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Genetic aspects of endometrial cancer

Abstract

The Lynch syndrome represents 2-5% of the total of endometrial cancer and 3% of the total adenocarcinoma of the colon. The risk of developing during life time an endometrial cancer for women with Lynch syndrome is up to 71% compared with 2.6% of the general population, and the average age for diagnosis comes down from 60-64 years to 46-54. The Lynch syndrome is an autosomal dominant disease determined by a mutation of the germ line appearing on the level of one of the genes responsible for deoxyribonucleic acid mismatch repair due to a deletion in the epithelial cell adhesion molecule gene. The Cowden syndrome is a genetic disorder with autosomal dominant transmission having as cause the mutation of the tumor suppressor gene phosphatase and tension homology deleted on chromosome ten, located on the 10q23 chromosome. The risk of developing endometrial cancer for these patients during their life span is estimated to be at 13-28%, cases of teenagers with cancer being reported. The screening by endometrial biopsy is recommended starting from 35-40 years or 5 years earlier than the diagnostic age of the first endometrial cancer in the family. Each patient found suffering from hereditary cancer needs the genetic testing of the family and the screening for endometrial cancer of the relatives affected by this disease.
Keywords: *Lynch syndrome, Cowden syndrome, endometrial cancer*

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Epidemiology of Endometrial Cancer

Endometrial cancer represents on global level 6% of the female cancer, in developed countries representing the most frequent form of genital cancer; beyond the genital sphere, the frequency for the appearance of endometrial cancer is under that of breast, colon and lung cancer[(1)]. The maximum incidence is situated post-menopausal between 60-64 years, but there are records of an increase of affecting pre-menopause women. The incidence of endometrial cancer has increased in the last 20 years in the entire world, while the incidence of cervical cancer has constantly decreased due to the implementation of screening and preventive healthcare. In Europe one of the 20 cancers of women is endometrial cancer[(2)]. The estimated risk for one woman to develop endometrial cancer during the life span is variable between 1-3%. The incidence between 40-50 years of age is estimated to be 10-40 cases for 100000 women, but goes up to 110 cases/100 000 women of 70 years, 75% of the endometrial cancers being diagnosed post-menopause, 25% in pre-menopause, of which 5% under 40 years; the aggressiveness increases with the growth in age. Over 90% of the endometrial cancers are sporadic, approximately 10% being associated with hereditary syndroms[(3)].

The family history including first-degree relatives with endometrial cancers seems to represent a risk factor, even if any candidate gene has not been constantly identified in the etiology of this type of cancer[(1,2)]. The breast cancer 1 (BRCA1) mutation carriers presents a high risk of ovarian and breast cancer, some studies suggesting the existence of the association of the BRCA1 mutations with endometrial cancer. A multinational cohort study involving 119847 carriers of this mutation reports a significant increase of the uterine cancer (RR 2.65, 95% CI 1.69-4.16), another prospective study sustains that the risk increases only for BRCA mutation carriers treated with tamoxifen, other reports sustaining the increase of the risk only for ovarian cancer. Future studies are needed to clarify these aspects[(3,4,5)].

The personal history of breast cancer represents a risk factor for endometrial cancer of women treated with tamoxifed, but also independently, both pathologies having as common risk factors obesity and nulliparity. The type of endometrial cancer frequently associated with the breast cancer is the ovarian one, an aspect unjustified taking in consideration that the serous tumors are typically estrogen independent, unlike breast tumors, the majority being estrogen dependent[(6,7)].

The Clinical Characteristics for a Family Cancer

The clinic characteristics that raising the suspicion for a family cancer or for a genetic susceptibility of cancer for a patient diagnosed with any type of malignity, include:

- cancer appearing at an unusual young age compared to any average diagnosis age;
- the development of multiple tumors in only one organ, or affecting bilateral pair organs;
- the development of more than one primary tumor in any type of malignity;
- family history of the same type of cancer or related, of one or more first-grade relative;
- high incidence of cancer in a family[(8)];
- cancer appearing in one individual or in a family with congenital anomalies or birth defects.

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The risk of women with hereditary nonpolyposis colorectal cancer (Lynch syndrome) for developing endometrial cancer during her life span is 27-71% compared with the 2.6% risk of the general population. The average age for diagnosis decreases from 60-64 years to 46-54 years. For women with endometrial cancer Society of Gynecologic Oncologists recommends genetic testing for the diagnosis of Lynch syndrome in the following categories:

- endometrial cancer diagnosed before 59 years;
- presence of colorectal tumors or other synchronous or methacronous Lynch-associated tumors;
- endometrial cancer with tumor-infiltrating lymphocyte, or histologically undifferentiated tumors, or tumors originated in the lower uterine segment, diagnosed for a woman under 60 years;
- one or more first-degree relative with Lynch associated tumor, with one of the cancers diagnosed under 50 years;
- endometrial or colorectal cancer diagnosed at 2 or more first or second degree relatives with Lynch associated tumors, no matter the age;
- patients with a first or second-degree relatives known to have mismatch repair gene mutations.

Determining the genetic predisposition or the genetic substrate responsible for a specific cancer type can be actually performed using usual molecular techniques[9].

The Lynch syndrome is characterized by the apparition of cancer at a young age, having usually multiple localizations and various forms especially on colon and endometrial level. The risk of developing endometrial cancer in the framework of this syndrome is equal or higher with the risk of developing colorectal cancer, Moreover there is a risk of 3-14% of developing ovarian cancer. Other localization of the cancer can be in the superior urinary tract, stomach, small intestine, and pancreas/gallbladder, cutaneous and cerebral tissue.

The Lynch Syndrome

Considering the multiple cancer localizations as part of this syndrome, the name after Dr. Henry Lynch, that has highlighted the importance of the family aggregation, is more and more frequently used as the old name of hereditary nonpolyposis colorectal cancer that tends to be abandoned. The risk of cancer as part of this syndrome also varies according to the environmental factors, age and the field that was affected[9].

The mark of the Lynch syndrome is represented of multitude of cancers. From the members of families with Lynch syndrome, 7-10% have more than one neoplastic localization in the moment of diagnosis (synchronous colorectal cancers), presenting a high risk for metachronous colorectal cancer, defined as primary colorectal tumor diagnosed more than 12 months after the diagnosis of other primary colorectal tumor, the aspect including 20-40% of the patients with Lynch syndrome. In this syndrome, the extracolonic cancers vary as frequency between 2-20%. The Muir-Torre syndrome and the Turcot syndrome are presently considered variants of the Lynch syndrome that associate the neoplastic sites defining for this sebaceous tumor, keratoacanthoma and visceral carcinoma part of this Muir-Torre syndrome, respectively brain tumors, typically gliomas, as part of the Turcot syndrome[10].

Lynch syndrome is an autosomal dominant disorder that is caused by a germline mutation in one of several deoxyribonucleic acid (DNA) mismatch repair (MMR) genes (MLH1, MSH2, MSH6, PMS2) or loss of expression of MSH2 due to deletion in the epithelial cell adhesion molecule (EPCAM) gene. It is considered that the defects of the MMR genes are present in 1/1300 person with ages between 15-74 years. The role of the MMR genes is to maintain the genome integrity by correcting errors caused by the substitution of some bases and small insertions-deletions, mechanisms that generate base mismatch errors during the DNA replication. Repairing the mismatch errors normally needs the coordinated function of some different protein-coding genes: MSH2 localized on the 2p16 chromosome, MLH1 localized on the 3p21 chromosome, postmeiotic segregation increased 1 (PMS1) and PMS1 localized on the 2q31 chromosome and respectively on the 7p22 chromosome, MSH6 localized on the 2p16 chromosome and MLH3, a gene that interacting with MLH1 but whose part in the Lynch syndrome has not been yet specified. The MLH1 mutations are responsible 32% of the Lynch syndrome cases, MSH2 for 39%, MSH6 for 15% and MPS2 detected in 14% of the total number of Lynch syndromes[8]. The terminal deletion of the EPCAM genes inactivates the neighboring MSH2 gene. The endometrial cancer risk seems to have increased especially in families with MSH2 and MSH6 mutations[9]. A defective repair follows the inactivation of both alleles of one of the genes of the MMR system. As a general rule, the patients with Lynch syndrome have a mutation present in the germ line on the level of one allele, the other being inactive by mutation, loss of heterozygosity or epigenetic inactivation by hypermethilation of the promoter. The biallelic inactivation of the MMR genes determines the genome instability due the failure to repair the mismatch DNA errors that frequently appear during the normal DNA synthesis (approximately 1 of each 106 bases). The DNA mismatch errors frequently appear in regions with repetitive nucleotide sequences names microsatellites. The main characteristic of the loss of the mismatch errors repair function on tumor level is the expansion or the contraction of these microsatellite regions, compared to the normal tissues; this genetic alteration is called microsatellite instability (MSI) and represents the molecular pathognomonic aspect of the Lynch syndrome associated cancers. The MMR system mutation determine a high mutation rate on the level of many other genes including those controlling the cell growth, of those that regulate the cell apoptosis, and also the DNA mismatch error repair genes. The accumulations of the mutations of these genes related to cancer determine the carcinogenic process of the Lynch syndrome[10].

The tumors can be tested for microsatellite instability by polymerase chain reaction (PCR), which highlights the presence of this aspect in over 30% of the tested markers of the tumor tissue (a result reported as a high level of MSI, MSI-H). The presence of MSI-H in the tumor tissue suggests the existence of the genetic defect of DNA mismatch error repair and is highly sensitive for the Lynch syndrome (90% of the tumors present MSI-H). Important is the fact that the MSH6 mutation associated cancers cannot present MSI-H, if the PCR panel does not include the mononucleotide repetitions, considering the fact that MSH6 is preferentially involved in this type of repair. The MLH1 methylation can determine in the endometrial tumors a high level of microsatellite instability through the epigenetic mechanism[11]. Unfortunately the MSI-H status cannot be used as a unique diagnostic test for the Lynch syndrome, as the specificity is very low.

The 15% sporadic colorectal cancers presenting MSI-H can be differentiated by the direct measuring of the tumor status of the MLH1 methylation or by the genetic analysis of the BRAF gene, which have a high sensitivity for sporadic forms.

The MSI-H tumors have distinctive histologic characteristics (lymphocyte infiltration, Crohn-like lymphocyte reaction, signet ring cell differentiation, medullary pattern increase) that can be used in the diagnosis presumption of the Lynch syndrome, needing subsequent genetic confirmation. Approximately 20% of the endometrial cancers are MSI positive, of which less than 5% are caused by the Lynch syndrome. In spite of the scarce specificity, the MSI testing remains one of the first steps in the identification of the individuals with Lynch syndrome. The mutations of the MMR genes result in the loss or structural alteration of the protein coded by this system[12].

From immunohistochemical point of view, using antibodies for the C-terminal head of the MMR proteins, the mutations of the MMR genes that have determined the protein alteration can be indirectly identified. The immunohistochemistry for MMR gene coding the protein compounds can be used, with or without MSI testing, as the first step in the screening protocol for individual with a high Lynch syndrome risk. The studies using immunohistochemistry for MSH2, MLH1, MSH6 and PMS2 have proved to have a predictive value virtually equal to the MSI testing, being superior to this in the detection of the PMS2 and MSH6 mutations. Due the high availability, the low cost price and the correct identification of the affected genes, the immunohistochemistry tends to be the first screening line in the identification of the Lynch syndrome, without needing the patient's informed consent, in many centers around the world[11,12].

The Bethesda criteria[13] identify, using history, individuals with Lunch syndrome - associated cancers who should undergo tumor testing for MSI. The MSI-H tumors further benefit from the genetic tests for identifying the mutations of the MMR genes. In 1990 The International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer has established the diagnosis criteria for the Lynch syndrome, criteria modified in 1999 (Amsterdam II criteria/rule 3,2,1)[14]:

- patient with three or more relatives presenting Lynch-associated cancers histologically verified, one of the relatives being of first-grade with the other 2;
- Lynch syndrome associated cancers affecting at least two generations;
- one or more diagnosed cancers before the age of 50.

Even if the Amsterdam criteria have been initially fulfilled, presently individual and family diagnosis is exclusively performed based on detecting the MMR gene mutation by molecular testing. The vastest adopted approach implies the genetic counseling given in a specialized clinic as a first step in the individual and family evaluation of Lynch syndrome suspicion. For patient with a family history that implies a high risk of suspicion, meeting the Bethesda or Amsterdam II criteria, or for patients with cancer part of the Lynch range, the family history evaluation for three generation is recommended regarding all forms of cancer, supported by histopathology reports and biopsy pieces, followed by MSI and immunohistochemistry testing of available colonic or endometrial tumors[14].

The MSI associated to the immunohistochemistry positivity for MLH1 recommends the protein called B-Raf (BRAF) mutation testing, followed by counseling and ulterior genetic testing only in the absence of the BRAF mutation.

The MSI accompanied by immunohistochemistry positive for MSH2, MSH2, MSH6, PMS2 or MLH1 in the absence of the mutation or the BRAF hypermethilation, with negative genetic testing is considered "non-informative genetic evaluation", imposing the screening of all the family members at risk, as if the family would have as proven the existence of a member with Lynch syndrome.

In the case when the tumor is not available for testing, it is recommended, if the possibility exists, the direct MMR gene testing of the family member who has developed colorectal cancer at the youngest age. The positive test imposes the genetic testing of the other family members at risk and the optimal screening according to the results of the genetic test[15].

Conclusions

The actual recommendation is that all the endometrial or colorectal cancer cases to be assessed for Lynch syndrome by MSI or immunohistochemistry or/and systematic analysis of the family history. The patients with molecular tumor studies or/and family history suggestive for Lynch syndrome must be counseled for genetic advice by a specialist in medical genetics in a specialized center for the assessment of high risk of cancer. The women with diagnosed Lynch syndrome or with suggestive family history must be notified on the risk of developing endometrial or ovarian cancer that they have. ■

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