergo periodic surveillance more frequently. In these high-risk groups colonoscopy is the recommended test. The age of beginning surveillance and the frequency of surveillance depends on the age of onset of the increased cancer risk and the quantitative risk of cancer. These indications are discussed elsewhere in this issue. Aside from periodic screening or surveillance, patients require colonoscopy to exclude colon cancer, adenomatous polyps, or other colonic diseases for specific acute indications, as listed in Box 2.

Testing for intramural penetration and extracolonic spread of colon cancer

CT

CT has been the standard modality to image the abdomen in patients with colorectal cancer. CT is relatively highly accurate at detecting liver metastases. For example, CT was 85% accurate in a multicenter study [184]. CT is much more sensitive at detecting large than small hepatic lesions [185]. CT is only moderately accurate at T staging. For example, the accuracy for T staging was only 74% in a large multicenter study [184]. CT errors typically occur from underestimating the T stage. CT is only about 50% to 70% accurate in N staging of rectal cancer [184].

<table>
<thead>
<tr>
<th>Box 2. Acute indications for colonoscopy to exclude colonic adenomas, colon cancer, or other colonic diseases</th>
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<td>Fecal occult blood</td>
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<td>Follow-up after colonoscopic removal of a large sessile proximal colonic polyp</td>
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<td>Abnormal radiologic study (barium enema, virtual colonoscopy) suggestive of colon cancer</td>
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<td>Colonic stricture</td>
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<td>Dye injection to label a malignant polyp for subsequent surgical removal</td>
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<tr>
<td>Intraoperative colonoscopy to localize a lesion for surgical removal</td>
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MRI

MRI seems to be superior to CT in detecting focal liver metastases from colon cancer. It is more sensitive than CT, particularly for small metastases, because of the typically sharp contrast between metastatic lesions and normal liver on MRI [186]. Administration of contrast agents, such as superparamagnetic iron oxide, further improves the sensitivity of MRI [187]. MRI is also more specific for hepatic metastases than CT. Hepatic metastases have a much shorter T2 sequence than hepatic hemangiomas or cysts [188]. Hepatic metastases typically demonstrate rapid and strong enhancement with intravascular contrast because of enhanced vascularity, but may enhance inhomogeneously because of nonperfused or hypovascular areas within metastases [189]. Although MRI has advantages over CT for detecting hepatic metastases, CT has been the standard test because of lower cost, greater machine availability, and more widely available expertise in image interpretation [190]. MRI is traditionally reserved for characterizing ambiguous hepatic lesions detected by abdominal ultrasound or CT.

Transrectal and colonic ultrasonography

The relative inaccuracy of CT for T and N staging of rectal cancer has led to application of endoscopic ultrasound for this purpose. Preoperative evaluation of the T stage (depth of mural invasion) and the N stage (nodal involvement) greatly impacts the therapy for rectal cancer. Patients with superficial cancer (T1N0) can be treated by local endoscopic or transanal resection without wide excision. Patients with T2N0 lesions are treated surgically without preoperative adjuvant therapy. Patients with deep intramural involvement (T3 or T4) or with nodal involvement (N1 or N2) should receive preoperative radiation and possibly chemotherapy. Patients without rectal sphincter involvement may avoid a colostomy.

Endoscopic ultrasound is more accurate than CT for T staging. For example, in a study of 80 patients with rectal cancer undergoing both CT and rectal ultrasonography, the accuracy of T staging by endosonography was 91% compared with 71% for CT [191]. This difference was statistically significant \((P = .02)\). Other studies report that rectal endosonography has about 85% accuracy for T staging [192–194]. Tumors generally appear at endosonography as homogeneous hypoechoic masses that disrupt the normal five-layer ultrasound structure of the rectal wall [195]. Errors in endosonographic T staging may be caused by distortion of the ultrasound image by inflammation in tissue just beneath cancer [196]. 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 [82]. Endosonography has about 80% accuracy for N staging [82,191]. At endosonography malignant lymph nodes tend to be large \((>1 \text{ cm})\); hypoechoic; have sharply demarcated borders; and a round, rather than an ovoid or flat, shape [195].
Rectal ultrasound has become the standard preoperative imaging modality for local T and N staging of rectal cancer because of relatively high accuracy. It has not yet, however, been proved to prolong survival [197]. The rectum is easily accessible to an ultrasound probe, using either a rigid probe inserted blindly or an echoendoscope inserted under endoscopic guidance. The procedure is very safe. Endoscopic ultrasound findings frequently change the treatment plan. For example, in a study of 80 patients, endoscopic ultrasound findings resulted in the addition of preoperative neoadjuvant therapy in 25 patients [191]. The accuracy of endoscopic ultrasound is operator dependent. Other factors affecting the accuracy of tumor staging include the ultrasound frequency, with higher frequency improving the resolution but decreasing the depth of penetration; the location of the tumor, with reduced accuracy for tumors low in the rectum; and prior radiotherapy caused by an increase in wall echogenicity after radiation [198].

There are scant data on the impact of endoscopic ultrasound–guided fine-needle aspiration in rectal cancer staging [82,199]. In one study of 41 patients, endoscopic ultrasound–guided fine-needle aspiration of a lymph node upgraded the N stage in one patient and downgraded the N stage in eight patients [191]. Unfortunately, these changes were incorrect in three of the nine cases. Although a fine-needle aspiration diagnosis of cancer in a lymph node is secure, a finding of benignity may be erroneous because of sampling error. The current data are insufficient to recommend standard use of fine-needle aspiration in N staging of rectal cancer [82].

Locally recurrent rectal cancer is potentially important to detect early so that patients can undergo salvage surgery for possible cure. Endoscopic ultrasound is currently the most reliable imaging study for detecting postoperative rectal cancer recurrence. It is superior to CT. In a study of 62 patients undergoing surveillance after rectal cancer surgery, endoscopic ultrasound detected all 11 cancer recurrences [200]. An array of other studies, including serial serum carcinoembryonic antigen levels, digital rectal examination, colonoscopy, and pelvic CT, failed to detect two of these cancer recurrences. The clinical benefit of early detection of rectal cancer recurrence is limited, however, by the low cure rate of salvage surgery [201].

The data on endosonography for colon cancer are much more limited than that for rectal cancer. Most patients with colon cancer without distant metastases undergo colonic resection, regardless of T or N stage. Colonic endosonography is also technically more demanding and time consuming than rectal endosonography. In a study of 50 small colon cancers, endosonography was 91.8% accurate in T staging, compared with 63.3% for magnifying colonoscopy [202]. This difference was statistically significant. Endosonography was, however, only 24.1% accurate for N staging in this study. In a study of 86 patients with colon cancer, endosonography using a balloon-sheathed miniprobe inserted during colonoscopy was 85% accurate for T staging and 73% accurate for N staging [203].
Prevention of colon cancer

Dietary modifications

Dietary fiber may reduce the risk of colon cancer. Proposed mechanisms include decreased mucosal exposure to intraluminal carcinogens caused by stimulated intestinal transit, decreased concentration of carcinogens in stool caused by increased stool bulk, increased concentrations of anticarcinogenic short-chain fatty acids, and stabilization of insulin levels caused by delayed starch absorption that might otherwise promote colonic carcinogenesis [86]. The effect of dietary fiber is controversial with numerous studies suggesting a large protective effect [97], and several studies suggesting no effect [93]. Regardless of the effect on colon cancer, a high-fiber diet is recommended because of other health benefits. Patient obesity and a diet rich in animal fat and red meat have been proposed as risk factors for colon cancer. The evidence for this is insufficient to recommend avoidance of these factors to reduce the incidence of colon cancer, but avoidance of these factors is recommended because of other, primarily cardiovascular, health benefits. The known effects of dietary factors on colon cancer prevention are summarized in Table 7. These effects are reviewed in detail elsewhere in this issue and in several other recent reviews [123,204].

Chemoprevention with aspirin and other nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce cellular proliferation, slow cell cycle progression, and stimulate apoptosis [86]. Experimental data suggest that NSAIDs may prevent colonic adenomas or cancer. For example, various NSAIDs prevent carcinogen-induced colon cancer in rodents [205]. Several NSAIDs inhibit adenoma formation in the Min-mouse model of human FAP [123,206]. Case-control and cohort epidemiologic studies also provide evidence of decreased adenoma incidence or decreased colon cancer mortality with regular chronic NSAID use, particularly of aspirin [207]. The Cancer Prevention Study II prospectively analyzed the effect of aspirin on colon cancer mortality during a 6-year period in more than 600,000 adults who provided information on their aspirin use at their enrollment in the trial. The relative mortality from colon cancer was about 0.6 in men and 0.58 in women who used aspirin 16 or more times per month compared with nonusers of the same sex [208]. The relative risk was unchanged when adjusted for dietary factors, physical activity, family history, or diseases that might affect colon cancer mortality or aspirin use. In the Nurses Health Study, the relation between chronic aspirin use and the incidence of colorectal cancer from 1984 through 1992 was analyzed. Women who took aspirin for at least 20 years had a relative risk of 0.56 for developing colon cancer compared with nonusers [209]. Other NSAIDs seem
to cause similar reductions in colon cancer incidence, although the effects are less well analyzed [210].

Waddell et al [211] first demonstrated that open-labeled treatment with sulindac, an NSAID, caused regression of colonic adenomas in patients with FAP. They reported disappearance of most rectal polyps in seven patients with a rectal stump status post–subtotal colectomy and of most colorectal polyps in another four patients with FAP with intact colons [211]. Subsequent trials have confirmed that sulindac causes regression of existing adenomas and suppression of new adenomas in patients with FAP [123].

NSAIDs are believed to reduce adenoma formation and inhibit colon cancer development by inhibiting the cyclooxygenase (COX) enzymes required for the synthesis of prostaglandin E2; prostaglandin E2 promotes cell proliferation and tumor growth [212]. NSAIDs may also retard carcinogenesis by effects on cell adhesion and apoptosis [204]. Cyclooxygenase has two isoforms, COX-1 and COX-2. Although nonselective NSAIDs inhibit both isoforms, several COX-2 selective inhibitors have been recently developed. COX-2 inhibitors are used clinically to avoid, or at least reduce, the gastrointestinal toxicity of nonselective NSAIDs [213]. 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 [214]. Celecoxib has shown some promise in causing regression of colonic adenomas in patients with FAP. In a study of 77 patients with FAP, patients receiving celecoxib, 400 mg twice daily, had a 28% reduction in the mean number of rectal polyps as compared with a 4.5% reduction in the placebo-treated group [215].

Several trials have examined the effect of NSAIDs on sporadic adenomas. The effects are generally less dramatic [123]. If the benefit of NSAIDs in patients with sporadic adenomas is less clinically significant than in patients with FAP, the toxicity of NSAIDs becomes a more important issue in these patients. Although data support that NSAIDs inhibit colonic carcinogenesis, the optimum specific NSAID, dosage, and duration of treatment are unknown. The role of COX-2 selective inhibitors versus nonselective COX inhibitors needs to be better analyzed and defined.

Colonoscopic polypectomy

Colonic polyps less than 0.8 cm in diameter are usually removed by hot biopsy, especially when sessile, whereas polyps that are larger than 0.8 cm in diameter are usually removed by snare polypectomy, especially when pedunculated [216]. Hot biopsy is performed cautiously in the cecum using a low amplitude and brief duration of current because the colonic wall is thinnest and most vulnerable to transmural necrosis in this region [217]. Diminutive polyps, less than 6 mm in diameter and sessile, may be removed
by cold snare polypectomy, wherein the polyp is snared and transected in
guillotine fashion without electrocautery. Cold snare polypectomy avoids
diathermy artifact in the resected specimen, but entails a theoretical risk
of incomplete removal of neoplastic tissue. Electrocautery, in contrast,
destroyed residual neoplastic tissue in the unremoved stump. Cold snare
polypectomy is safe, with a low risk of postpolypectomy hemorrhage [218].
Ultradiminutive (<4 mm) polyps may be removed by repeated cold biopsies
without electrocautery.

Large polyps that are likely or obviously malignant should be extensively
sampled by multiple biopsies to increase the diagnostic yield, but not
removed in toto by polypectomy to avoid the extra risks of polypectomy
when cancer surgery is likely to be subsequently required [219]. Sessile
polyps between 2 and 3 cm in diameter may be removed by snare
polypectomy after creating a pseudopedicle by injecting normal saline or
another solution into the polyp base, as described next under endomuco-
sectomy [218]. Sessile polyps more than 3 cm in diameter may be
unamenable to conventional snare polypectomy, but may be removed by
sequential piecewise polypectomy during several colonoscopic sessions [220].
Pedunculated polyps more than 5 cm in diameter or occluding the lumen
may be unamenable to conventional colonoscopic polypectomy because of
the technical difficulty of looping a snare around these polyps. These polyps
may require surgical resection even when benign.

The complication rate of therapeutic colonoscopy is about 1.4% [171,172].
The most common major postpolypectomy complications are gastrointesti-
nal bleeding, colonic perforation, and the postpolypectomy syndrome. In the
postpolypectomy syndrome, a patient develops abdominal pain, pyrexia,
leukocytosis, and localized peritoneal irritation from an almost transmural
burn from polypectomy. This occurs in up to 1% of polypectomies [221]. This
syndrome is usually managed medically, with cessation of oral intake,
intravenous hydration, and antibiotic administration [222].

The pathophysiology of the adenoma-to-carcinoma sequence and the
molecular pathophysiology of colon carcinogenesis strongly suggest that
polypectomy of adenomas should substantially prevent colon cancer. This is
strongly supported by clinical trials. For example, in the National Polyp
Study 699 patients underwent surveillance colonoscopy at 1, 3, and every 2
subsequent years after detecting at least one adenomatous polyp at an index
colonoscopy [223]. The 699 patients had only five colorectal cancers detected
during a mean surveillance period of 5.9 years. This represented a 76% to
90% decline in the incidence of colon cancer compared with three historical
reference groups. All the cancers were detected early.

Endomucosectomy

Endomucosectomy, or endoscopic mucosal resection, adapts the classic
principles of conventional snare polypectomy combined with submucosal
injection to remove more deeply affected mucosa or submucosa by resecting through the middle or deep submucosa. Endomucosectomy provides an alternative to surgery for deeper superficial lesions without evident penetration of the deep muscle layer, regional lymph nodes, or distant metastases. Sessile villous adenomas, adenomas with carcinoma in situ (T0 lesions), and some early cancers invading the submucosa (T1N0M0) lesions are candidates for endomucosectomy in suitable patients. Usually the tumor is characterized by endoscopy, sampled by endoscopic biopsy, and locally staged by endosonography before considering endomucosectomy. Patients are evaluated for the suitability of endomucosectomy based on tumor size; endoscopic appearance; pathology of the initial endoscopic biopsy; and the estimated depth of tumor penetration (T stage). Endomucosectomy is usually applied to polypoid (protruding) lesions, but can be applied to flat or even minimally depressed lesions provided the previously mentioned criteria are satisfied. Endomucosectomy has an advantage over endoscopic ablative therapy (using laser, argon plasma coagulation, or photodynamic therapy) because the entire treated specimen is removed and available for histologic analysis and pathologic staging. Endomucosectomy has an advantage over the alternative of surgical resection of less procedure morbidity and minimal mortality.

The basic technique of endomucosectomy is deep submucosal injection of normal saline or another solution to thicken the colonic wall at the polypectomy site to permit deep resection of the submucosa without incurring a risk of a transmural burn or frank colonic perforation. This injection also tamponades the feeding artery to reduce postpolypectomy bleeding, promotes vasospasm, and increases tissue liquidity and electrical conductivity at the polyp base to facilitate electrocautery. The effects of the submucosal injection are carefully evaluated during endoscopy. A lesion that lifts during submucosal injection is amenable to endomucosectomy; a lesion that partly lifts may be amenable to endomucosectomy after due consideration; and a lesion that fails to lift (nonlift sign) is not amenable to endomucosectomy because of a high risk of invasive carcinoma [224,225]. Deep carcinomatous invasion is the major cause of adherence of submucosa to deep muscle and the nonlift sign [225]. Failure to lift also increases the risk of endomucosectomy because of poorly defined tissue planes for endoscopic resection.

The tumor may then be resected by conventional snare polypectomy to resect subcutaneous tissue. Adjunctive techniques used to increase the depth of endoscopic resection include the following. (1) The use of a special shark tooth snare with small hooks along the wire loop. The hooks dig into the lesion to prevent slippage of the lesion during snare closure. (2) The use of a transparent cap inserted at the tip of the endoscope. The cap contains an internal rim at the tip in which an open snare is prepositioned. After the lesion is sucked into the cap using endoscopic suction, the snare is closed on the suctioned tissue (neopolyp) and electrocautery is applied to remove deeper tissue. (3) The use of a double-channel endoscope with a biopsy
forceps and a snare advanced through separate channels and with the snare loop opened around the biopsy forceps. The lesion is grasped and lifted by the biopsy forceps and the snare is then closed around the lifted submucosal tissue.

Endomucosectomy has been frequently used by Japanese and European endoscopists, but is increasingly being used by American investigators. It is most commonly applied to remove early gastric cancers or esophageal lesions but is being increasingly used to remove colorectal lesions, particularly large adenomas.

Complications of endomucosectomy include abdominal pain, bleeding, perforation, and stricture formation. The risks of bleeding vary from 1.5% to 24%, depending on the size and type of the lesion and the definition of bleeding [224]. Endoscopic hemostasis is frequently required during endomucosectomy because of transection of submucosal vessels. The endoscopist must be experienced and highly competent at endoscopic hemostasis to address the problem promptly. The simplest technique of hemostasis is endoscopic clipping.

The major problem of endomucosectomy is that it is insufficient therapy for locally extensive or metastatic disease. This occurs much more frequently for lesions staged as T1 than T0 by endosonography. About 10% of apparently T1 lesions turn out to be more deeply invasive cancers, including about 5% with residual cancer in the bowel wall and about 5% with undetected nodal metastases [226,227]. Such patients usually require cancer surgery for cure following endomucosectomy. Endomucosectomy is described in greater detail elsewhere in this issue.

New and evolving developments

Colon cancer incidence and survival has improved only slightly in the United States during the past decade despite the apparent efficacy of colonoscopic polypectomy at cancer prevention [228]. This failure is caused by insufficient implementation of colonoscopy screening partly because of the expense, invasiveness, discomfort, and risks of colonoscopy. New simpler, less invasive, and safer tests are being designed to overcome these barriers to universal screening for colon cancer.

Stool genetic markers

DNA from colon cancer is shed into the fecal stream in greater quantities than DNA from normal colonic mucosa. Cancerous DNA is not degraded with time or by contiguity with stool during colonic passage [229]. Much as minute quantities of blood in stool are detected by guaiac testing, minute quantities of DNA in stool can be assayed by polymerase chain-reaction amplification. This technique has shown clinical promise in preliminary clinical studies for noninvasive detection of cancerous DNA in stool.
specimens. For example, a multiarray assay for common mutations in colon cancer, including APC, p53, K-ras, and BAT-26 (a marker for microsatellite instability) mutations had a sensitivity of 91% and specificity of 100% for detection of colon cancer in a study of 22 patients with colon cancer and 28 patients with endoscopically normal colons [230,231]. In another study, an assay for genetic mutations in TP53, BAT-26, and K-ras detected mutations in 36 (71%) of 51 patients with colon cancer [232]. Most of the detected cases, however, had histologically advanced and clinically symptomatic colon cancer; an ideal screening test should also detect early asymptomatic and potentially curable colon cancer [233]. Genetic stool screening has the potential test advantages of noninvasiveness and user friendliness, but needs further refinement in technique and testing in large clinical trials [229,231]. Incorporation of additional molecular markers may further improve test sensitivity and specificity.

Colorectal cancer can also be detected in the serum, but the clinical studies are so far preliminary and small. The studies have shown low test sensitivity [234,235]. With further technical refinements, these molecular and noninvasive approaches could become highly useful for screening for colon cancer.

**Virtual colonoscopy**

Vining introduced virtual colonoscopy in 1994 to maintain the desirable features of colonoscopy of ease of lesion detection while avoiding the undesirable features of colonoscopy of test invasiveness, patient discomfort, need for sedation and analgesia, and test risks [236]. In virtual colonoscopy CT images are obtained in the prone and supine positions during a prolonged breathhold. The CT images are reformatted into two-dimensional images in the three orthogonal (axial, sagittal, and coronal) planes, or reconstructed into three-dimensional endoluminal (virtual colonoscopy) images that simulate the conventional colonoscopic view. Like colonoscopy, virtual colonoscopy generally requires colonic preparation with oral laxatives. Application of digital stool subtraction technology with administration of oral contrast may, however, obviate the need for colonic preparation [237]. Unlike colonoscopy, sedation and analgesia are not required. CT colonography is extremely safe with rarely reported significant complications [238,239]. Unlike colonoscopy, virtual colonoscopy can visualize extracolonic intra-abdominal organs. It can provide cancer staging simultaneous with colon cancer detection, and can visualize intra-abdominal abnormalities, such as extracolonic malignancies and aneurysms [240].

Virtual colonoscopy is currently under intense analysis. The accuracy is controversial, with conflicting data. For example, Pickhardt et al [239] reported in 2003 that CT colonography had a sensitivity of 93.8% for polyps at least 10 mm in diameter, 93.9% for polyps at least 8 mm in diameter, and 88.7% for polyps at least 6 mm in diameter. In this study CT colonography
was an excellent screening test for colonic polyps with a very high sensitivity and specificity. Contrariwise, Cotton et al [241] reported in 2004 in a study of 600 patients undergoing both CT colonography and colonoscopy that the sensitivity of CT colonography was only 39% for lesions less than 6 mm in diameter, and only 55% for lesions sized more than 10 mm in diameter. In this study CT colonography was so poorly sensitive and specific as not to be useful as a screening test [242]. The wide discrepancy between the various studies may be caused by different CT technology, especially use of 4- versus 16-slice scanners, use of supine versus supine and prone views, different computerized software for colonic fly-through endoluminal views, different levels of radiologist training and expertise, and administration of dual oral contrast versus single oral contrast versus no oral contrast for tagging stool [242]. In all studies the accuracy of virtual colonoscopy is a function of polyp size. It is much more accurate for lesions larger than 10 mm than for lesions less than 5 mm [239,243,244]. It is consequently more accurate at detecting cancers than adenomas because cancers tend to be larger [244,245]. The most important disadvantage of virtual colonoscopy is the inability to remove polyps for histologic analysis and definitive therapy; the inability to biopsy masses for histologic classification; and the inability to apply other therapies, such as injection or ablation, which are available by colonoscopy. Detection of a polyp or mass at virtual colonoscopy currently requires colonoscopy as a second test for polypectomy or biopsy. Virtual colonoscopy is reviewed in detail elsewhere in this issue.

**Videocapsule endoscopy**

The videocapsule is delivered perorally to the small intestine by peristalsis to provide wireless endoscopy by radiofrequency transmission [246]. The videocapsule contains a miniaturized image-capturing system, battery, light source, and transmitter, all of which are contained within an 11-by-30 mm capsule.

Videocapsule endoscopy has developed a niche in the evaluation of jejunoileal bleeding [247,248]. Although chronic blood loss is usually caused by an upper or lower gastrointestinal lesion, the bleeding occasionally arises from the jejunoileum. The jejunoileum is poorly accessible by traditional tube endoscopy. Only the distal 20 to 30 cm of the ileum is potentially accessible during colonoscopy [249]. Likewise traditional tube esophagogastroduodenoscopy can be extended by push enteroscopy into, but not beyond, the proximal jejunum because of instrumental looping [250]. The videocapsule has shown significant potential for jejunoileal evaluation.

Videocapsule endoscopy might potentially provide effective screening examination of the colon in the average-risk patient if the technology becomes reasonably priced [251]. Videocapsule endoscopy is theoretically attractive as a screening test because of examination simplicity, noninvasiveness, minimal patient discomfort, and an apparently high safety profile.
The test has serious practical disadvantages for colonic examination because of the high cost of the technology and poor sensitivity in the presence of stool; the instrument is unable to wash away, aspirate, or navigate around stool. Stool is a greater problem for colonic than small intestinal examination. The videocapsule lacks biopsy capability. It lacks therapeutic capabilities of injection, decompression, ablation, and polypectomy. The videocapsule moves passively from proximal to distal by gastrointestinal peristalsis. The videocapsule cannot rotate to view different sides of mucosa and to inspect lesions from different angles. The videocapsule currently provides telecommunications for only 6 hours; this is insufficient to examine the entire colon. Peristalsis is relatively slow in the colon and the videocapsule travels slowly through the colon. The weak illumination provided by the videocapsule, while adequate for the small-caliber small intestine, is inadequate for the large-caliber large intestine. At colonoscopy, the colon is insufflated to distend and display the colonic wall. The videocapsule lacks air insufflation capabilities and collapsed portions of the colon may be poorly visualized. Ideally, if these deficiencies are corrected, videocapsule endoscopy could provide an initial screening examination of the colon; a lesion detected by this examination would prompt colonoscopy, for direct colonoscopic confirmation, for a histologic diagnosis by colonoscopic biopsy, and for possible colonoscopic polypectomy.

Summary

Epidemiologists, basic researchers, clinicians, and public health administrators unite! Develop and implement a simple, safe, and effective preventive and screening test for colon cancer. The public will willingly and enthusiastically accept such a test. Many thousands of lives are at stake every year.

References


