National genetic screening for endometrial cancer

Abstract
Endometrial cancer is the most common gynecologic malignancy in developed countries, with an average incidence of 14.7/100,000 women and ranks second place after cervical cancer in developing countries, with an average incidence of 5.5/100,000. The global average incidence in 2012 was 8.2/100,000 women, representing 319,605 cases of cancer of the endometrium. The reported incidence in 2012 of cancer of the endometrium for Romania was 8.46/100,000 women, within Europe the same year average was 13.6/100,000 women. In Romania, pick the incidence occurs in the age group 60-64 years (42.8/100,000 women), the cumulative risk being 1%. According to World Health Organization predictive estimates for Romania is expected for 2015 an increase in the number of new cases by 2.92% to 10.07% for 2025 and for 2035 with 15.33%, of whom, under the age of 65 years in 2015 will be 990 new cases, in 2025 will be 986 new cases and in 2035 under this age will be 1027 new cases of cancer of the endometrium. The data for the period 2005-2015 was investigated coming from reports of family doctors, the national registry for cancer and (SIUI). Of the total of admissions for diagnosed endometrial cancer, 10% have affected women under 50 years, and 2.78% women under 40 years. Studying the National Registry for Cancer for 2005-2007, regarding new cases reported by district oncology cabinets, an average number of 108 new endometrial cancer cases/year has resulted and respectively 237 new colorectal cancer cases for women under 50. The total number is significant, representing the patients whose genetic testing is essential for defining an important high risk group for familial cancer, a fact that is universally accepted, the screening which is intended for.

Keywords: Lynch syndrome, Cowden syndrome, MMR genes, endometrial cancer

Introduction
Endometrial cancer as part of the Lynch syndrome represents 2-5% of the total of endometrial cancer cases. The average age for diagnosis as part of the Lynch syndrome is of 46-54 years compared to the average age of 60 of the general population. The women with Lynch syndrome can develop endometrial cancer before 40 years for a percent of 18% [4]. Synchronous and metachronous cancers have an unpredictable high risk of apparition as part of the Lynch syndrome; a study including 117 women with Lynch syndrome reports 14% of primary colorectal and gynecologic tumors appearing simultaneously [5,6].

Even if the information is limited regarding the efficiency of the supervision in reducing the risk of developing endometrial or ovarian cancer at women with Lynch syndrome, Cancer Genetics Consortium in agreement with National Comprehensive Cancer Network recommends as screening as part of this syndrome the endometrial biopsy by annual aspiration starting with the age of 30-35 or 5-10 before the youngest age of diagnosis of a Lynch syndrome associated cancer form in the family [6,7]. Not being able to affirm with certitude that the screening can reduce the mortality and morbidity of ovarian cancer for women with Lynch syndrome, their screening is made of gynecologic examination every year along with transvaginal ultrasound and the quantitative determination of cancer antigen (CA)-125 performed every 6-12 months starting from the age of 30-35, or 5-10 years before the youngest diagnosis age of Lynch syndrome associated cancer in the family.

The hysterectomy with bilateral adnexitomy performed for reducing the risk of developing cancer on these levels seems to be efficient [8,9], the average age for this surgical intervention being 41, after finishing the family planning. The preoperative evaluation for performing the surgical intervention for reducing the risk is comprised of endometrial biopsy, transvaginal ultrasound, CA-125 determination and high microsatellite instability (positive test)/low (negative test). Without any comparative studies existing, surgery is a definitive option implying perioperative risks and high costs, while the biopsy is a monitoring method that must be performed during the years, having a cumulative risk of infection and uterine perforation, time consuming, with significant costs [10,11,12,13].

Women with Cowden syndrome, a autosomal dominant syndrome having as genetic basis a mutation of the tumor suppressing gene PTEN manifests characteristics mucocutaneous lesions, have a high prevalence of uterine leiomyoma and a high risk to develop cancer on endometrial, breast, thyroid, colorectal and kidney level. The data regarding this
syndrome are reduced, the risk of developing an endometrial cancer during the life span is assessed to be 13-19%[14,15,16].

Combined oral contraceptive pills reduce the risk of endometrial cancer with more than 50%, according to a meta-analysis of 19 observational studies. The protective effect persists for 10-20 years after ceasing the use[17,18]. The benefit of hormonal contraceptives is caused by the progesterone component that suppresses the endometrial proliferation, the protective effect of contraceptives with exclusive progesterone content including intrauterine devices with slow levonorgestrel release (LNG) have been studied[19,20]. A national study taking place in Finland performed on 98000 women with ages between 30-49 years using LNG 20 treated for menorrhagia reports a significant decrease of the incidence of endometrial carcinoma (RR: 0.5)[21,22].

Methods

Researching for the period 2005-2013 the data regarding the reports of the family doctors, the national registry for cancer and unique integrated informational system (SIUI) of the National Health Insurance Agency, on national level, for endometrial and colorectal cancer cases.

Results

The age interval with the maximum incidence for the main diagnosis of endometrial cancer was 60-64 years, but is important to observe the fact that the presence of this pathology has an increasing progressive incidence for the age intervals of 30-34 years, 35-39 years, 40-44 years and 45-49 years. From the total of admissions for diagnosed endometrial cancers, 10% have affected women under 50 and 2.78% women under 40, the literature data observing for endometrial cancer under 40 an apparition frequency of 5%[22]. The case segment is extremely important due to the fact that according to the recommendation of the international specialized forums, the endometrial tumors appearing at women under 50 have a high risk of belonging to the hereditary cancer category and their testing for establishing the genetic diagnosis is mandatory due the individual risk of these patients, but also the family risk to develop multiple forms of cancers during their life span. Every year the average number of admissions having endometrial cancer as main diagnosis is of 4814 (a slight increase trend), and the average number of admission less than 50 year is of 505 cases. The absence of hereditary cancer from the national statistics data has imposed a thoroughness of the study on colorectal cancer cases with an apparition under 50 years raises the same suspicion degree of the genetic etiology. From the reports of the family doctors it results the fact that yearly an average number of 2493 new colorectal cancer cases for women is registered. From the study of the National Register for Cancer for the years 2005-2007, regarding the new cases reported by the district oncology cabinets it has resulted an average number of 108 new endometrial cancer cases/year and respectively 237 new colorectal cancer cases/year for women under 50. The total number is significant, representing the patients for whom the genetic testing is essential for defining an important high risk group for family cancer, a risk group which, universally accepted, screening is for. The national registry for rare disease, recently created, still not functioning, the Lynch syndrome being absent in the statistics, even if it represent 5% of the colorectal cancers and 3% of the endometrial ones, therefore approximately 334 new cases every year, young women who would benefit from investigations and genetic specialty diagnosis, also to be added descendants and relatives.

Discussions

For increasing the precious diagnosis rate of endometrial cancer we have systematized the actual criteria used to define the high-risk class of genetic cancer, for whom the screening for endometrial cancer is recommended.

Identification of the population with high Lynch syndrome risk:

Amsterdam criteria II[28]:
- at least 3 relatives with Lynch associated cancer (colorectal, endometrial, small intestine, urethral or kidney pelvis);
- one of the relatives must be of first-degree with the other two
- at least 2 successive affected generations;
- at least 1 case of diagnosed cancer under 50 years;
- familial adenomatous polyposis must be excluded from the category of colorectal cancer;
- the tumors must be histopathologically examined

The revised Bethesda criteria[29] for the MRI testing of the colorectal tumors:
- diagnosed colorectal cancer for a patient under 50 years;
- presence of the synchronous/metachronous colorectal tumor or Lynch associated, no matter the age;
- colorectal cancer with histology of high-level microsatellite instability (MSI-H) diagnosed type for a patient under 60 years (tumor-infiltrating lymphocyte, Chron-like lymphocyte reaction, mucous differentiation/seal ring, medullary increase pattern;)
- diagnosed colorectal cancer diagnosed for a patient or one or more first-degree relatives with Lynch-associated tumors, one of the cancers diagnosed under 50 years;
- diagnosed colorectal cancer for a patient with 2 or more first/second degree relatives with Lynch associated tumors, no matter the age

The SGO[30] guides regarding the assessment of the Lynch syndrome risk:
- Lynch syndrome risk >20-25% (recommended genetic testing);
- endometrial/ovarian cancer with synchronous/metachronous colorectal cancer, the first cancer diagnosed under 50 years;
- endometrial or colorectal cancer that meets the Amsterdam II criteria;
- first/second degree relatives with one mismatch repair (MMR) gene mutation diagnosis.

Lynch syndrome risk >5-10% (useful genetic testing):
- endometrial/ovarian cancer with synchronous/metachronous colorectal cancer or other Lynch associated cancer no matter the apparition age of the first cancer;
- endometrial or colorectal cancer diagnosed under the age of 50;
endometrial or colorectal cancer with two or more first/second degree relatives with Lynch associated cancers; 
- first/second degree relative that meet up the previous criteria for the risk group.

The certitude diagnosis for the Lynch syndrome is performed based on the genetic determination of the mutation of the germ line of one of the MMR gene or epithelial cell adhesion molecule (EPCAM). Due to the fact that the testing of the germ line of all the patients suspected of Lynch syndrome would be prohibitively expensive, a sequential genetic evaluation must be performed that starts with tumor testing by polymerase chain reaction for MSI (MSI-H = positive test) and/or by immunohistochemistry for the expression of the MMR genes (loss of protein coloration=positive test). The majority of experts recommends the testing by MSI and immunohistochemical of all colorectal or endometrial cancers. The MSI and immunohistochemical testing is mandatory for the following categories:
- endometrial cancer diagnosed before 50 years;
- endometrial cancer with tumor or peritumor-infiltrating lymphocyte or histologically undifferentiated tumors or with origins in the lower uterine segment diagnosed for a woman under 60 years;
- first-degree relatives of the patients diagnosed with mutations of the MMR/EPCAM genes;
- family cancer history, meeting the Amsterdam II criteria or revised Bethesda guide.

Negative MSI and immunohistochemistry infirm the belonging of the tumor to the Lynch syndrome. The MSI positive patients or with the alteration of the MMR gene expression on IHC, patients for whom the MSI and immunohistochemistry tumor testing is not available, but for whom there is a strong clinical suspicion (Bethesda criteria), and also for those that meet up the Amsterdam II criteria in the absence of tumor testing need the germ line testing to determine the MMR/EPCAM mutations.

Management of patients with Lynch syndrome includes the supervision by screening, chemoprevention and risk reducing surgery. Endometrial cancer screening consists of endometrial biopsy performed every year starting from 30-35 years or 5-10 years before the most precocious age of diagnosis of a Lynch associated cancer (HNPPC) in the family. For the patients with genetic positive diagnosis of Lynch syndrome, after finishing the family planning, the total hysterectomy with bilateral adnexectomy for risk reducing is recommended (Cancer Genetics Consortium) (Figure 1).

Cowden syndrome is a genetic condition with autosomal dominant transmission having as basis the mutation of the tumor suppressor phosphatase and tensin homolog (PTEN) protein localized on the 10q23 chromosome. The risk for developing endometrial cancer for these patients during their life span is believed to be of 13-28%, endometrial cancer cases at teenagers being reported.

Clinical criteria for the diagnosis of Cowden syndrome (adopted by the National Comprehensive Cancer Network):
- Major criteria:
  - breast cancer;
  - endometrial cancer;
  - thyroid cancer (follicular);
  - gastrointestinal hamartomas (including ganglioneuromas, excluding hyperplastic polyps ≥3);
Lhermitte-Duclos disease (adult); macrocephalia (>97 percentiles: 58 cm for women, 60 cm for men); macular pigmentation of the glans penis; multiple mucocutaneous lesions (any of the below); multiple trichilemmoma (≥3, at least one proven by biopsy); acral keratoses (≥ palm-plantar or/and acral keratotic papules); mucocutaneous neurilemmomas (≥3); oral papillomas (especially tongue and gum), multiple (≥3); biopsy proof/dermatology diagnosis Minor criteria
autistic type disorder range;
renal cell carcinoma; testicular lipomatosis; mental retardation; lipomas ≥3; glycogenic acanthosis of the esophagus ≥3; colon cancer; autistic type disorder range; oral papillomas (especially tongue and gum), multiple mucocutaneous neurilemmomas (≥3); acral keratoses (≥ palm-plantar or/and acral keratotic papules); structural thyroid lesions (adenomas, multinodular goiter); vascular anomalies (including multiple intracranial venous anomalies of development).

Operational individual diagnosis (any of the following): 1. Three or more major criteria, of which one is mandatory: macrocephalia, Lhermitte-Duclos disease or gastrointestinal hamartomas; 2. Two major criteria and 3 minor criteria. Operational diagnosis in families with one individual meeting up the individual diagnosis criteria and/or with PTEN genetic mutation diagnosis:

Conclusions
The endometrial biopsy screening is recommended starting from 35–40 years or 5 years earlier than the age of diagnosis for the first endometrial cancer case in the family. For women in menopause an annual transvaginal ultrasound is recommended.