Population Screening for Hereditary Colorectal Cancer

Heather Hampel, MS, LGC

KEYWORDS

• Lynch syndrome • Cancer genetics • Hereditary • Colon cancer • Screening

KEY POINTS

- Hereditary colorectal cancer is common, with Lynch syndrome accounting for 4% of all colorectal cancer cases.
- All colorectal cancers should be screened for Lynch syndrome at the time of diagnosis.
- Other hereditary cancer syndromes can be identified in colorectal cancer patients at an appreciable frequency.
- It may be time to consider offering genetic counseling and testing to all colorectal cancer patients.

INTRODUCTION

Approximately 136,000 Americans will be diagnosed with colorectal cancer (CRC) this year.[1] Population studies have shown that 4% of these CRC cases are due to Lynch syndrome (LS).[2–4] Tumor screening for Lynch syndrome among all newly diagnosed CRC patients using either the microsatellite instability test or immunohistochemical staining for the 4 mismatch repair genes has been recommended by several professional organizations.[5–7] In addition, it has been recently shown that patients with microsatellite unstable colorectal cancer can benefit from immunotherapy using anti-PD1 and anti-PDL1 inhibitors.[8] Unfortunately, universal tumor screening for Lynch syndrome has not been implemented at all hospitals yet.[9] More recent studies have found that the prevalence of all hereditary cancer syndromes among unselected colorectal cancers is around 10%, and for those diagnosed under age 50, it closer to 16%.[10] At these levels of risk, it may be time to consider offering genetic counseling and testing to all colorectal cancer patients.

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Division of Human Genetics, Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center, 2012 Kenny Road, Room 257, Columbus, OH 43221, USA
E-mail address: Heather.Hampel@osumc.edu

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LYNCH SYNDROME

Lynch syndrome is an autosomal dominant condition that leads to increased risks for CRC, as well as endometrial, ovarian, gastric, and several other cancers (Table 1). Lynch syndrome is caused by mutations in the mismatch repair (MMR) genes *MLH1*, *MSH2* (including deletions involving the upstream gene *EPCAM*, *MSH6*, and *PMS2*). When one of these genes is mutated in the germline, there is a high chance that the individual will acquire a second somatic mutation in the other copy of that gene in an at-risk cell during his or her lifetime. When that occurs, there will be no more MMR protein in the cell, so it will no longer be able to repair mismatch mutations in the DNA. This leads to both characteristics of Lynch syndrome that can be screened for in tumors to identify patients who are more likely to have this condition. The first is absence of an MMR protein(s) as demonstrated by immunohistochemical (IHC) staining (Fig. 1). If the MMR genes are functioning, the MMR proteins should be present in the tumor. If an MMR gene is not working because of a germline mutation plus a second somatic mutation, then the protein (and possibly its partner protein) will be absent in the tumor. The second characteristic that can help identify patients who are more likely to have Lynch syndrome is microsatellite instability (MSI). This is the result of defective MMR (dMMR), whereby the microsatellites, which are repetitive elements in human DNA such as the famous long tracts of 25 and 26 adenines in a row found in the BAT-25 and BAT-26 markers, become unstable. It is difficult for the DNA replication mechanism to copy these repeats exactly during mitosis. As a result, a few of the repeats might be lost or gained in a cell. If the MMR genes are working, they would repair these errors and continue to have the same number of repeats. If the MMR genes are not working, which is the case in tumors with mutations in both copies of the gene, these errors cannot be repaired, and the tumor will have a different number of repeats than the normal adjacent tissue or blood from that individual in which MMR is working properly. These tumors are called MSI-high tumors and are more likely to be caused by Lynch syndrome.

UNIVERSAL TUMOR SCREENING FOR LYNCH SYNDROME

MSI and IHC tests can be performed in the pathology department at the time of diagnosis of CRC. These tests can identify patients who are more likely to have Lynch syndrome; however, they are not diagnostic, because one can have a dMMR tumor because of either inherited mutations of the MMR genes (Lynch syndrome) or acquired mutations of the MMR genes (*MLH1* promoter methylation or double somatic MMR gene mutations). To reduce the number of patients requiring follow-up genetic counseling and testing for Lynch syndrome, most hospitals perform follow-up testing

Table 1
Lifetime cancer risks associated with Lynch syndrome

Cancer Type	General Public (%)	MLH1 & MSH2 (%)	MSH6 (%)	PMS2 (%)
Colon cancer	5.5	40–80	10–22	15–20
Endometrial cancer	2.7	25–60	16–26	15
Stomach	<1	1–13	≤3	6
Ovarian	1.6	4–24	1–11	6

Data from Bonadona V, Bonaiti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA 2011;305:2304–10; and Senter L, Clendenning M, Sotamaa K, et al. The clinical phenotype of Lynch syndrome due to germ-line PMS2 mutations. Gastroenterology 2008;135:419–28.