The Genetics of Colorectal Cancer

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KEYWORDS

• Hereditary colon cancer • Lynch syndrome • Familial adenomatous polyposis
• MUTYH-associated polyposis • Peutz-Jeghers syndrome • Juvenile polyposis

KEY POINTS

- Multigene tests using next-generation sequencing technologies are becoming more widely used in clinical practice.
- Multigene tests do not replace the need for genetic counseling or a thorough evaluation of the personal and family history.
- Universal tumor testing of all colorectal and endometrial cancers is cost-effective and therefore recommended by many societal guidelines.
- Involvement of genetics in the development, implementation, and tracking of these programs is important for the success of these programs.
- The colonic polyposis conditions are a heterogeneous group; a detailed reporting of all endoscopy findings, including the histopathology of polyps, skin findings, and cancer history, is critical in making a correct diagnosis.

INTRODUCTION

The hereditary colorectal cancer (CRC) syndromes comprise a heterogeneous group of conditions with varying cancer risks, gastrointestinal (GI) polyp types, nonmalignant findings, and inheritance patterns. Although each one is unique in its own right, these syndromes often have overlapping features, making diagnoses difficult in select cases. Obtaining accurate polyp history (histologic type, number, location, and age of onset), cancer history (location, type, and age of onset), and other nonmalignant features is imperative in determining the likely disease diagnosis and thereby the appropriate genetic tests for precise diagnosis in a timely fashion. This process often necessitates collaboration among surgical oncology team members and genetic counselors.

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Advances in genetic testing technologies have improved the detection of various hereditary CRC syndromes. Here, some of these improvements, including the current state of genetic testing for hereditary CRC syndromes, are highlighted. Lynch syndrome (LS), familial adenomatous polyposis (FAP), MUTYH-associated polyposis (MAP), juvenile polyposis, and Peutz-Jeghers syndrome (PJS) are reviewed in detail. The genetic causes, inheritance patterns, cancer risks, and additional characteristic features are covered. **Table 1** includes a summary of the characteristic features of these syndromes, in addition to other causes of hereditary CRC, which will not be addressed in this review in detail. Last, also highlighted are the management issues revolving around various syndromes (**Table 2**), genetic testing guidelines are reviewed, and the implications of newer genetic testing technologies on clinical practice, especially as it relates to surgical oncology, are highlighted.

LYNCH SYNDROME

The understanding of LS has greatly increased since 1885, when pathologist Aldred Warthin first made the astute observation that his seamstress had a striking family history of cancer, particularly colon, uterine, and small bowel.[1] This particular kindred, which was called family G, was later confirmed to have LS.[1] Various names have been used for LS; the most notable was hereditary nonpolyposis colorectal cancer (HNPCC), which helped differentiate it from FAP.[2] LS is now deemed a more fitting name, given it is well-known that CRC is only one of many associated cancers.

LS is the most common cause of hereditary colon and endometrial cancer, accounting for 2% to 6% of all cases.[3–5] LS is also one of, if not the most, common cancer-related syndromes known,[1] even more prevalent than hereditary breast and ovarian cancer caused by *BRCA1* or *BRCA2* mutations. Like most other hereditary CRC predispositions, LS is inherited in an autosomal-dominant manner. It is caused by mutations in one of the mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*). LS may also occur from mutations in the *EPCAM* gene, as 3′ deletions in *EPCAM* result in *MSH2* hypermethylation, thereby acting like an *MSH2* mutation. CRC is the characteristic tumor, although the risk of endometrial cancer (EC) in some LS families is higher than the risk of CRC.[6] The incidence of LS is estimated at 1 in 370 individuals or even higher.[7] Other cancers are also increased in LS, including gastric, ovarian, urinary tract, hepatobiliary, brain, pancreas, and sebaceous skin (see **Table 1**). It is still questionable whether breast and prostate are LS cancers. A systematic review of the literature in 2013 was inconclusive as to whether breast cancer is associated with LS, although microsatellite instability (MSI) was found in some of the tumors, highlighting the possible link between the two.[8] In a similar review, it was revealed that prostate cancer risk was moderately elevated in LS,[9] although selection biases may have influenced those data.

Features

Although LS is defined as a single condition, the clinical phenotypes can vary quite significantly depending on the gene involved. As outlined in **Table 1**, not only do many different types of cancers occur in LS, but also the cancer risks are variable depending on the underlying genetics. In *MLH1* and *MSH2* mutation carriers, early estimates of CRC risk approached 80%, while the risk of EC was 40% to 60%.[10] These early studies were weighted toward high-risk families, which likely resulted in overestimations of cancer risk. Recent estimates are assuredly more precise. In a large study of more than 17,500 members of *MLH1* and *MSH2* families, the CRC risk to age 70 was estimated to be 34% to 47%, while the EC risks were 18% to