Lynch Syndrome

Overview

- What is Lynch Syndrome?
  Lynch syndrome is a hereditary genetic condition that increases the risk of developing cancer, especially colon cancer. A diagnosis of Lynch syndrome is made in a patient when a harmful change called a mutation is found in the blood or saliva in one of the five genes that cause Lynch syndrome. The Lynch syndrome genes include *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*. The mutation can be passed on from a parent with Lynch syndrome to their children.

  Many Lynch syndrome cancers occur at a younger age. The highest risk of cancer includes colorectal (up to 70%) and endometrial (up to 70%), followed by ovarian (up to 20%), stomach and small bowel (up to 13%), urinary organs (up to 25%), bile ducts and pancreas (up to 4%), and brain (up to 4%). Individuals with Lynch syndrome can develop unusual skin tumors including sebaceous carcinoma, keratoacanthomas, and sebaceous adenomas.

Cancer Type	Lifetime Risk of Developing Cancer in Lynch Syndrome	Lifetime Risk of Developing Cancer in the Average Person	Average Age (Years) at Cancer Diagnosis in Lynch Syndrome	Average Age (Years) at Cancer Diagnosis in the Average Person
Colorectal cancer				
MLH1/MSH2 Female	22-53%			
MLH1/MSH2 Male	27-74%		27-46	
MSH6 Female	10-18%	5.5%	54-63	69
MSH6 Male	18-22%		47-66	
PMS2 Female	15%			
PMS2 Male	20%			
Endometrial cancer				
MLH1/MSH2	14-54%		48-62	
MSH6	17-71%	2.7%	54-57	65
PMS2	15%		49	
Stomach cancer	0.2-13%	<1%	49-55	65-74
Ovarian cancer	4-20%	1.6%	43-45	55-64
Hepatobiliary tract cancer	0.02-4%	<1%	54-57	55-64
Urinary tract cancer	0.2-25%	<1%	52-60	55-64
Small bowel cancer	0.4-12%	<1%	46-49	55-64
Brain/central nervous system cancer	1-4%	<1%	50	55-64
Skin cancer (sebaceous carcinoma, keratoacanthomas, sebaceous adenomas)	1-9%	<1%	Unknown	Unknown
Pancreas cancer	0.4-4%	1.5%	63-65	65-74
Prostate cancer	16.2%	9-30%	59-60	65-74
Breast cancer	12.4%	5-18%	52	55-64

Symptoms

- What are the Symptoms?
  Other than skin tumors, there are no physical signs or symptoms that might alert healthcare providers that someone has Lynch syndrome. However, the cancers that are associated with Lynch syndrome can cause symptoms. Please see the Colon Cancer Health Topic for more information about symptoms of colon cancer.

Causes

- What Causes Lynch Syndrome?
  Lynch syndrome is caused by genetic alterations or mutations in one of the Lynch syndrome genes. They are known as the "mismatch repair" genes: *MLH1*, *MSH2*, *MSH6*, and *PMS2*. When a Lynch syndrome gene is altered, it cannot produce its protein, which is necessary to repair damage that naturally occurs in our DNA (the building blocks that make up our genes). Without the normal ability to repair DNA damage, cancers are prone to develop.

Risk Factors/Diagnosis

- What are the Risk Factors for Lynch Syndrome, and How is it Diagnosed?
  Lynch syndrome is estimated to occur in 1 in 280 to 440 individuals. It is the cause of up to 3% of colorectal cancers and 2% of endometrial cancers.

  Family History of Cancer
  A diagnosis of Lynch syndrome may be suspected based on a family history of cancer. The types of cancer, number of relatives and generations affected with cancer, and age of onset of cancer in the family can help identify someone or a family at risk of a hereditary colon cancer syndrome (Table 1).

  The Amsterdam I Criteria:

1. Three or more relatives with colorectal cancer, one of whom is a first-degree relative (mother, father, sister, brother, daughter, or son) of the other two
2. Two or more generations with colorectal cancer
3. At least one individual with colorectal cancer in the family who was diagnosed before age 50
4. The family does not have a different inherited colorectal cancer condition called "familial adenomatous polyposis"

Amsterdam II Criteria:

1. Three or more relatives with HNPCC-associated cancers (colorectal, endometrial, small bowel, ureter, or renal pelvis) cancer, one of whom is a first-degree relative of the other two
2. Two or more generations with the above cancer(s)
3. At least one individual with the above cancer(s) in the family who was diagnosed before age 50
4. The family does not have a different inherited colorectal cancer genetic condition called "familial adenomatous polyposis"

About 50% of families who meet the Amsterdam I or Amsterdam II Criteria have Lynch syndrome, meaning they have a mutation in the Lynch syndrome genes *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM*.

Importantly, many people with Lynch syndrome do not meet Amsterdam I or II criteria. The diagnosis of Lynch syndrome may be suspected if someone is diagnosed with a colorectal or endometrial cancer before the age of 50 or if a person has been diagnosed with more than one of the Lynch syndrome-related cancers.

Family History of Lynch Syndrome

The greatest risk factor for having Lynch syndrome is having a relative with this condition. The first-degree relatives of an individual with Lynch syndrome (mother/father, brothers/sisters, and children) have a 50% chance of having the same mutation. Depending on who else in the family has inherited the mutation, more extended relatives such as aunts/uncles, grandparents, grandchildren, and cousins could also have Lynch syndrome.

As an example, Suzie is a 46-year-old woman with colon cancer due to a mutation in the MSH2 gene causing Lynch syndrome. She has two daughters. Her brother has two sons. Both of her parents are still living. Her brother undergoes genetic testing for Suzie's MSH2 mutation (see below) and does not have it. Therefore, he does not have Lynch syndrome and his two children are not at risk of Lynch syndrome. Both of Suzie's daughters are tested, and one is found to have the MSH2 mutation. This daughter has Lynch syndrome. She has a 50% chance to pass the mutation on to her children. Her other daughter is negative for the MSH2 mutation. Neither she nor her children are at risk of Lynch syndrome. Suzie's mother and father are tested and her father is found to have the same mutation as Suzie. Suzie's maternal relatives, therefore, do not have a risk of having Lynch syndrome. Suzie's father's brothers and sisters have a 50% chance of inheriting Lynch syndrome, and need to be tested for Suzie's mutation in order to determine if they also have Lynch syndrome and if their children also have a risk of having Lynch syndrome.

Screening Tests for Lynch Syndrome

The best approach to make the diagnosis of Lynch syndrome is by testing a colorectal cancer for genetic alterations seen in Lynch syndrome.

Lynch syndrome results in damage to genetic areas of DNA called "microsatellites." A high level of microsatellite damage ("MSI-H") is a sign of Lynch syndrome. Approximately 90-95% of colorectal cancers caused by Lynch syndrome will be MSI-H. Another tumor test for Lynch syndrome includes immunohistochemistry (IHC). IHC colors the proteins produced by genes. A mutation in a Lynch syndrome gene will result in a lack of staining of the corresponding protein. Approximately 88% of colorectal cancers caused by Lynch syndrome will have an abnormal IHC result.

At some medical centers, all patients with colorectal and/or endometrial cancer will automatically have tests of their cancer done to evaluate for Lynch syndrome. This is called universal testing.

Genetic or "Germline" Testing

If someone has a compelling personal or family history of cancer, or abnormal MSI/IHC results suspicious for Lynch syndrome, "germline" genetic testing should be considered. Germline testing is typically done on a blood or saliva sample. The testing is most often covered by insurance. Genetic test results can take anywhere from 2 weeks to 3 months to complete. One of the following three results will be found on germline testing:

- "Positive" or abnormal: This confirms that the individual has Lynch syndrome. This also allows the healthcare provider to offer genetic testing to other family members.
- "Negative" or normal: This means that no Lynch syndrome mutation was found. This negative result could mean a few different things, depending upon whether the patient was the one with cancer, a relative of someone with cancer, or a relative of someone with known Lynch syndrome:
  - The cancer in the family is not due to Lynch syndrome.
  - There is a harmful mutation in the gene(s) that could not be found with current genetic testing technology.
  - There is a harmful mutation in another gene that was not tested.
- "Uncertain" or variant of uncertain significance (VUS): A VUS is a genetic alteration that is not established if it leads to disease or has no health consequences. A VUS can neither confirm nor deny the diagnosis of Lynch syndrome. It should not be used to test other relatives or determine what type of cancer screening a person needs.

Genetic testing can be a complex process. Additionally, it can raise medical, emotional, familial, social, financial, legal, and ethical concerns for people at risk of, suspected of, or diagnosed with Lynch syndrome. It is recommended that individuals pursuing genetic testing have pre- and post-test genetic counseling by an appropriately trained healthcare professional. This might include a genetic counselor or medical geneticist. During a pre-testing genetic counseling visit, the healthcare provider will collect a medical and family history to determine if genetic testing, is appropriate. The healthcare provider will educate the patient about Lynch syndrome cancer risks, management options, inheritance patterns, the genetic testing process, and support and counseling related to emotional concerns. Importantly, information will be shared about insurance coverage and costs for genetic testing, protections against genetic discrimination, and a plan for how test results will be shared with the patient and family members. Upon completion of genetic testing, the healthcare provider will provide an interpretation of the genetic test results and help the patient understand the implications for their health, as well as for his or her family members. The National Society of Genetic Counselors (www.nsgc.org) has a search feature to find a genetic counselor near his or her home. For individuals who do not have a genetic counselor in their area, there are telephone genetic counseling services available from companies such as InformedDNA (informeddna.com).

Management

- How is Lynch Syndrome Managed?

  The goal of identifying a patient with Lynch syndrome is to prevent cancer from developing or to find it at an early stage when it is curable or only minimal treatment is required. There is no way to cure Lynch syndrome. This includes:

Organ being screened	Type of screening	Age to start	How often to repeat
Colon and rectum	Colonoscopy	20-25 years or 2-5 years earlier than the youngest person with colon cancer in the family, whichever is younger.	Every 1-2 years
Uterus and ovaries	Biopsies of the uterus lining and transvaginal ultrasound	30-35 years	Every year
Stomach and duodenum	Upper endoscopy (EGD)	30-35 years	Every 2-3 years
Urinary tract	Urinalysis	30-35 years	Every year

While there are other cancers associated with Lynch syndrome, there is no evidence that screening other organs reduces the cancer risk or increases lifetime span. It would be best to discuss any of the above options with your gastroenterologist and/or genetic counselor to determine which test would be recommended specifically for your situation and family history.

Chemoprevention

Chemoprevention means taking a medication to help reduce the risk of developing a cancer. There is some evidence to show that taking long-term, daily aspirin may help to reduce colorectal and other cancers in Lynch syndrome. The exact dosage of aspirin is not known. Any decision to take aspirin should occur after discussion with a physician, taking into account the potential risk of taking aspirin.

Surgery

Women with Lynch syndrome should consider hysterectomy and bilateral salpingo-oophorectomy (removal of the uterus and both fallopian tubes and ovaries) to prevent uterine and ovarian cancer when they have finished childbearing or are over 40 years old.

For individuals with Lynch syndrome who develop colon cancer polyps that cannot be removed safely by colonoscopy, colorectal surgery may be recommended. It has been shown the risk of recurrent colon cancer in Lynch syndrome is substantially decreased if a longer segment of the colon is removed than in standard colon cancer operation. This might include a colectomy with ileorectal anastomosis (removal of the colon with attachment of the end of the small bowel to the top of the rectum). The risk of developing another colorectal cancer after an initial colorectal cancer diagnosis and only partial colon resection is 16-19% at 10 years, 41-47% at 20 years, and up to 62-69% at 30 years.

Author(s) and Publication Date(s)

Brandie Heald Leach, MS, LGC, Genetic Counselor, Cleveland Clinic, Cleveland OH – Published October 2016.

External Links

Collaborative Group of the Americas on Inherited Colorectal Cancer Hereditary Colon Cancer Takes Guts Informed DNA Lynch Syndrome International Lynch Syndrome Screening Network National Society of Genetic Counselors