CHAPTER OBJECTIVES

- Describe signs and symptoms associated with colorectal cancer.
- Identify colorectal cancer screening tests.
- Differentiate between sporadic and hereditary colorectal cancer.
- Detail genetic causes of familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer.

KEY TERMS

Adenoma
Adenomatous
Adenomatous polyposis coli (APC)
Amsterdam criteria
Apoptosis
Colectomy
Deletion
Familial adenomatous polyposis (FAP)
First-degree relative
Frameshift mutation
Hereditary nonpolyposis colorectal cancer (HNPCC)
Insertion
Microsatellite instability
Nonsense mutation
Polyp
Proctocolectomy

CHAPTER 8

Colorectal Cancer

Colorectal cancer—also called colon cancer or rectal cancer—refers to any cancer in the colon from the beginning (at the cecum) to the end (at the rectum). Colorectal cancer occurs when cells that line the colon or the rectum become abnormal and grow in an out-of-control manner. **Polyps** are usually benign growths that protrude from a mucous membrane in the colon and rectum. If left untreated, these **adenomatous** polyps may eventually evolve into cancer.

Like many cancers, colon cancer may occur sporadically in a population or in a familial pattern. In addition, numerous cancer syndromes involve cancer of the colon. Although the majority of colon cancers are sporadic and occur randomly, it is important to recognize familial or hereditary patterns early in individuals. Based on this knowledge, screening and management guidelines have been developed for both patients and their relatives. The primary goal of these guidelines is to prevent colorectal cancer and other complications associated with these diseases.

Many patients with colorectal cancer do not experience any symptoms until the disease is quite advanced. For this reason, it is important to take a good family history and to assess risk factors for all patients. The risk of colon cancer in a **first-degree relative** of an affected individual can increase an individual's lifetime risk of colon cancer anywhere from 2-fold to 4.3-fold. Signs and symptoms of colorectal cancer are listed in **Box 8-1**. Beginning at age 50, both men and women at average risk for developing colorectal cancer should take the American Cancer Society screening tests identified in **Table 8-1**.

KEY TERMS

Polyp: a usually nonmalignant growth or tumor protruding from the mucous lining of an organ such as the nose, bladder, or intestine, often causing obstruction.

Adenomatous: relating to an adenoma and to some types of glandular hyperplasia.

First-degree relative: any relative who is one meiosis away from a particular individual in a family (i.e., parent, sibling, offspring).

BOX 8-1 Signs and Symptoms Associated with Colorectal Cancer

Blood in the stool
Weight loss with no known reason
Diarrhea that is not the result of diet or illness
A long period of constipation
Crampy abdominal pain
Change in bowel habits
Persistent decrease in the size or caliber of stool
Frequent feeling of distention in the abdomen or bowel region (gas pain, bloating, fullness, with or without cramping)
Vomiting and continual lack of energy

American Cancer Society. (2009, May). *Detailed guide: Colon and rectum cancer: How is colorectal cancer diagnosed*? Retrieved from http://www.cancer.org/docroot/CRI/content/CRI_2_4_3X_ How _is_colon_and_rectum_cancer_diagnosed.asp?sitearea=; Mayo Clinic Staff. (2009, July). *Colon polyps: Symptoms*. Retrieved from http://www.mayoclinic.com/health/colon-polyps/DS00511/DSECTION =symptoms; Johns Hopkins Medicine. (2009). *Familial adenomatous polyposis: Introduction*. Retrieved from http://www.hopkinsgi.org/GDL _Disease.aspx?CurrentUDV=31&GDL_Disease_ID=FA5AAA54-14DE -4A8E-B535-6191153083E3&GDL_DC_ID=D03119D7-57A3-4890-A717 -CF1E7426C8BA.

TABLE 8-1 American Cancer Society Screening Tests

Tests That Find Polyps and Cancer	Tests That Mainly Find Cancer
Flexible sigmoidoscopy every 5 years*	FOBT every year*†
Colonoscopy every 10 years	FIT every year*†
Double-contrast barium enema every 5 years*	sDNA test, interval uncertain*
CT colonography (virtual colonoscopy) every 5 years*	

*Colonoscopy should be done if test results are positive.
†For FOBT or FIT used as a screening test, the take-home multiple sample method should be used. An FOBT or FIT done during a digital rectal exam is not adequate for screening.
CT: computerized tomography; FIT: fecal immunochemical test; FOBT: fecal occult blood test; sDNA: stool DNA test.
American Cancer Society. (2009). *Colon cancer: Signs, symptoms, and screening*. Retrieved from https://www.cancer.org/cancer/colon-rectal-cancer.html

Familial Colorectal Cancer

The occurrence of colorectal cancer in more than one family member may be due to chance alone, or it may result from shared exposure to a cancer-causing substance (carcinogen) in the environment or from similar diet or lifestyle factors. It could also mean that the potential for developing colorectal cancer has been passed from one generation to the next, although the exact gene involved has not been identified. Relatives of a person with colorectal cancer may be more likely to develop it themselves. It has been estimated that 15–30% of colorectal cancers are familial. Familial colon cancer may be a result of single-gene mutations, multiple-gene mutations, or the combined effect of gene mutations and environmental risk factors. A family history of one or more members with frank colorectal cancer or premalignant polyps should be considered significant. Additionally, patterns within a family that exist without the identification of a specific mutation are considered familial colorectal cancers.

Hereditary Colorectal Cancer

The hereditary causes of two hereditary colorectal cancer syndromes, **familial adenomatous polyposis (FAP)** and **hereditary nonpolyposis colorectal cancer (HNPCC)**, have been identified. Like other diseases, colon cancer may occur sporadically, in familial patterns, or such that kindreds have the exact same mutations among those persons affected in a family. Mutations in cancer susceptibility genes predispose a person to inherited types of colorectal cancers.

Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is an inherited disorder characterized by the presence of multiple colorectal adenomatous polyps (typically more than 100). In patients affected by this disease, it may be the first case in the family (sporadic). Attenuated FAP is a variant form of FAP in which affected individuals develop fewer polyps (0–500), typically at a later age, than those persons with classical FAP. Although people with attenuated FAP tend to develop colon cancer at a later age than individuals with classical FAP, they still have a near 100% lifetime risk of colon cancer.

People with FAP have a 50% chance of passing the condition to each of their children. The condition can be passed on to offspring even if the patient has had his or her own colon removed. In contrast, children who do not inherit the condition from their parent cannot pass it to their own children. Approximately one-third of people with FAP do not have an affected parent. Individuals who inherit a mutated ***adenomatous polyposis coli (APC)*** gene

KEY TERMS

Familial adenomatous polyposis (FAP): an inherited colorectal cancer syndrome that leads to hundreds—sometimes even thousands—of polyps in the colon and rectum at a young age.

Hereditary nonpolyposis colorectal cancer (HNPCC): an inherited colorectal cancer syndrome in which only a small number of polyps are present or not present at all. Also known as Lynch syndrome.

Adenomatous polyposis coli (APC): a tumor suppressor gene on chromosome 5. Mutations in this gene result in familial adenomatous polyposis.

KEY TERMS

Adenoma: a benign epithelial neoplasm in which the tumor cells form glands or glandlike structures.

Apoptosis: programmed or gene-directed cell death.

Insertion: a chromosome abnormality in which material from one chromosome is inserted into another nonhomologous chromosome; a mutation in which a segment of DNA is inserted into a gene or other segment of DNA, potentially disrupting the coding sequence.

Deletion: absence of a segment of DNA; it may be as small as a single base or large enough to encompass one or more entire genes.

Nonsense mutation: a single base-pair substitution that prematurely codes for a stop in amino acid translation (stop codon).

have a very high likelihood of developing colonic **adenomas**; this risk has been estimated to be more than 90%. Most people with FAP are asymptomatic until they develop cancer. Nonspecific symptoms such as rectal bleeding, diarrhea, and abdominal pain may be suggestive of FAP. Diagnosing presymptomatic patients is essential. The age of onset of adenomas is variable. By age 10 years, only 15% of FAP gene carriers manifest adenomas; by age 20 years, the probability rises to 75%, and by age 30 years, 90% will have presented with FAP.

Genetics of Familial Adenomatous Polyposis

Familial adenomatous polyposis is an autosomal dominant condition caused by mutations in the *APC* tumor suppressor gene on chromosome 5. Most of these mutations lead to premature stop codons that result in truncation of the *APC* gene product, a protein that plays an important role in the regulation of cell adhesion and **apoptosis**. More than 800 different mutations have been reported. The majority of these changes are **insertions**, **deletions**, and **nonsense mutations** that lead to **frameshift mutations** and/or premature stop codons during gene transcription. The location of the mutation affects the number of polyps formed and the type of extracolonic features seen.

Recently, mutations in the *MYH* gene—a gene involved with base excision repair—have been identified in patients with the classic and attenuated forms of FAP who do not have mutations of the *APC* gene. The FAP caused by *MYH* mutation is inherited in an autosomal recessive fashion; hence, a family history of colorectal cancer may not be evident. Of patients with classic FAP, approximately 90% have a mutation in the *APC* gene and 8% in the *MYH* gene. In contrast, among patients with 10–100 adenomatous polyps and suspected attenuated FAP, *APC* mutations are identified in 15%, but *MYH* mutations are identified in 25%.

Genetic Counseling and Testing

Genetic counseling and testing should be offered to patients with a diagnosis of FAP that has been established by endoscopy and to all at-risk relatives of patients with the disease. Testing should also be done to confirm a diagnosis of attenuated disease in patients with 20 or more adenomas. Commercial *APC* gene testing is available. Genetic testing is best performed by sequencing the *APC* gene to identify disease-associated mutations, which are found in approximately 90% of cases of typical FAP. Mutational assessment of *MYH* should be considered in patients with negative test results and in patients with suspected attenuated FAP. Children of patients with FAP should undergo genetic screening beginning at age 10 years.

Screening Recommendations

If genetic testing cannot be done or is not informative, family members at risk should undergo a yearly colonoscopy beginning at 12 years of age. Once the diagnosis has been established, complete **proctocolectomy** or **colectomy** is recommended, usually before age 20 years. Extracolonic manifestations include polyp formation in the upper gastrointestinal tract occurring in 30–100% of patients with FAP. Upper endoscopic evaluation of the stomach, duodenum, and periampullary area should be performed every 1–3 years to look for adenomas or carcinoma. The upper endoscopy is preferred since sulindac and cyclooxygenase-2 selective agents have been shown to decrease the number and size of polyps in the rectum but not in the duodenum.

If attenuated FAP is suspected within a family, it is important that family members be screened with colonoscopy rather than flexible sigmoidoscopy because polyps are not evenly distributed throughout the colon. Given that the number of polyps and age of onset can vary greatly from one family member to another in a family with attenuated FAP, screening should begin at age 15 and be repeated every 1–3 years.

Gardner syndrome was originally used to describe families with colonic polyposis and extracolonic manifestation including desmoid tumors, lipomas, and juvenile nasopharyngeal angiofibromas. A phenotypic variant of FAP, it manifests as bumps or lumps on the bones of the legs, arms, skull, and jaw; cysts of the skin; teeth that do not erupt when they should; and frecklelike spots on the inside lining of the eyes.

Hereditary Nonpolyposis Colorectal Cancer

Hereditary nonpolyposis colorectal cancer is also known as Lynch syndrome. "Nonpolyposis" means that colorectal cancer can occur when only a small number of polyps are present or none at all. In HNPCC, cancer usually affects the right side of the colon. It often occurs at a younger age than sporadic colon cancer. Other cancers may arise in these families as well, including cancer of the uterus, ovaries, stomach, urinary tract, small bowel, and bile ducts.

This autosomal dominant condition accounts for 3–5% of all colorectal cancers. Affected individuals have a 60–80% lifetime risk of developing colorectal carcinoma and a more than 40% lifetime risk of developing endometrial cancer. Unlike individuals with FAP, patients with HNPCC develop only a few adenomas. In contrast to the traditional polyp to cancer progression (which may take several years), the polyps in HNPCC are believed to undergo rapid transformation from normal tissue to adenoma to cancer.

Research criteria used to define Lynch syndrome were originally developed in 1990 and referred to as the **Amsterdam criteria**; these criteria were revised

KEY TERMS

Frameshift mutation: an insertion or deletion involving a number of base pairs that is not a multiple of three and consequently disrupts the triplet reading frame, usually leading to the creation of a premature termination (stop) codon and resulting in a truncated protein product.

Proctocolectomy: a surgical procedure involving the excision of the colon and rectum and the formation of an ileoanal reservoir or pouch.

Colectomy: surgical excision of part or all of the colon.

Amsterdam criteria: research criteria for defining Lynch syndrome established by the International Collaborative Group meeting in Amsterdam.

KEY TERM

Microsatellite instability: a change that occurs in the DNA of certain cells (e.g., tumor cells) in which the number of repeats of microsatellites (short, repeated sequences of DNA) is different than the number of repeats that appeared in the DNA when it was inherited. The cause of microsatellite instability may be a defect in the ability to repair mistakes made when DNA is copied in the cell.

in 1999 and are now called the Amsterdam criteria II. The latter criteria include the following specifications to warrant a diagnosis of HNPCC:

1. There should be at least three relatives with a Lynch syndrome–associated cancer (colorectal cancer or cancer of the endometrium, small bowel, ureter, or renal pelvis).
2. One should be a first-degree relative of the other two.
3. At least two successive generations should be affected.
4. At least one family member should be diagnosed before age 50 years.
5. Familial adenomatous polyposis should be excluded in the colorectal cancer cases.
6. Tumors should be verified by pathological examination.

Genetics of Hereditary Nonpolyposis Colorectal Cancer

A defect in one of several genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) that are important in the detection and repair of DNA base-pair mismatches causes HNPCC. Germline mutations in *MLH1*, *MSH2*, and *MSH6* account for more than 90% of the known mutations in families with HNPCC. Mutations in any of these mismatch repair genes result in a characteristic phenotypic DNA abnormality known as **microsatellite instability**. In more than 95% of cancers in patients with HNPCC, microsatellite instability is readily demonstrated by expansion or contraction of DNA microsatellites (short, repeated DNA sequences). Microsatellite instability also occurs in 15% of sporadic colorectal cancers, usually due to aberrant methylation of the *MLH1* promoter, which results in decreased gene expression.

Genetic Counseling and Testing

A thorough family cancer history is essential to identify families whose members may be affected with HNPCC so that appropriate genetic and colonoscopic screening can be offered. Families with suspected HNPCC should be evaluated first by a genetic counselor and should give informed consent in writing before genetic testing is performed. Patients whose families meet any of the revised Bethesda criteria have an increased likelihood of harboring a germline mutation in one of the mismatch repair genes and should be considered for genetic testing. The Bethesda criteria include the following specifications to warrant a diagnosis of HNPCC:

1. Colorectal cancer before age 50
2. Synchronous or metachronous colorectal or HNPCC-associated tumor regardless of age (endometrial, stomach, ovary, pancreas, ureter and renal pelvis, biliary tract, brain)

3. Colorectal cancer, plus one or more first-degree relatives with colorectal or HNPCC-related cancer, with one of the cancers occurring before age 50
4. Colorectal cancer, plus two or more second-degree relatives with colorectal or HNPCC cancer, regardless of age
5. Tumors with infiltrating lymphocytes, mucinous/signet ring differentiation, or medullary growth pattern in patients younger than 60

These criteria will identify more than 90% of mutation-positive HNPCC families.

Tumor tissues of affected individuals or family members meeting the revised Bethesda criteria should undergo immunohistochemical staining for *MLH1*, *MSH2*, *MSH6*, and *PMS2* (using commercially available assays), testing for microsatellite instability (polymerase chain reaction (PCR) amplification of a panel of DNA markers), or both. Individuals whose tumors have normal immunohistochemical staining or do not have microsatellite instability are unlikely to have germline mutations in mismatch repair genes and do not require further genetic testing. However, if patients have early-age-onset colon cancer or features of hereditary colon cancer syndrome, they should be treated and managed based on their family history; these steps might include intensive cancer surveillance.

Germline testing for gene mutations is positive in greater than 90% of individuals whose tumors show no histochemical staining of one of the mismatch repair genes and in 50% of those patients whose tumors have a high level of microsatellite instability. Germline testing is also warranted in families with a strong history consistent with HNPCC when tumors from affected members are unavailable for assessment. If a mutation is detected in one of the known mismatch genes in a patient with cancer, genetic testing of other at-risk family members is indicated.

Screening Recommendations

If genetic testing documents an HNPCC gene mutation, affected relatives should be screened with colonoscopy every 1–2 years beginning at age 25 (or at an age 5 years younger than the age at diagnosis of the youngest affected family member). If cancer is found, subtotal colectomy followed by annual surveillance of the rectal stump should be performed. Upper endoscopy should be performed every 2–3 years to screen for gastric cancer. Women should undergo screening for endometrial cancer beginning at age 25–35 years with pelvic examination, CA-125 assay, endometrial aspiration, and transvaginal ultrasound. Prophylactic hysterectomy and oophorectomy may be considered, especially in women who have completed their families (i.e., who are done with childbearing). Similarly, consideration should be given for increased cancer surveillance in family

members in proven or suspected HNPCC families who do not wish to undergo germline testing.

Chapter Summary

- Colorectal cancer occurs when cells that line the colon or the rectum become abnormal and grow in an out-of-control manner.
- The risk of colon cancer in a first-degree relative of an affected individual can increase an individual's lifetime risk of colon cancer anywhere from 2-fold to 4.3-fold.
- The genetic causes of two hereditary colorectal cancer syndromes—familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer—have been identified.
- If attenuated familial adenomatous polyposis is suspected within a family, it is important that family members be screened with colonoscopy rather than flexible sigmoidoscopy because polyps are not evenly distributed throughout the colon.

Chapter Review Questions

1. _____ are usually benign growths that protrude from a mucous membrane in the colon and rectum.
2. Gardner syndrome is a phenotypic variant of _____ _____.
3. When discussing sporadic versus hereditary colorectal cancer, it is important to know that _____ is more common.
4. Hereditary nonpolyposis colorectal cancer is also known as _____.
5. If genetic testing documents a gene mutation associated with hereditary nonpolyposis colorectal cancer, affected relatives should be screened with colonoscopy every _____ years beginning at age 25.

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