

# Lynch syndrome

**Lynch syndrome** (hereditary non-polyphonic colorectal cancer, HNPCC) is a hereditary disease with an autosomal dominant type of inheritance with high penetrance, in which there is an early development of colorectal cancer, endometrial cancer and other malignancies. The molecular basis in the vast majority of cases is a mutation of mutator genes, one variant is caused by a mutation of the gene for the cytokine receptor. On the basis of Lynch syndrome, about 1–3% of colorectal cancers and 2% of endometrial cancers occur. Incidence Lynch syndrome is quite high, estimates range from 1/2000 to 1/550.

## Molecular variants

- Lynch syndrome 1 – mutation of the MSH2 gene
- Lynch syndrome 2 – mutation of the MLH1 gene
- ~~Lynch syndrome 3 – mutation of the PMS1 gene~~ **pathogenic effect of the mutation not proven**
- Lynch syndrome 4 – mutation of the PMS2 gene
- Lynch syndrome 5 – mutation of the MSH6 gene
- Lynch syndrome 6 – mutation of gene for type 2 receptor for TGFβ
- Lynch syndrome 7 – mutation of the MLH3 gene

## Clinical picture

### Colorectal cancer

The most common manifestation is colorectal cancer, which usually appears at a younger age of the patient, the median age is 42–61 years. The lifetime risk of developing colorectal cancer is higher in men, depending on the specific type of Lynch syndrome. Lynch syndrome 2 has the highest risk, where colorectal cancer occurs in about 80% of patients. Conversely, in Lynch syndrome 4, the risk of colorectal cancer is about half.

Clinically, colorectal cancers based on Lynch syndrome are interesting mainly because they have a significantly lower potential to establish metastases compared to sporadic colorectal cancers, which probably leads to colorectal cancers having a better prognosis.

### Endometrial carcinoma

Endometrial carcinoma most often occurs at the age of 47–55 years, i.e. at an age lower than in the control population. The risk of developing endometrial cancer is between 30–60%

### Other tumors

Lynch syndrome poses a risk for the development of a number of tumors. The most common ones are the following:

- ovarian tumours with a risk of 6–7%,
- stomach tumours with a risk of 6–9%,
- small intestine tumours with a risk of 3–4%,
- pancreatic tumors with a risk of 1–4%,
- liver tumours with a risk of 1%,
- urinary tract tumors with a risk of 3–8%,
- brain tumours with a risk of 2–3%,
- keratoacanthoma and sebaceous skin tumours (sebaceous adenoma, sebaceous carcinoma and sebaceous epithelioma) and with a risk of 1–9%.

## Molecular biology

### Disorders of mutator genes

The causal mutation can be a mutation of mutator genes (mismatch repair genes) MLH1, MSH2, MSH6 or PMS2, most often the first two. With a congenital mutation, the loss of function is not complete, without a somatic mutation and a second allelic, cancer will not occur.

### Microsatellite instability

Microsatellites are short repetitive DNA sequences. For physical reasons, these sequences are more prone to more frequent replication failures that the intact mismatch repair system can correct. Disturbances in the length of microsatellites are referred to as microsatellite instability. Because microsatellites are also present in some genes regulating cell cycle transmission, microsatellite instability may be the immediate cause of tumor formation.

### TGFBR2

The germ mutation of the gene type II for TGF- $\beta$  receptor also phenotypically manifests itself as Lynch syndrome. Tumor formation occurs in a different way than in other forms of Lynch syndrome, the role is probably played by the fact that cells with a mutated receptor do not respond adequately to the inhibitory action of TGF- $\beta$ .

## Modifying genes

Because phenotypic manifestations, especially the age at which tumors appear, are relatively variable, it is searched for factors that can influence the course of the disease. Genetic factors, i.e. polymorphisms of genes without their own pathogenic potential, are uncontrollable factors, but they can serve to identify patients at high risk. Polymorphisms of the following genes and groups of genes come into consideration:

- genes influencing the metabolism of xenobiotics and micronutrients (N-acetyl transferase, uncertain findings relate to glutathione-S-transferase and CYP1A1),
- genes involved in cell cycle control (p53 and MDM2 polymorphisms, disputed results relate to cyclin D1, Aurora-A protein),
- genes involved in DNA repair (poor data only),
- genes involved in the function of the immune system (only analogy with sporadic colorectal cancer),
- genes for growth factors (possible influence of IGF-1 polymorphism),
- genes involved in the development of hemochromatosis,
- methylenetetrahydrofolate reductase,
- DNA (cytosine-5-)methyltransferase 3 $\beta$ .

## Diagnostics and management

Because compared with familial adenomatous polyposis, the first symptoms may appear quite late. Characteristic is familial accumulation of tumors rather at a younger age, especially colorectal cancer.

### Diagnostic criteria

#### Criteria Amsterdam II (Vasen 1999)

A family meets the lynch syndrome diagnostic criteria if it meets all of the following criteria:

- Three or more relatives have been diagnosed with colorectal cancer, endometrial cancer, small bowel cancer, ureter cancer or renal pelvic cancer.
- At least one of these is a first degree relative of the remaining two
- At least two consecutive generations are affected.
- At least one tumor was diagnosed before the age of 50.
- Familial adenomatous polyposis was excluded.
- The tumor was histologically verified.

The disadvantage of these diagnostic criteria is that small families may not meet all the requirements.

#### Revised Bethesda criteria (Umar 2004)

Meeting at least one of the following points means a recommendation for microsatellite instability testing (MSI):

- Colorectal cancer diagnosed before the age of 50.
- The presence of synchronous or metachronous colorectal cancer or other tumors associated with Lynch syndrome, regardless of age.
- Histology of carcinoma corresponding to MSI-H before the age of 60.
- Colorectal cancer diagnosed in a patient whose at least one first-degree relative has a tumor associated with Lynch syndrome; at least one tumor must appear before the age of 50.
- Colorectal cancer diagnosed in a patient whose at least two first- or second-degree relatives have a tumor associated with Lynch syndrome; regardless of age.

Testing the instability of microsatellites can be carried out in two ways:

1. direct demonstration by DNA examination by PCR method,
2. immunochemical evidence of loss of expression of corresponding mutator genes.

## Histopathology

Histological types of tumors are most often:

- mucinous carcinoma (more than 50% of mucin),
- ring cell carcinoma (more than 50% of tumor cells have the character of seal ring-shaped cells),
- medullary carcinoma.

Regardless of the histological type of tumor, the following features are characteristic:

- Tumor infiltrating lymphocytes are present, mostly CD3 and CD8 coexpressing T lymphocytes.
- In the tumor, Crohn-like lesions can be observed, that is, pronounced nodular lymphoid nodules on the infiltrating side of the tumor.
- Quite common is poor differentiation of the tumor.

## Differential diagnostics

Colorectal cancer can develop in three ways:

1. the classic FAP/APC mutation pathway,
2. microsatellite instability pathway (MSI)
3. serrated pathway

Lynch syndrome leads to the formation of tumors through a disorder of mutator genes with subsequent instability of microsatellites. One of the ways of resolution is the analysis of microsatellite instability, which is typical for the MSI pathway and also for the serrated pathway, and the analysis of the BRAF gene, which is mutated in carcinomas formed by the serrated pathway, but is usually not damaged in carcinomas formed by the pathway of damage to mutator genes.

## Clinical management

DR recommendations for clinical management (Vasen et al., 2013) can be summarized in the following points, all of which are recommendations with a lower degree of plausibility:

- It would be advisable to test all cases of colorectal and endometrial carcinomas, or at least in persons under 70 years of age for the presence of microsatellite instability, or to immunochemically investigate the expression of mutator genes.
- The interval between control colonoscopies should be 3 years, in case of detection of colorectal cancer shorten the interval to 1-2 years.
- Screening methods for early detection of endometrial cancer are still a subject of discussion. Similarly, preventive hysterectomy with oophorectomy is the subject of discussion.
- The extent of colectomy in the detection of colorectal cancer is a subject of debate.

## Other intervention

- Patients with Lynch syndrome have a growing risk of developing colorectal cancer with BMI and smoking. Intervention in this sense is therefore desirable.
- Prophylactic administration of acetylsalicylic acids significantly reduces the incidence of colorectal cancer. Doses ranging from 75 to 1200 mg per day have been tested, the optimal dose is under discussion.

## Links

## Source

- ws:Lynchův syndrom

## Literature

- DE LA CHAPELLE, A.. The incidence of Lynch syndrome. *Fam Cancer*. 2005, vol. 4, no. 3, p. 233-7, ISSN 1389-9600.
- SCHNEIDER, R. – SCHNEIDER, C. – KLOOR, M., et al. Lynch syndrome: clinical, pathological, and genetic insights. *Langenbecks Arch Surg*. 2012, vol. 397, no. 4, p. 513-25, ISSN 1435-2451.
- TALSETH-PALMER, B.A. – WIJNEN, J.T. – GRICE, D.M., et al. Genetic modifiers of cancer risk in Lynch syndrome: a review. *Fam Cancer* [online]. 2013, vol. 12, no. 2, p. 207-16, Available from <<https://link.springer.com/article/10.1007%2Fs10689-013-9614-2>>. ISSN 1573-7292.
- VASEN, H.F. – BLANCO, I. – AKTAN-COLLAN, K., et al. Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. *Gut* [online]. 2013, vol. 62, no. 6, p. 812-23, Available from <<https://gut.bmj.com/content/62/6/812.long>>. ISSN 1468-3288.