Hereditary Colorectal Cancer Syndromes

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KEYWORDS

• Inherited colon cancer • Hereditary nonpolyposis colorectal cancer
• Lynch syndrome • Familial adenomatous polyposis • MUTYH-associated polyposis
• Serrated polyposis syndrome

KEY POINTS

- Hereditary colorectal cancer syndromes are rare and affected patients are at increased risk for early onset, synchronous and metachronous colorectal malignancies, and extracolonic malignancies.
- Understanding the genetic basis of cancer syndromes and unique genotype-phenotype profiles allows clinicians to tailor surveillance and treatment strategies based on individual risk.
- Lynch syndrome follows an autosomal-dominant inheritance pattern characterized by early onset, aggressive colorectal cancer, and extracolonic malignancies. The genetic basis is a defect in mismatch repair genes.
- Familial adenomatous polyposis (FAP) follows an autosomal-dominant inheritance pattern characterized by intestinal polyposis and extracolonic malignancies. Patients exhibit a spectrum of disease severity from attenuated to extensive disease with clinical overlap with *MUTYH*-associated polyposis.
- Serrated polyposis syndrome is characterized by multiple, sometimes large, serrated polyps and associated with increased colorectal cancer risk. The morphology of the precursor polyps makes endoscopic management challenging, underscoring the need for short interval surveillance.

INTRODUCTION

It is estimated that 20% to 30% of colorectal cancers (CRCs) are familial with 5% to 10% related to a known genetic syndrome.[1,2] The hereditary CRCs are broadly divided into nonpolyposis and polyposis syndromes. Individuals with hereditary CRC syndromes are at risk for earlier development of cancer, increased risk of

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metachronous cancers, and extracolonic manifestations. As such, identification of these individuals is critical for prevention and early detection and treatment of associated malignancies to reduce associated morbidity and mortality. Although there are a multitude of hereditary syndromes associated with increased risk of CRC, this article focuses on the most common nonpolyposis and polyposis syndromes.

HEREDITARY NONPOLYPOSIS COLORECTAL CANCER/LYNCH SYNDROME

Hereditary nonpolyposis CRC (HNPCC), also often used synonymously with the term Lynch syndrome, is the most common hereditary CRC syndrome, accounting for at least 2% to 3% of all CRCs. Lynch syndrome and HNPCC are associated with a predisposition to CRC and other cancers following an autosomal-dominant inheritance pattern, although rare sporadic mutations are described.[3] HNPCC defines a patient who meets particular clinical criteria (**Box 1**), regardless of the results of genetic assessment. Lynch syndrome is reserved for patients with a known mismatch repair (MMR) gene mutation regardless of whether they fulfill the clinical criteria for HNPCC (**Fig. 1**).

Both syndromes are associated with onset of CRC earlier than the general population with a mean age at CRC diagnosis of 45 years. Cancers are typically proximal to the splenic flexure; have a high degree of microsatellite instability (MSI-high); and have histologic features including poor differentiation, Crohn's-like host-lymphocytic infiltration, lymphoid aggregation at the tumor margins, and mucinous features.[4,5] They are associated with synchronous cancers,[6,7] and metachronous cancers are common with an annual incidence rate of 2.1%.[8,9] Despite the apparent high-risk histologic features, HNPCC-related CRC demonstrates less nodal and distant metastatic spread compared with sporadic CRC.[5,10] The "nonpolyposis" label of HNPCC can be misleading to less experienced physicians, because colorectal adenomatous polyps are the precursor lesions in these syndromes, with adenomas typically demonstrating a villous growth pattern and having a high degree of dysplasia.[4,11] Degeneration through the adenoma-carcinoma sequence is accelerated with CRC developing within a 5-year interval compared with 10 or more years in the case of sporadic CRC.[12,13]

Risk of Cancer

Regardless of the patient populations studied, the risk of CRC extracolonic malignancy is clearly elevated in HNPCC. Most studies present these risks reported in

Box 1
Revised HNPCC criteria (Amsterdam criteria II)

Criterion

1. There should be at least three relatives with an HNPCC-associated cancer (CRC, 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 should be diagnosed before age 50
5. Familial adenomatous polyposis should be excluded in the CRC cases if any
6. Tumors should be verified by pathologic examination

From Vasen HF, Watson P, Mecklin JP, et al. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. Gastroenterology 1999;116(6):1455; with permission.