CME

Recognizing hereditary colorectal cancer

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ABSTRACT

Colorectal cancer is the second-leading cause of cancer death in the United States. About 25% of patients have a personal or family history that suggests a hereditary colorectal cancer syndrome. This article describes the clinical and pathological characteristics of hereditary colorectal cancer, appropriate screening tests, and when to refer patients to a genetic counselor.

Keywords: hereditary colorectal cancer, Lynch syndrome, familial adenomatous polyposis, attenuated familial adenomatous polyposis, family history, genetic counselor

Learning objectives

- Describe the clinical and pathological characteristics of hereditary colorectal cancer.
- Recommend screening tests for colorectal cancer.
- Refer appropriate patients with colorectal cancer to genetic counseling.

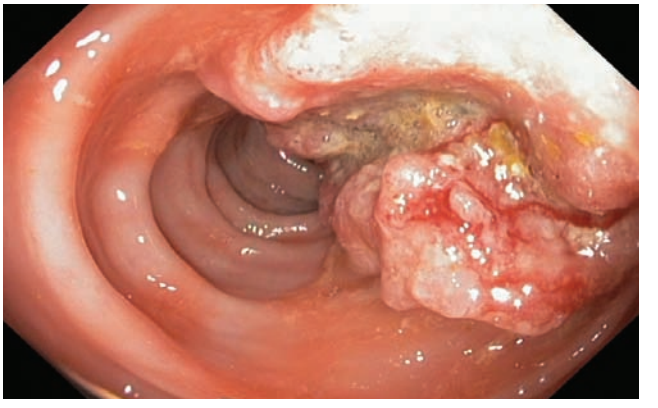

FIGURE 1. Colorectal cancer

Colorectal cancer (**Figure 1**) is the second-leading cause of cancer death in the United States.[1] The National Cancer Institute estimated that in 2013, more than 140,000 Americans would be diagnosed with colorectal cancer and more than 50,000 would die from the disease.[1] Most cases of colorectal cancer are sporadic, but 25% of patients have a personal or family history suggesting a hereditary colorectal cancer syndrome.[1] This syndrome increases the chance of early-onset cancer and raises the patient's lifetime cumulative risk of cancer. In addition, patients with hereditary colorectal cancer are more likely to have extracolonic carcinomas.[1]

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PAs must recognize the clinical criteria and the pathologic characteristics of tumors associated with hereditary colorectal cancer to be able to recommend screening tests and genetic counseling. With this knowledge, patients can be screened early to detect polyps and cancerous lesions, potentially improving outcomes. This article describes the most common hereditary colorectal cancer syndromes, diagnosis, screening guidelines, and management. The article also reviews the importance of taking an accurate personal and family history and the role of the genetic counselor.

LYNCH SYNDROME

Lynch syndrome, also called hereditary non-polyposis colorectal cancer, was first recognized in 1913 by Dr. Alfred Scott Warthin, whose seamstress proclaimed that because her family members had died young of stomach or gynecologic cancer, she inevitably would too.[2] Her eventual death from endometrial cancer prompted Warthin to study her family history. However, not until the 1960s did Dr. Henry Lynch begin reviewing Warthin's work and comparing it to his research of similar family pedigrees. He also was able to identify colorectal cancer risks and the association with extracolonic manifestations.[3] Lynch syndrome is the most common hereditary colon cancer syndrome, accounting for 2% to 4% of all colorectal cancer.[4]

Lynch syndrome is defined as hereditary colorectal cancer in the setting of few or no polyps and an association

Key points

- About 6% of colorectal cancers have a genetic component.
- Genetic mutations can raise a patient's lifetime risk for colorectal cancer to 70% to 80%.
- Understanding various types of hereditary colorectal cancer syndromes can guide patient screening and testing and may improve outcomes. In some patients, screening may begin as early as age 10 years.
- Obtaining an accurate family history can help identify patterns of hereditary colorectal cancer.

with other carcinomas. A patient with Lynch syndrome has a specific germline mutation that increases the lifetime risk for colorectal cancer to 70% to 80%; in comparison, patients without these mutations have a 6% risk for sporadic cancer.[4]

Mutations in the genes *MSH2, MLH1, MSH6, PMS2,* and *EPCAM* are associated with Lynch syndrome.[5] The genetic mutation that causes Lynch syndrome can be inherited from either parent (autosomal dominance), and carriers have a 50% chance of passing the gene to each of their offspring. Patients with Lynch syndrome can develop early-age onset of colorectal cancer (mean age is 43 years). In comparison, sporadic colorectal cancer usually occurs in patients over age 60 years.[6]

Synchronous (simultaneous) or metachronous (subsequent) lesions are more prevalent in patients with Lynch syndrome. Compared with sporadic cancer, in Lynch syndrome, 70% to 80% of tumors are proximal to the splenic flexure, a pattern that can aid in diagnosis (**Table 1**). Tumors are usually poorly differentiated and show mucin production. More importantly, a patient with Lynch syndrome is at risk for early onset of extracolonic cancers such as uterine, gastric, ovarian, pancreatic, ureter and renal pelvis, biliary tract, brain, and small bowel cancer, and sebaceous neoplasms or keratoacanthomas.[7] The lifetime cumulative risk of endometrial cancer for women with Lynch syndrome is 40% to 60%, which equals or exceeds their risk of colorectal cancer.[4]

TABLE 1. Comparison of sporadic and hereditary colorectal cancer[3]

	Sporadic colorectal cancer	Hereditary non-polyposis colorectal cancer
Average age at onset (years)	60s	40s
Most common tumor location	descending colon	ascending colon
Polyp progression to cancer	7-10 years	2-3 years
Microsatellite instability	15%	90%

TABLE 2. Revised Bethesda Guidelines[10]

- Colorectal cancer diagnosed at younger than age 50 years
- Synchronous or metachronous colorectal cancer or other hereditary non-polyposis colorectal cancer-associated tumors at any age
- Colorectal cancer with high microsatellite instability histology (tumor-infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous/signet ring differentiation, or medullary growth pattern) in a patient under age 60 years
- Colorectal cancer in a patient with one or more first-degree relative with a hereditary non-polyposis colorectal cancer-related cancer, with one of the cancers diagnosed before age 50 years
- Colorectal cancer in a patient with two or more first-degree or second-degree relatives with hereditary non-polyposis colorectal cancer-related cancers, regardless of age.

Diagnostic testing The Amsterdam criteria, created in 1990 and revised in 1999, followed a 3-2-1 rule, recommending testing in patients if:

- *Three* or more family members diagnosed with colorectal cancer and/or an extracolonic cancer, one of whom is a first-degree relative of the other two
- *Two* generations of the family diagnosed with cancer
- *One* affected member diagnosed before the age of 50.

Although easy to understand, these criteria only detected about 39% of patients with a mutation.[8] The Revised Bethesda Guidelines (**Table 2**), published in 2004, fail to identify 25% of patients with mutations.[8] Consequently, most hospitals perform universal screening for Lynch syndrome using immunohistochemistry testing of all patients with colorectal, small bowel, or endometrial cancer.[4]

Tumors can be tested via immunohistochemistry and for microsatellite instability (phenotypic evidence that DNA mismatch repair is not functioning properly) to screen for Lynch syndrome. Microsatellites are noncoding areas on the genome that are repeated several times, and normally are constant from cell to cell within a person. Microsatellite instability is defined as variations in the number of repeated segments from cell to cell within a person. Patients also normally have two copies of the DNA mismatch repair genes, which function as tumor suppressor genes. If one gene is mutated and the other is damaged, tumor suppression does not occur and cancer cells can replicate.

Microsatellite instability and immunohistochemistry testing not only identify the likelihood of Lynch syndrome, but also direct serum testing for a specific germline mutation.

Immunohistochemistry testing on the tumor can identify any loss of protein expression of the four DNA mismatch repair genes (*MSH2, MLH1, MSH6, and PMS2)* that cause Lynch syndrome. *EPCAM,* which is not a DNA mismatch repair gene, is tested separately.[9]

The following surveillance testing is recommended for patients with a Lynch syndrome mutation or who meet clinical criteria for hereditary non-polyposis colorectal cancer, and at-risk family members. Management is based on test findings.[10]

Colonoscopy: Performed in patients at age 20 to 25 years or 2 to 5 years before the earliest colorectal cancer if the affected family member was diagnosed before age 25 years. Repeat the colonoscopy every 1 to 2 years. If adenomas are not endoscopically resectable or have high-grade dysplasia, or if adenocarcinoma is found, a subtotal or total colectomy or total proctocolectomy is recommended based on the tumor location. Monitor any residual colon or rectum every 1 to 2 years.

Transvaginal ultrasound, endometrial sampling, CA-125 testing: Most institutions recommend these tests annually in women of childbearing age, starting at age 20 to 25 years, although these tests have not been shown to be sensitive or specific enough to recommend. Prophylactic hysterectomy with bilateral salpingo-oophorectomy is recommended in women who have completed childbearing.

Upper endoscopy (esophagogastroduodenoscopy or EGD): Although no clear statistics recommend this test, an EGD with extended duodenoscopy with consideration of a capsule endoscopy should be performed between age 30 to 35 years, and then every 2 to 3 years.

Urinalysis: Consider testing patients annually, starting at age 25 to 30 years.

Annual physical examination: Starting at age 25 to 30 years, to evaluate for central nervous system cancers.

FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

FAP is also autosomal dominant, but differs greatly from hereditary non-polyposis colorectal cancer in that the patient with FAP can have hundreds to thousands of adenomatous polyps in the colon (**Figure 2**). These polyps are secondary to a germline mutation in the adenomatous polyposis coli (APC) gene.[10] Twenty percent of patients have a *de novo* mutation, meaning they are the first person in their family identified with the mutation.[10] If FAP is left untreated, colorectal cancer occurs earlier than normal, at a mean age of 39.[11] Patients with classic FAP have a near 100% risk of developing colorectal cancer in their lifetime.[11] APC gene testing is performed from a blood sample, and early surveillance is recommended in patients with APC mutations or a family history of phenotypical FAP. Flexible sigmoidoscopy or colonoscopy should be performed annually, beginning at age 10 to 15 years.

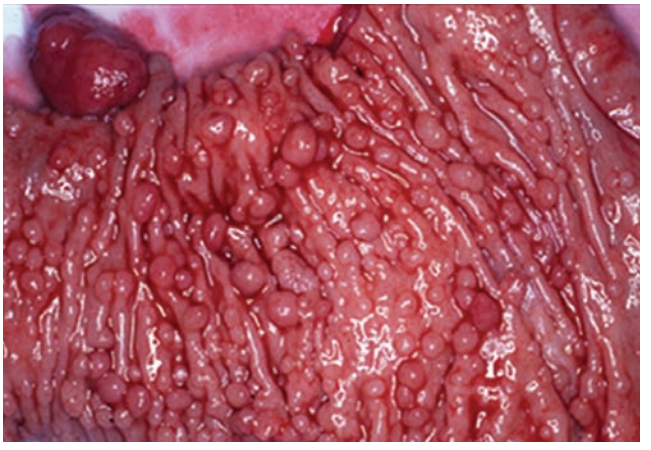

FIGURE 2. Hundreds to thousands of polyps in a patient with FAP

A total colectomy with ileorectal anastomosis or total proctocolectomy with an ileopouch anal anastomosis or ileostomy is recommended for patients with innumerable adenomatous polyps, a dysplastic polyp, or colorectal cancer. Surgery should be performed soon after diagnosis. Continued surveillance is important to reduce the risk of recurrent cancer and to detect advanced polyps. Endoscopic evaluation of the rectum every 6 to 12 months is recommended in patients who underwent total colectomy with ileorectal anastomosis. Patients who underwent an ileopouch anal anastomosis or ileostomy should have endoscopic evaluation of the ileal pouch or ileostomy every 1 to 3 years, with more frequent testing for large, flat polyps that have villous or high-grade dysplasia.

Like Lynch syndrome, FAP carries extracolonic manifestations , so the patient's other organ systems should be screened (**Table 3**). The National Comprehensive Cancer Network (NCCN) recommends considering chemoprevention in the form of a nonsteroidal anti-inflammatory drug (NSAID) in conjunction with endoscopic surveillance.[10] Recent studies have suggested that NSAIDs may inhibit tumor growth.[12]

ATTENUATED FAMILIAL ADENOMATOUS POLYPOSIS

Attenuated FAP (AFAP) also is associated with a mutation in the APC gene, but is differentiated by fewer adenomatous polyps (usually 10 to 100) and a frequent right-sided distribution of polyps. More importantly, AFAP carries a lower cancer risk and a later age of onset of adenomas and cancers (mean age is greater than 50 years).[10] APC gene testing is performed to confirm the diagnosis. As with FAP, extracolonic manifestations also occur with upper gastrointestinal (GI) findings and a thyroid cancer risk. Screening recommendations differ from those for FAP: Colonoscopy screening begins in the late teens, and then every 2 to 3 years until polyps are found. Once polyps are found, polypectomy is performed with continued surveillance every 1 to 2 years. Once polyposis is unmanageable

or colorectal cancer is found, a total colectomy with ileorectal anastomosis or a total proctocolectomy with ileopouch anal anastomosis is recommended. As with classic FAP, once surgery is performed, any remaining rectum should be evaluated endoscopically every 6 to 12 months depending on the polyp burden.

Extracolonic surveillance consists of a baseline upper endoscopy with side-viewing duodenoscopy at age 25 to 30 years, with further recommendations based on the number of polyps and dysplastic polyps found. An annual physical examination and thyroid examination also are recommended.

MUTYH-ASSOCIATED POLYPOSIS

In 2002, *MUTYH*-associated polyposis (MAP) was identified as associated with APC gene mutations. Patients with MAP have a 43% lifetime risk of developing colorectal cancer (or nearly 100% without adequate polyp surveillance).[13] Between 7% and 22% of patients with clinical FAP and 10% to 22% of patients with clinical AFAP have MAP.[13] Autosomal recessive, MAP occurs if one mutated gene is inherited from each parent. MAP is phenotypically similar to AFAP, in which the majority of patients have 10 to a few hundred adenomatous polyps. A patient can develop between 1 and 10 adenomas before age 40 years. However, some patients with MAP develop colorectal cancer without any polyposis. Three percent of patients who develop colorectal cancer before age 50 years have *MUTYH* mutations.[13,14] Patients also may have hyperplastic polyposis.

Similar to AFAP, MAP has a median age of presentation of 45 to 59 years. Patients also are at risk for extracolonic tumors such as duodenal polyposis, but this occurs less frequently than in AFAP. Other late-onset malignancies can occur in the ovary, bladder, or skin. More recent studies are also noting thyroid abnormalities, such as nodules and papillary thyroid cancer.[13]

The following surveillance testing for MAP is recommended; management is based on the findings.

Colonoscopy: Performed every 1 to 2 years beginning at age 25 to 30 years. Suspicious polyps should be removed. If polyps are too large or too numerous to be managed endoscopically, a subtotal colectomy or total proctocolectomy is recommended. Continued surveillance of residual colon or rectum every 1 to 2 years is necessary.

Upper endoscopy with side-viewing duodenoscopy: Every 3 to 5 years beginning at age 30 to 35 years. Any duodenal polyps with dysplasia or villous changes should be removed. Depending on polyp size, number, and histology, endoscopy may be needed as often as every 6 months to 1 year.

Thyroid examination: Although no definite recommendations are established, yearly thyroid examinations are recommended. If abnormalities are found, refer the patient to a thyroid specialist.[10]

TABLE 3. Extracolonic manifestations of FAP and surveillance[10,11]

- Congenital hypertrophy of retinal pigment epithelium
- Osteomas, supernumerary teeth, odontomas
- Desmoid or epidermoid cysts
- Duodenal and other small bowel adenomas. Surveillance: upper endoscopy with side-viewing scope; consider MRI with or without CT.
- Gastric fundic gland polyps. Surveillance: upper endoscopy.
- Medulloblastoma, found in fewer than 2% of cases. Surveillance: annual physical examination.
- Papillary carcinoma of the thyroid, found in fewer than 2% of cases. Surveillance: annual thyroid examination, starting in late teenage years.
- Hepatoblastoma, found in children age 5 years and younger. No established recommendation but the following can be performed: liver palpitation, abdominal ultrasound, alpha-fetoprotein measurement every 3 to 6 months for 5 years.
- Pancreatic cancers, found in fewer than 1% of cases. No established recommendation for surveillance.
- Gastric cancers, found in fewer than 1% of cases. Surveillance: upper endoscopy.

OTHER HEREDITARY COLON CANCER SYNDROMES

Other inherited colorectal cancer syndromes are beyond the scope of this article but are worth mentioning:

- Peutz-Jeghers syndrome, juvenile polyposis syndrome, and *PTEN* hamartoma tumor syndrome are characterized by GI hamartomatous polyps.
- Hereditary mixed polyposis syndrome consists of an increased risk for adenomas, juvenile polyps, hyperplastic polyps, and polyps with mixed histology.
- Hyperplastic polyposis syndrome, also called serrated polyposis, includes the presence of multiple hyperplastic polyps.

Refer to http://www.nccn.org for specific characteristics, screening, and management for these disorders.

OBTAINING AN ACCURATE FAMILY HISTORY

Taking the time to procure an accurate family history is vital to recognizing hereditary colorectal cancer. Obtain the history of the patient's first-degree relatives and their second-degree relatives. Asking beyond this to include cousins can help detect generational patterns that are typical in hereditary syndromes. Remember to obtain the specific type of cancer, the age at diagnosis, and where the family member was treated (so that records may be checked if needed). If possible, ask the patient to speak

with relatives and get permission to obtain a copy of their pathology reports to confirm malignancy.

When discussing polyps, ask patients the number of polyps and the relative's age at diagnosis. Ask about the common extracolonic cancers that are associated with hereditary colorectal cancer (for example, uterine and stomach cancer, associated with Lynch syndrome). Obtain the age at diagnosis for any family members affected. An accurate family history will help clinicians recognize specific patterns of cancer in the patient's family, so they can determine recommended screening and refer the patient to a genetic counselor.

GENETIC COUNSELORS

Genetic counselors are master's-level trained professionals who evaluate and recommend specific genetic testing. These counselors can educate and counsel patients and families about hereditary syndromes such as hereditary colorectal cancer, and help them decide if testing is appropriate. The Genetic Information Nondiscrimination Act (GINA), passed in 2008, ensures that genetic tests results are kept private, and protects patients against an insurer or employer denying coverage or employment based on genetic test results.[15]

Testing is offered first to the proband, the person who presents with a phenotypical pattern or has a pathologic diagnosis of cancer. When test results return, proper disclosure takes place. If a result is positive for a specific mutation, testing is offered to the family and recommended screening guidelines are provided for the patient and family. If a known mutation is found within the family and the family member's testing is negative, this family member can follow screening guidelines similar to an average-risk patient. If the proband's result is negative, but specific clinical criteria are present, screening guidelines for a specific syndrome may still be recommended. A variant of undetermined significance also may be found, and recommendations may be based on the patient's personal or family history.

The genetic counselor's role goes beyond disclosing results. The counselor also takes into account ethical considerations and can refer patients to psychological counseling if needed to cope with unfavorable news.

CONCLUSION

Primary care providers must recognize the clinical and pathological criteria of hereditary colorectal cancer so they can recommend the proper screening tests and refer patients to a genetic counselor. Obtaining an accurate personal and family history is essential. Features of hereditary colorectal cancer include multiple family members with the same or related types of cancer across generations, young age at time of diagnosis (under 50 years), patients with more than one primary cancer, rare cancers, multiple polyps, and cancers with certain pathological features. By screening patients and families early, healthcare providers can detect polyps and early cancerous lesions when they might be curable. **JAAPA**

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