

LYNCH SYNDROME (LS)

PATIENT INFORMATION

What is Lynch syndrome?

Lynch syndrome, also known as Hereditary Non-Polyposis Colorectal Cancer (HNPCC) is the most common hereditary form of colorectal and uterine cancer. About 2-3% of people who have colorectal or uterine cancer have Lynch syndrome. Families with Lynch syndrome usually have several family members with colorectal or uterine cancer. Other cancers can also be seen, including different cancers of the gastrointestinal tract, ovarian cancer, upper urinary tract cancers, uncommon skin cancers and rarely, brain tumors. People with Lynch syndrome often start to develop pre-cancerous colorectal polyps or cancers at an earlier age than the general population (as early as 20 years old).

Lynch syndrome is due to problems in the way that our cells repair themselves through alterations in genes. We all have about 25,000 genes in almost every cell in our body. Each of these genes is made up of a series of four chemical letters in a certain order (our DNA). As the cells grow and divide, exact copies of these genes need to be made for the new cell that is formed. When mistakes are made during this copying process, the wrong chemical letter may end up in the new gene that is created. Some of our genes, through the proteins that they make, act as spellcheckers to detect these “typos.” One set of genes helps to find and correct a certain kind of typo, known as a DNA mismatch. So far, five genes that are part of or associated with the DNA mismatch repair process have been shown to cause Lynch syndrome. They are called ***MLH1***, ***MSH2***, ***MSH6***, ***PMS2***, and ***EPCAM*** (also known as *TACSTD1*).

Below are the lifetime risks of cancer in people with *MLH1* and *MSH2* gene alterations without screening or follow-up, as compared to the general population. Families with *MSH6* and *PMS2* gene alterations may have lower risks than those shown here and may develop cancers later in life but are still followed closely. Women with *MSH6* alterations may have a higher risk of uterine cancer than shown here.

Cancer	Lynch Syndrome Risk	General Population Risk
Colorectal	52-82%	5-6%
Uterine	25-60%	2-3%
Stomach	6-13%	<1%
Ovary	4-12%	1-2%
Bile Duct (Hepatobiliary)	1.4-4%	<1%
Small bowel	3-6%	<1%
Urinary tract	1-4%	<1%
Brain/Central Nervous System	1-3%	<1%
Skin (Sebaceous) tumors	1-9%	<1%
Pancreas	1-6%	<1%

[Reference: NCCN Guidelines Version 2.2013 Lynch Syndrome]

What causes Lynch syndrome?

About 80% of people with Lynch syndrome have an alteration in either the *MLH1* or *MSH2* gene. *MSH6* gene alterations are responsible for about 5-10% or more of families with this syndrome, and *PMS2* alterations are found in less than 5% of families. A small number (fewer than 5%) of families with Lynch syndrome are also found to have alterations in the *EPCAM* gene. There are also some families with Lynch syndrome who have a gene alteration that cannot be found by today's technology.

If a person has inherited an alteration that is harmful (a mutation) in one of these five genes from one of their parents, then they are at risk for developing the cancers seen in Lynch syndrome. All of us have two copies of almost every gene (one from each parent), so even if one is altered, the other one can work normally. However, if the second copy of the gene is damaged by chance, the cell no longer has a working copy of the gene to help protect it from DNA errors. As the genes in the cell acquire more DNA errors, the cell may lose the ability to grow and divide normally and eventually turn into cancer.

How is Lynch syndrome inherited?

Lynch syndrome is inherited in an “autosomal dominant” manner. Autosomal means that both men and women can have LS and pass it on to their children. Dominant means that it takes only one altered copy of a gene in order to cause LS.

If you have an altered gene, here are the chances that other relatives might have inherited it:

- **Your Children** –50% risk for each child
- **Your Mother or Father** – almost a 50% risk. In most cases, you will have inherited the altered gene from either your mother or your father. In rare cases, neither of your parents will have the altered gene, because it has occurred as a new genetic event in you.
- **Your Brothers and Sisters** – 50% risk if one of your parents had the alteration. If neither of your parents had the alteration, then your siblings have a very low risk of having the alteration.
- More distant relatives like your **aunts, uncles, cousins, nieces, and nephews** may have inherited this gene alteration depending on where they are in the family tree. Please talk to your health care team about risks for specific relatives.

How is Lynch syndrome managed?

There are a number of medical recommendations to help manage these increased risks that should be considered. Although we do not currently have any perfect strategies for reducing cancer risks, we do know that by close monitoring, some cancers can be detected in their earliest stages when they are most amenable to treatment. Screening is testing that is done in an effort to identify and treat cancer early. Risk reduction strategies are used to try to prevent cancer.

Screening:

For both men and women:

- colonoscopies every 1-2 years (beginning at age 20-25)



- upper endoscopies every 3-5 years (beginning at age 30-35)
- dermatology evaluation at least once a year
- annual physical exam (beginning at age 20-25)

For women beginning at age 30-35:

- transvaginal ultrasounds to visualize the uterus and ovaries once a year
- uterine sampling (biopsies) once a year
- routine pelvic exams

For certain families:

- urine testing
- small bowel cancer screening
- pancreatic cancer screening

Risk Reduction:

- Although colonoscopy is a very effective screening tool, some individuals also consider removing the colon as a preventive measure. Any type of surgery requires careful consideration of the risks and benefits.
- Because the screening for uterine cancer has not been proven to be very effective at detecting early cancer, women may consider removal of the uterus (and sometimes ovaries) after they have completed their families and are physically and emotionally ready.
- Some people with Lynch syndrome who take high doses of aspirin daily for over 2 years have a reduced risk of Lynch syndrome-associated cancer. Our knowledge about the preventive effects of aspirin in Lynch syndrome is rapidly evolving and we would be happy to discuss whether this strategy may be right for you in person.

Where can I find more information?

Dana Farber Cancer Institute, Cancer Genetics & Prevention
www.dana-farber.org/cancergenetics

Collaborative Group of the Americas on Inherited Colorectal Cancer (CGA)
<http://www.cgaicc.com/>

Colon cancer alliance
<http://www.ccalliance.org/>

American Cancer Society
www.cancer.org

National Cancer Institute
www.cancer.gov

References

- NCCN Guidelines Version 2.2013 Lynch Syndrome
- PDQ Cancer Information Summaries [Internet]. Bethesda (MD): National Cancer Institute (US); 2002-. Genetics of Colorectal Cancer (PDQ®): Health Professional Version. [Updated 2012 Jul 20]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK65788/>