Prevention and Screening of Gastrointestinal Cancers

Suzanne M. Mahon

Objectives: *This article reviews the current recommendations and data supporting various screening and prevention strategies for colorectal cancer (CRC) in average and high-risk individuals.*

Data Sources: *Published research reports, epidemiologic data, and published guidelines from professional organizations.*

Conclusion: *Properly applied screening tools can potentially decrease the morbidity and mortality associated with CRC.*

Implications for Nursing Practice: *Nurses need to be aware of current recommendations for the early detection of CRC so they can provide patients with an accurate assessment of risk for developing CRC and education about the appropriate CRC screening guidelines.*

Key Words: *Colorectal cancer, screening, prevention, risk assessment, colonoscopy.*

Together, gastrointestinal (GI) cancers comprise a significant percentage of cancers. To date, most efforts in screening and prevention have been directed toward colorectal cancer (CRC), which has a high incidence. Recommendations for the early detection of CRC have been modified over time and there is solid scientific evidence that these measures decrease the morbidity and mortality associated with CRC. More recently, guidelines have been released by the American College of Gastroenterology (ACG) for screening in patients with Barrett's esophagus, and a Japanese group has issued some early guidelines for gastric cancers.[1,2] This article includes an overview of the risk factors and early detection strategies for Barrett's esophagus and gastric cancer and a detailed discussion of risk assessment, prevention, and early detection strategies for CRC.

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Barrett's Esophagus

Barrett's esophagus (BE) is a progressive metaplasia of the distal esophagus. It often occurs as a result of prolong reflux esophagitis and gastroesophageal reflux. It is considered by many to be a precursor to the development of adenocarcinoma of the esophagus. The exact prevalence of BE in the general population is not known. The overall prevalence of BE is estimated to be 1.6%,

with a prevalence rate of 2.3% in those with reflux symptoms and 1.4% in those without reflux symptoms.[3] Major risk factors for development include male sex, advanced age, chronic gastroesophageal reflux disease (GERD) and, possibly, family history. Screening is further complicated by the fact that a large number of patients lack reflux symptoms and there is not a clear means to identify these persons. BE is a histologic diagnosis. An esophagogastroduodenoscopy (EGD) is performed to obtain tissue samples. Samples are usually taken from the distal esophagus just above the lower esophageal sphincter, where BE primarily occurs. Patients diagnosed with BE should be screened regularly with an EGD with biopsy.

Screening for BE remains controversial because of the lack of a clear algorithm for how and whom to screen and whether screening has a significant impact on mortality.[1] Currently esophageal capsule endoscopy appears to be a promising technique to screen for BE. This video endoscopy is accomplished by having the patient swallow a small camera about the size of a vitamin capsule. The camera emits a light and takes two pictures per second as it traverses the GI tract. The pill is easily swallowed and transmits the images to a recording device worn around the waist. These images are then downloaded to a computer where they are reviewed by a physician to determine if abnormalities are present. It provides a noninvasive means to detect a columnar line esophagus, which is suggestive of BE,[1] but the expense prohibits this test from being utilized routinely. Because of these limitations, the ACG does not routinely recommend screening for BE in the general population.

Once BE is identified in a patient, there should be a discussion regarding the relative strengths of surveillance endoscopy and the risk of developing esophageal adenocarcinoma, which has limited treatment options and poor survival (less than 13% 5-year survival rate).[1,3] It is recommended that persons with GERD be placed on proton pump inhibitor therapy to decrease inflammation so surveillance is more likely to be effective and decrease the cellular changes that result in dysplasia.[3,4] Algorithms are available, depending on the degree of dysplasia, to determine the interval for endoscopy with biopsy. For those patients without dysplasia, endoscopy can be performed every 3 years. Those with low-grade dysplasia should have annual endoscopy until no dysplasia is detected for 2 years. Patients with high-grade dysplasia need aggressive and thorough surveillance every 3 months.

Patients diagnosed with BE require education on how to manage their disease. They need to be aware of the importance of regular endoscopic screening and follow-up. Patients should be informed to avoid foods and beverages that either irritate the esophageal mucosa or decrease lower esophageal sphincter pressure. These include tomato and citrus-based foods, spicy foods, onions, garlic, peppermint, chocolate, caffeine, and alcohol.[4]

Gastric Cancer

Gastric cancer is a significant problem and contributes to 600,000 deaths worldwide,[2,5] In the United States it accounts for 21,500 new cases and 10,880 deaths annually.[6] Risk for gastric cancer is increased in those with Helicobacter pylori (H pylori) infections, and those with certain genetic changes that predispose to developing gastric cancer. These include persons with a family history of gastric cancer as well as persons with a known or suspected mutation for hereditary nonpolyposis colorectal cancer (HNPCC).[5] Other persons at risk include those that consume diets high in salt, smoked, poorly preserved foods, nitrites, and nitrates.

Persons with a known mutation or suspected mutation in their family should be referred to a genetics professional for more detailed evaluation. Genetic testing is readily available for HNPCC, and testing for diffuse gastric cancer is available on a more limited basis. Identifying persons with a hereditary predisposition is important because this population may benefit from aggressive screening including gastroduodenoscopy.[2]

Colorectal Cancer

CRC continues to be a significant health problem in the United States. There is clear evidence that screening is the key to reducing the morbidity and mortality associated with this disease; when screening is performed consistently, correctly, and polyps are removed.[7] Polyps, especially the adenomatous ones, are considered to be precursors to CRC. Screening directly impacts how early a malignancy is detected and long-term survival. The estimated 5-year survival

is 90% if the disease is diagnosed while still localized (confined to the wall of the bowel), but only 68% for regional disease (lymph node involvement), and only 10% if distant metastases are present.[8]

Selection of the appropriate screening interval and modality is based on cancer risk assessment. Guidelines for CRC cannot be uniformly applied to the entire population; some individuals have a greater risk of developing CRC than others. The most important step in CRC screening is an accurate assessment of the risk for developing CRC.

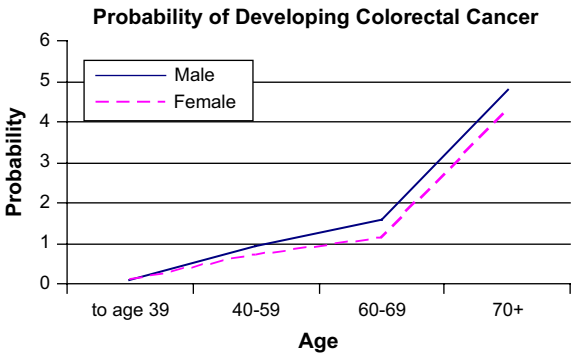

FIGURE 1. **The lifetime probability for males for developing CRC is 5.65 (1 in 18 males) and for females is 5.23 (1 in 19 females). (Source: American Cancer Society.[6])**

Colorectal Cancer Risk Factors

An individual's risk for CRC is stratified into one of three categories. Most of the population has an average risk of developing the disease; some have a slightly higher risk based on personal risk factors. Those with a known or suspected mutation in a cancer susceptibility gene have a very high risk for developing the disease. It is important to note that no one has zero or low risk for developing CRC.

Population at Average Risk

The lifetime risk of developing CRC is approximately 48.2 cases per 100,000 population.[6] Incidence increases with age (90% of cases occur after age 50) and is relatively similar between males and females (as shown in Fig. 1). Table 1 identifies a number of other modifiable and nonmodifiable risk factors for CRC.

There are a variety of myths and misconceptions about CRC that healthcare providers need to address. For instance, it is often incorrectly assumed there are persons at low risk for CRC. At the very minimum, everyone is at average risk. Many individuals are surprised to learn that some risk factors can be adjusted to reduce the risk of developing CRC. When a risk factor can be modified, individuals should be instructed about how to address their particular risk. When it cannot be modified, the healthcare provider should discuss how this risk factor is considered in selecting the appropriate cancer screening modality. People may also be confused about their risk related to a personal or family history of polyps or cancer. Knowing the age of onset can help clarify risk. Individuals with a single first-degree relative diagnosed with CRC or an adenomatous polyp after age 60, or with affected relatives who are more distant than first degree, can be considered to be at average risk.[7-9]

Populations at High Risk

Approximately 15% to 20% of CRCs occur among people at increased risk or high risk (approximately twice the average risk).[6] People who have been diagnosed as having adenomatous polyps are clearly at higher risk. A family history of either CRC or colorectal adenomas increases one's risk of developing CRC.[7] Risk is increased for individuals with a family history involving first-degree relatives, and is even higher if a first-degree relative (parent, sibling, or offspring) has had a CRC or an adenomatous polyp diagnosed before age 60 years, and/or if more than one first-degree relative has been affected at any age. Inflammatory bowel disease, which includes ulcerative colitis and Crohn's disease, is a condition in which the colon is inflamed over a protracted period of time and these conditions have an increased risk of developing CRC.[9]

Hereditary Risk

Persons with a known hereditary mutation are at high risk for developing CRC. The clinical indicators of hereditary CRC syndromes are shown in Table 2. The goal of genetic testing in families is to offer appropriate screening guidelines to individual family members by identifying who carries the mutation and who does not. For those who test positive for a known mutation, screening begins at a very early age (such as age 25 for HNPCC carriers) and is performed at more frequent intervals (annually) throughout their lifetime. Individuals who test negative for a known

TABLE 1.
Risk Factors for Developing Colorectal Cancer

Risk Factor	Etiologic Basis	Modifiable	Significance
Age	As the body ages, all tissues are at increased risk for cellular changes leading to cancer	No	90% of colon cancers are diagnosed after age 50. Implication for screening to begin at age 50
Polyps	Many polyps progress in an orderly fashion from a polyp to malignancy over a period of years	Probably not	Polyps need to be removed during colonoscopy. Depending on findings, interval for screening may be decreased
Personal history of cancer	Same risk factors that led to the first cancer can lead to a second CRC in another section of the colon	No	Risk is higher in those with cancer diagnosed before age 60
Inflammatory bowel disease and Crohn's disease	Associated with dysplasia and increased risk of developing CRC especially if the disease is long-term	No	Screening is probably indicated at a younger age and more frequently
Family history of CRC	20% of persons diagnosed with CRC have at least one relative with the disease which is probably related to modifier genes	No	Risk increases with the number of relatives with adenomatous polyps or CRC
Persons with a mutation in FAP	Form hundreds of polyps; most start to occur about age 20	No	Penetrance is nearly 100% and accounts for about 1% of all CRC
Persons with HNPCC syndromes	Polyp to CRC syndrome is short; often occurs before age 40	No	Penetrance is 80% to 85% and accounts for about 4% of all CRC
Ethnicity	African Americans have highest incidence and mortality; about 6% of Ashkenazi Jews have mutations that put them at increased risk	No	Develop screening programs targeting high-risk populations
Dietary factors	Risk is increased in persons who consume a diet high in red and processed meats	Yes	Risk is decreased in persons who eat a diet rich in fruits and vegetables
Physical inactivity	Reason for increased risk is not clear	Yes	Risk is increased in inactive persons
Obesity	Reasons for increased risk is not clear	Yes	Risk is increased in both men and women, but even higher in men
Smoking	Carcinogenic substances enter the gastrointestinal system	Yes	Risk increases with the number of pack years
Alcohol use	Those who consume increased amounts of alcohol may have lower levels of folic acid	Yes	Consume no more than 1 alcholic beverage per day
Type II Diabetes	Reason for increased risk is not completely understood	Possibly	May be associated with a poorer prognosis, once the cancer is diagnosed

Abbreviations: CRC, colorectal cancer; FAP, familial adenomatous polyposis gene; HNPCC, hereditary non-polyposis colorectal cancer gene.
Data from Bernard et al,[7] American Cancer Society,[8] Levin et al,[9] and Lynch and de la Chapelle.[10]

mutation in their family can pursue the screening recommendations for those at average risk.

The most common hereditary CRC syndrome is an autosomal dominant syndrome known as HNPCC, which accounts for 3% to 5% of all CRC.[10] It is also associated with endometrial cancer, ovarian cancer, gastric cancer, bile duct cancer, and small bowel, renal pelvis, and ureter cancer.[11] The majority of mutations responsible for HNPCC occur in four mismatch repair genes, MSH2, MLH1, PMS2, and MSH6.[12] Patients with a mutation in MLH1 and MSH2 have an 80% lifetime risk of developing CRC as compared with a 6% risk in the general population. Women with mutations in these genes have a 60% lifetime risk for developing endometrial cancer and a 12% lifetime risk for developing ovarian cancer.[13]

Persons with HNPCC-related cancers are more likely to have poorly differentiated tumors with an excess of mucoid and signet-cell features.[11]

Although not associated with large numbers of polyps, persons with HNPCC who do form adenomatous polyps are more likely to do so at an earlier age, to develop right-sided colon cancer, and to exhibit a rapid progression to malignancy (ie, 1 to 3 years instead of the 5- to 10-year pattern seen in the general population).[11,14]

Risk assessment is the key to identifying families with an HNPCC mutation. There are several strategies to consider in identifying these patients and any suspected family should be referred to a genetics professional to identify the most cost-effective and efficient strategy for genetic testing. The Amsterdam and Bethesda criteria (Table 3) assess the number of relatives affected by CRC or other HNPCC-related cancers, with particular emphasis on the age of onset.[10,15,16]

Immunohistochemistry staining can be performed on tumor tissue from persons who fulfill Bethesda criteria to determine the presence or absence of MLH1, MSH2, MSH6, and PMS2 proteins. This can predict a mismatch repair defect and thereby avoid unnecessary, expensive, and time-consuming DNA analyses.[12] If immunohistochemistry is positive for all four proteins in a family that fulfills Amsterdam criteria, the next strategy to determine if it is appropriate to test an individual is to perform an MSI (microsatellite) assay on the affected family member's colorectal tumor.[10] In HNPCC, mutations in the DNA repair genes result in a phenomenon known as MSI instability. Microsatellites are repeated sequence of DNA that are a defined length for each individual. Because of the accumulation of errors, these sequences can become abnormally longer or shorter; this is referred to as MSI.[15] An MSI high phenotype is reported in 85% to 92% of HNPCC colon cancers and approximately 15% of sporadic cancers.[12] MSI testing is also an appropriate strategy for Amsterdam-negative families who are positive by the Bethesda criteria.

Familial Adenomatous Polyposis (FAP), an autosomal dominant trait, is characterized by numerous (usually > 100) adenomatous colon polyps and accounts for about 1% of all cases of CRC.[10] The FAP gene is nearly 100% penetrant, so if a person is not treated they will develop CRC because of the sheer number of polyps. The mean age of cancer onset is 39; although as many as 75% will have developed adenomas by age 20.[17,18] A less severe form of FAP called "attenuated familial adenomatous polyposis" (AFAP) is characterized by less than 100 polyps (usually about 20) at presentation and later onset of CRC. There are over 800 mutations in the APC gene associated with FAP.[12] Deleterious mutations in this tumor suppressor gene result in the premature truncation of the APC protein.[18,19] There is also an autosomal recessive gene on chromosome

TABLE 2.
Key Indicators of Hereditary Colon Cancer Syndromes

HNPCC
- Personal history of CRC diagnosed before age 50
- Personal history of endometrial cancer diagnosed before age 50
- First-degree relative with CRC before age 50
- Two or more relatives with CRC or an HNPCC-associated cancer (including endometrial, ovarian, gastric, hepatobiliary, small bowel, renal pelvis or ureter cancer). One relative must be a first-degree relative of another
- CRC occurring in two or more generations on the same side of the family
- A personal history of CRC and a first-degree relative with adenomas diagnosed before age 40
- An affected relative with a known HNPCC mutation

FAP
- Patient has a clinical diagnosis of FAP (100 or more polyps)
- Patient has suspected FAP or AFAP (15 to 99 polyps)
- Patient is a first-degree relative of FAP or AFAP patient
- Patient has an affected relative with a known FAP or MYH mutation
- Patient with any number of adenomas in a family with FAP

Abbreviations: CRC, colorectal cancer; HNPCC, hereditary non-polyposis colorectal cancer; FAP, familial adenomatous polyposis.
NOTE. The presence of one or more of these factors in an individual or family history is suggestive of hereditary risk for CRC and warrants further evaluation.
Data from Lynch and de la Chapelle,[10] Vasen et al,[16] Balmana et al,[17] Calvert and Frucht,[18] and Jeter et al.[19]

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