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Endometrial cancer, Lynch syndrome and screening: Literature review

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Bárbara Barbosa dos Santos Teixeira
Specialist in Gynecology and Obstetrics, Federal University of Rio de Janeiro Institution: Clementino Fraga Filho University Hospital Address:R. Prof. Rodolpho Paulo Rocco, 255, Cidade Universitária da Universidade Federal do Rio de Janeiro, Rio de Janeiro - RJ, CEP: 21941-617
E-mail: barbarabstmeduerj@gmail.com

Luiza Marques Monteiro de Oliveira
Graduated in Medicine Institution: Federal University of the State of Rio de Janeiro (UNIRIO) Address: Av. Pasteur, 296, Urca, Rio de Janeiro -RJ, CEP: 22290-250
E-mail: luiza.mmo@icloud.com

Fábio Marchon Leão
Specialist in Gynecology and Obstetrics Institution: Hospital Federal de Ipanema Address: R. Antônio Parreiras, 67, Ipanema, Rio de Janeiro -RJ, CEP: 22411-020
E-mail: fabiomarchonleao@hotmail.com

ABSTRACT

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The incidence of Endometrium cancer (EC) has increased in recent years. Hereditary predisposition is the risk factor responsible for 5% of cases and Lynch Syndrome (LS) and the most frequent. Conversely, the cumulative risk in developing EC related to LS carriers is around 71%, behind colorectal cancer (RCC), which represents 80%. In addition, women with LS have 40 to 60% chance to develop EC, as the first clinical manifestation of this disease, behaving as a sentinel tumor. Such information serves as a timely tool for early screening in patients with family history, compatible with LS suggesting the importance of early screening for early diagnosis. In LS occurs mutations in genes germ inheritance responsible for encoding DNA incompatibility repair proteins, i.e.: hMLH1, hMSH2, hMSH6, hPMS2 and EPCAM. The understanding and change of attitude towards this finding are challenging, due to, a compreensive part of professionals in charge with this area, do not have a solid basis of the clinical-pathological characteristics of the EC related to LS. The methodology used, was a literature review, conducted through the search and collection of data in pubmed, VHL and Scielo databases ALL in English and Portuguese, published in national and international journals in the last 10 years. The selection of articles was made through a diacritical analysis, in which we relate the information and then the solutions. EC research in LS is still in the initial phase, that reduces the number of consistent studies and the level of evidence of recommendations regarding optimal screening and, therefore, conclusive early detection and treatment. The high risk of developing EC in women with LS, as well, as the parallel development of primary tumors throughout life, indicates the great value, in understanding this condition, as it directly implies the attendant attention of professionals assisting these patients. This reflects, in addition to attention, surveillance and screening through family history and screening exams.

Keywords: Cancer, Endometrial cancer, Nonpolypoid colorectal cancer, Lynch Syndrome, Tracking.

1 INTRODUCTION

It is estimated that 5% of EC cases can be attributed to a specific hereditary predisposition. LS, also known as hereditary nonpolypoid colorectal cancer syndrome (HNPCC), is responsible for most inherited endometrial cancers. Mutations in Mismatch Repair (MMR) genes, MLH1, MSH2, MSH6,

PMS2, and EPCAM, have been identified in patients with LS (RYAN et al., 2019).

LS is the most common presentation of CCRHNP when compared to Familial Adenomatous Polyposis (FAP) and accounts for 2-5% of all colorectal cancer (CRC) cases. Studies have shown significant progress in understanding LS-related CRC in terms of molecular pathogenesis, risks, genetic basis, and prevention of cancer per se.

In addition, similar studies have demonstrated, through algorithms developed for universal screening for LS in individuals affected by CRC, a significant reason for performing it. The main justification is the analysis of survival, cost-effectiveness, and efficiency in screening (WANG et al., 2013). The NSC related to LS was extensively studied in order to understand its association with the CCRHNP. Women with LS have a 40-60% chance of presenting with CS as the first clinical manifestation of the condition. From a clinical point of view, the confirmation that a CS is related to LS has the potential to indicate and influence the screening, prevention, and early detection of other cancers associated with LS (AHADOVA et al., 2018).

The objectives of this study were:

1 - Describe LS and its relevance in the care of patients with FB;

2 - To conduct a brief literature review, observing the clinical-pathological characteristics of FB associated with LS.

3 - Analyze the genetic characteristics linked to LS;

4 - Present clinical recommendations for the diagnosis of individuals with LS and, subsequently, the screening and prevention of secondary cancers.

A concise bibliographic research was carried out, intending to update this knowledge. The articles searched were separated and qualified by:

1 - Be analytical with a relevant "n";

2 - Come from recognized research centers in the academic sphere;

3 - Published in English and Portuguese;

4 - Published in national and international journals in the last 10 years;

5 - The search was performed in the Pubmed, BvS and Scielo databases.

The research was carried out in two stages. Initially, the search for bibliographies in the above-mentioned form, selection of articles through a diacritical analysis, where we relate the information and then the solutions. Finally, a text was prepared with the interpretation of the data obtained.

2 HISTORICAL

In 1895, Aldred Scott Warthin of the University of Michigan Medical School observed that his German seamstress was depressed imagining that, like members of her family, she would also develop gastric, colonic, or uterine cancer. In fact, he died of CE at an early age.

In analyzing the case of the seamstress, Warthin published in 1913 the pedigree of 10 affected family members, describing the generations affected with colon, stomach, and uterine cancer. Auditing 3,600 cancer cases diagnosed in his laboratory between 1895 and 1912, he found that approximately 15 percent of them had a positive family history of carcinoma. Hence, he concluded that there was some influence of heredity on cancer.

A similar study by the same author on another family (G) in 1925 showed a higher familial preponderance for cancers of the gastrointestinal tract and uterus. These cancers affected family members at a mean age of 37.9 years with a tendency to develop CRC (BOLAND; LYNCH, 2013).

In 1966, Henry Lynch described two families, one from Nebraska (N) and one from Michigan (M) that had similar cancer patterns involving several generations similar to the aforementioned G family. By analyzing more than 650 members of Family G, he published the article "Cancer Family 'G' Revisited" (1971) which evidenced the syndromic characteristics of this condition with an autosomal dominant inheritance pattern and an early onset age (mean onset <45 years), with CRC, FB and stomach cancer. Other similar studies describing CCRHNP were published in the mid-1980s with clinical classification schemes developed for research (SEHGAL et al., 2014).

In 1989, the International Collaborative Group on HNPCC (ICG-HNPCC) was created, which formulated a set of criteria known as the "Amsterdam Criteria" for the diagnosis of CCRHNP, to facilitate the identification of causative genes. Expanded in 1999, it incorporated extra-colonic tumors and from then on came to be known as the "Amsterdam II Criteria".

With the identification of several mutations within the MMR genes,[1] the National Cancer Institute held an international workshop on LS in Bethesda (1997), when it was created a standardized diagnostic panel of microsatellite analysis[2] (MSI)[3] in conjunction with the Bethesda Guidelines for selecting patients with CRC.

These guidelines were reviewed and published (2004) including family history and specific pathological features of CRC, such as signet ring cell features, Crohn's disease-like reaction, mucinous features, and tumor location in the right colon. There are limitations to these guidelines, as many families with LS do not meet the "Amsterdam Criteria" or the "Bethesda Guidelines". On the other hand, despite meeting such criteria or guidelines, some families do not have germline alterations in any of the MMR genes in the DNA.

In 2008, Hampel et al. enabled large-scale immunohistochemistry (IHC) to aid genetic testing.

[1] The mismatch repair (MMR) system is involved in the repair of point mutations, ensuring the fidelity of replication. It recognizes and corrects random DNA polymerase errors during the replication process, significantly increasing the accuracy of this process.
[2] Microsatellites (MS) are short, repeated sequences of DNA that have 1 to 6 base pairs. These regions are randomly distributed and most are close to coding regions.
[3] Microsatellite Instability (MSI). The absence or deficiency of the DNA repair function, more precisely the inactivation of proteins by alterations in MMR genes, results in contractions or expansions of microsatellites. When there are failures in this repair system, the errors are not corrected, resulting in the instability of microsatellites.

In 2009, the Jerusalem Workshop recommended routine MSI testing or histochemistry for all immunodiagnosed RCCs in patients under the age of 70. These recommendations were incorporated into the Assessment of Genomic Application in Practice and Prevention (EGAPP) evidence report (BOLAND; LYNCH, 2013).

3 EC EPIDEMIOLOGY

Studies on the prevalence of cancer of the uterine body ranks sixth worldwide, with the most common type being endometrial cancer. In 2018, there were 370,000 new cases, with an estimated risk of 9.9/100,000 women. About 2/3 of these cases occur in countries with a high human development index (HDI), such as North America and Central and Eastern Europe (INCA, 2019).

Obesity and a sedentary lifestyle account for 70% of EC cases (American Cancer Society, 2019) Other risk factors include: genetic predisposition, diabetes mellitus, endometrial hyperplasia, chronic anovulation, previous pelvic radiotherapy, hormone replacement, early menarche, late menopause, nulliparity, and LS.

In Brazil, uterine cancer is expected to increase the number of new cases by 6,540 for each year of the 2020-2022 triennium. This corresponds to an estimated risk of 6.07 new cases per 100,000 women. Excluding non-melanoma skin tumors, cancer of the body of the uterus ranks eighth.

Figure 1 – Proportional distribution of the ten most incident types of cancer estimated for 2020 by sex, excluding non-melanoma skin

Localização Primária	Casos	%	Homens	Mulheres	Localização Primária	Casos	%
Próstata	65.840	29,2%			Mama feminina	66.280	29,7%
Cólon e reto	20.520	9,1%			Cólon e reto	20.470	9,2%
Traqueia, brônquio e pulmão	17.760	7,9%			Colo do útero	16.590	7,4%
Estômago	13.360	5,9%			Traqueia, brônquio e pulmão	12.440	5,6%
Cavidade oral	11.180	5,0%			Glândula tireoide	11.950	5,4%
Esôfago	8.690	3,9%			Estômago	7.870	3,5%
Bexiga	7.590	3,4%			Ovário	6.650	3,0%
Linfoma não Hodgkin	6.580	2,9%			Corpo do útero	6.540	2,9%
Laringe	6.470	2,9%			Linfoma não Hodgkin	5.450	2,4%
Leucemias	5.920	2,6%			Sistema nervoso central	5.220	2,3%

*Números arredondados para múltiplos de 10.

Source: INCA (2019).

As for the distribution by geographic regions, in the Southeast Region (7.45/100 thousand), it occupies the sixth position; Midwest (5.27/100 thousand), seventh; Northeast (5.10/100 thousand), eighth; North (2.41/100,000), tenth and South (6.53/100,000), eleventh position. In 2017, there were 1,827 deaths and the crude mortality rate from uterine cancer in Brazil was 1.77/100,000.

Graph 1 – Geographical distribution of EC in Brazil

Source: INCA (2019).

A systematic review selected 53 studies and included 12,633 patients with CS. The global proportion of endometrial tumors through microsatellite instability (IMS) or immunohistochemistry (IHC) detected the deficiency in Mismatch Repair (MMR), one of the mechanisms of DNA repair, which alters susceptibility to cancer. Of women with abnormal tests, germline analyses to evaluate pathogenic variants associated with LS; The study suggested that the prevalence of LS in patients with CE is approximately 3%, similar to that of CRC (RYAN et al., 2019).

In 2020, the first report on the prevalence of LS in SC in Brazil was published. This was a study with 242 patients diagnosed with FB, with screening by IHC and IMS to detect DNA incompatibility repair deficiency or MMR, in addition to MLH1 methylation to identify sporadic cases. Ten patients (10/37, 27%) were detected with pathogenic, or probably pathogenic, germline variants, most of them in the MSH6 gene (4/10, 40%). Thus, the prevalence of LS in this cohort was at least 4.1% (ROSA et al. 2020).

In order to detect and prevent CRC early, some countries have begun screening patients with CS to identify cases of LS. As a result, they detected and treated CRC early. (DILLON et al., 2017). It is estimated that 50% of patients with LS have FB as their first manifestation. Thus, the diagnosis of LS at the time of diagnosis of FB, although not proven, may be a cost-effective approach in clinical management. Notably, because the mortality of CRC is much higher than that of CE (AHADOVA et al. 2018).

3.1 ENDOMETRIAL CANCER (EC)

FB has become a disease of increasing interest in recent decades, for different reasons. The incidence is increasing, especially in developing countries. With the increase in life expectancy of the female population, the prevalence of overweight, obesity and morbid obesity has also increased.

Therefore, it also greatly increased the risk for these patients, which are therefore the main risk factors for CS. Staging surgery is the basis of treatment and, therefore, of the staging of the disease itself.

FB has two distinct classifications: Type I and Type II, with very distinct epidemiological, demographic, and pathological characteristics. Type I, which is more frequent, results from intrinsic or extrinsic estrogenic hyperstimulation, is preceded by endometrial hyperplasia, and affects obese women in the peri- and postmenopausal periods. The most frequent histological type is endometrioid carcinoma, with less aggressive behavior. Type II occurs in older women, is not related to obesity and hyperestrogenism, does not have endometrial hyperplasia as a precursor lesion and consists of the histological types serous carcinoma and clear cell carcinoma, which have a worse prognosis.

The prognostic factors of CS are: histological type; histological grade; depth of myometrial invasion; lymph node involvement; peritoneal cytology and presence of extrauterine secondary cancer. The histological types are: endometrioid adenocarcinoma (80%), the most frequent; serous papillary and clear cell carcinoma, the most aggressive, mucinous, squamous, undifferentiated and mixed.

The histological grade represents the amount of cancer cells similar to glandular cells, i.e., cells similar to those of the endometrium (undifferentiated). The higher the grade, the fewer glandular cells are present and therefore the more differentiated cancer cells, thus being more aggressive. In grade 1 more than 95% of the tumor forms glands, in grade 2, 50 to 94% and in grade 3, the most aggressive, also called high grade, less than 50% form glands. Regarding the degree of myometrial involvement, when it affects more than 50% of the endometrium, the prognosis will be worse (NCCN, 2017).

Table 1 – Staging of the EC of the International Federation of Gynecology and Obstetrics (FIGO)

Stadium	Description
I	Tumor limited to the uterine body
WOULD	Tumor limited to the endometrium or < 50% myometrial invasion
IB	≥ 50% myometrial invasion
II	Tumor invades the cervical stroma but does not extend beyond the uterus
III	Tumor with local and/or regional extension
IIIA	Tumor involves uterine serosa and/or adnexa(s)
IIIB	Parametrial or vaginal involvement
IIIC	Metastases to pelvic and/or para-aortic lymph nodes
IIIC1	Metastases to pelvic lymph nodes
IIIC2	Metastases to para-aortic lymph nodes with or without metastases to pelvic lymph nodes
IV	Intra- or extra-abdominal metastases
VAT	Invasion of the bladder or intestinal mucosa
IVB	Distant metastases (including intra-abdominal and/or inguinal lymph node metastasis)

Source: YOSHIDA et al (2020).

Table 2 – Classification of risk groups to guide adjuvant treatment of FB

Groups of risk	Characteristics
Low	Stage I endometrioid EC, grade 1 or 2, < 50% myometrial invasion, invasion Linfovascular (-)
Intermediary	Endometrioid FB, grade 1 or 2, > 50% myometrial invasion, lymphovascular invasion (-)
High Intermediate	Stage I endometrioid FB, grade 3, < 50% myometrial invasion, regardless of the lymphovascular invasion status; Endometrioid FB, grade 1 or 2, lymphovascular (+) invasion, regardless of the degree of Myometrial invasion
High	Stage I endometrioid FB, grade 3, ≥ 50% myometrial invasion, independent lymphovascular invasion status; CE stage II; stage III endometrioid FB, without residual disease; CE serous or clear cells, or undifferentiated or carcinosarcoma
Advanced	Stage III CE with residual disease and stage IVa CE
Metastatic	CE stage IVb

Source: YOSHIDA et al (2020).

Treatment for the low-risk group is total hysterectomy with SOB. Lymphadenectomy (pelvic only or pelvic and paraaortic) may be considered for surgical staging, however, a Cochrane review (2017) showed that there is no evidence of better survival in stage I FB. Studies show increased detection of lymph node metastasis, with low false negatives, on sentinel lymph node mapping in women with disease restricted to the uterus. In more advanced stages, there is a need for a combination of surgical enlargement (lymphadenectomy, omentectomy and/or radical hysterectomy) with radio/chemotherapy and even hormone therapy.

In 2005, CE was identified as the most frequent sentinel cancer among women with LS. In 2013, based on the studies of the TCGA (The Cancer Genome Atlas), whose objective was to catalog and discover the genomic alterations that cause EC — until then classified from a purely morphological point of view (type I and type II) — it could be defined as four molecular subgroups of behaviors and natural history that were very different from each other. This opened the possibility for the molecular characterization of ECs, which enabled therapies based on the molecular profile: POLE (better prognosis), microsatellite instability, wild-type p53 and mutated p53 (worse prognosis).

The TransPORTEC[4] study team and another group called the Vancouver Project translated the molecular information into immunohistochemical profiles, with results that are very close to the molecular information and can now be incorporated into clinical practice.

In the face of so many changes in the epidemiological knowledge of FB, risk factors, diagnostic methods, surgical and radiotherapeutic treatment, and systemic treatment of FB - as well as the new

[4] International consortium that was established for translational research in high-risk ECs.

demands for knowledge that this disease is beginning to awaken in the field of human reproduction, oncogenetics, immunotherapy, among others - it requires a more intense and robust review of the acquisition of new concepts that better define the current ones.

4 THE SL

LS, or CCRHNP (Hereditary Nonpolypoid Colorectal Cancer, HNPCC), is an inherited disease with autosomal dominant transmission of genes responsible for encoding DNA mismatch repair proteins with mutations. It is characterized by an increased risk of CRC and SC, as well as other primary cancers such as renal pelvis, ovarian, ureter, and small bowel. The estimated risk of developing CRC in women is 40 to 60%, and in men it is as high as 80%. SC is the second most frequent cancer in LS, second only to CRC. However, several studies show that the risk of CE outweighs the risk of CRC. In addition, about 50% of the time it precedes CRC, behaving like a sentinel tumor (LYNCH et al. 2017).

4.1 GENETICALLY BASED

LS results from mutations in the MMR genes of DNA (hMLH1, hMSH2, hMSH6, hPMS2 and EPCAM), inherited in the autosomal dominant form. Individuals with LS inherit a non-functional allele. When subsequent loss of the corresponding allele occurs, DNA repair becomes defective in the target tissue. Germline mutations in hMLH1 and hMSH2 are responsible for more than 90% of diagnosed cases of LS (BOLAND; LYNCH, 2013).

Prior to the discovery of the genetic mutations responsible, the diagnosis of LS was based on clinical criteria. These criteria were initially named the "Amsterdam Criteria". The first criterion, or "Criterion I", was based on the aspects, clinical presentations, and epidemiological behavior of CRC. Criteria include (1) three or more relatives with LS-associated cancer, (2) two affected relatives in successive generations, or (3) one or more relatives with LS-associated cancer diagnosed before age 50 (LYNCH et al., 2017).

4.2 IDENTIFICATION OF PATIENTS WITH LS

According to Moreira et al. (2012), general guidelines aid in the suspicion of a hereditary cancer syndrome that includes early age of onset, presence of multiple and/or bilateral primary cancers, and multiple affected family members.

To assist in the specific and most efficient identification of patients at risk for LS, the Education Committee of the Society of Gynecologic Oncologists has recently published guidelines to determine which patients may have a 20% to 25% chance of being carriers of LS, for whom genetic risk assessment is recommended, and even in patients with a slightly lower risk (5 to 10%) this same genetic risk assessment may be useful (Table 3).

Chart 3 – Society of Gynecologic Oncologists: Guidelines for Genetic Risk Assessment for LS

20 to 25% chance of hereditary predisposition	5 to 10% chance of predisposition
Genetic risk assessment is RECOMMENDED	Genetic Risk Assessment Is HELPFUL
Patients with EC or CCR than Meet To revised Amsterdam criteria: ✓ At least 3 relatives with Lynch/HNPCC-associated cancer (CCR, EC, small intestine, ureter or renal pelvis) in a lineage. Patients with CE or CRC ✓ An affected individual must be a relative of diagnosed < age 50 of the other two. ✓ At least 2 successive generations must be affected. ✓ At least 1 cancer associated with HNPCC It must be diagnosed < age 50.	Patients with CE or CRC diagnosed < age 50

Source: Adapted from MOREIRA et al. (2012).

In a population-based prevalence study, Bartley et al. (2012) identified a 1.8% prevalence of germline mutations in hMLH1, hMSH2 or hMSH6 among unselected patients with FB. Landon et al. (2015) stated that two studies evaluating patients with FB under 50 years of age indicated a 9% prevalence of germline mutations in hMLH1, hMSH2 or hMSH6. One study noted that 18% of individuals with CRC and synchronous or metachronic SC had LS. However, the finding of SC and synchronous ovarian cancer does not indicate the same risk.

Lim et al. (2012) found that only 7% of a cohort of women with SC and synchronous OC met clinical or molecular criteria for LS. Each of these patients also had a previous history of a tumor associated with LS or a first-degree relative with a history of a tumor associated with LS. It was then concluded that limiting genetic evaluation to women with FB and synchronous OC who also have a family history suggestive of LS may be more appropriate than testing all women with FB and synchronous OC.

5 THE SCREENING

LS has come to be understood as the representation of various molecular entities, and even with the introduction of the revised Bethesda guidelines, up to 28% of carriers of MMR gene mutations are lost. The Amsterdam and Bethesda guidelines have been criticized for lack of specificity and sensitivity, making them difficult to implement in clinical practice (VASEN et al., 2013). Other studies have indicated that these Bethesda guidelines lose 6 to 25 percent in diagnosis in mutation carriers. It is necessary to properly document the family history through study and genetic mapping, identifying the families affected by LS. (COHEN, 2014).

Screening programs for LS tumors are available. However, protocols vary widely. The current algorithm for diagnosing LS must meet the criteria established in the Bethesda guidelines. If not met, there is no advantage in performing other genetic tests (LYNCH et al., 2017).

Some authors indicate routine screening of CRC tissue samples for MSI and MMR immunohistochemical expression (IMQ). This approach indicated better identification of mutation carriers when compared to Bethesda guidelines. The Working Group on the Evaluation of Genomic

Applications in Practice and Prevention (EGAPP) advocates screening for LS in all patients newly diagnosed with CRC to identify at-risk relatives (MOREIRA et al., 2012).

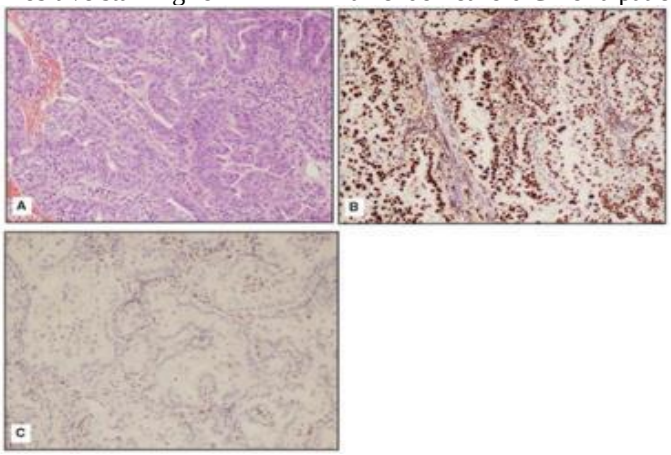
Recently, revised guidelines for the clinical management of LS recommended that all CRCs (<70 years) and all ECs (<70 years) should be tested for IHC or MSI to identify patients potentially with LS. These recommendations have been incorporated into the updated NCCN guidelines for genetic/familial risk assessment: colorectal version I.2014 (LYNCH et al., 2017).

5.1 TISSUE TEST TO IDENTIFY SL

Although family history information is important in identifying individuals who may benefit from genetic testing and genetic counseling, the presence of MSI in tumors of LS patients is a useful adjunct to screening for DNA repair germline mutations. Tissue testing (IHC or MSI analysis) has emerged as a practical first step in the assessment of women at risk for LS. This test is especially useful in cases where, due to family or personal history of cancer, individuals fall into the lower risk category of 5 to 10% risk of LS, such as individuals diagnosed with CE before the age of 50 years (STRAFFORD, 2012).

Broaddus et al. (2006) state that it is possible to analyze IHC for hMLH1, hMSH2, hMSH6 and hPMS2 and IMS in tissues. Antibodies are commercially available and there is no need for special handling of tissues or samples. For IHC tests, it is important to select non-tumor cells, as they behave as comparative controls. The images in Figure 2 show positive staining for hMLH1 in an endometrioid-type FB of a patient with LS. This tumor did not stain to hMSH2.

Figure 2 – Positive staining for hMLH1 in an endometrioid CE of a patient with LS



Source: BROADDUS et al. (2006).
Caption:
(A) Hematoxylin-eosin (HE) staining of endometrioid-type FB from a patient with SL/CCRHNP (power 10 ×);
(B) Endometrioid-like CE of a patient with SL/HNPCC with positive staining for hMLH1;
(C) EC endometrioid type of a patient with SL/HNPCC staining negative for hMSH2.

Broaddus et al. (2006) also performed MSI analyses in parallel with IHC. For MSI analysis,

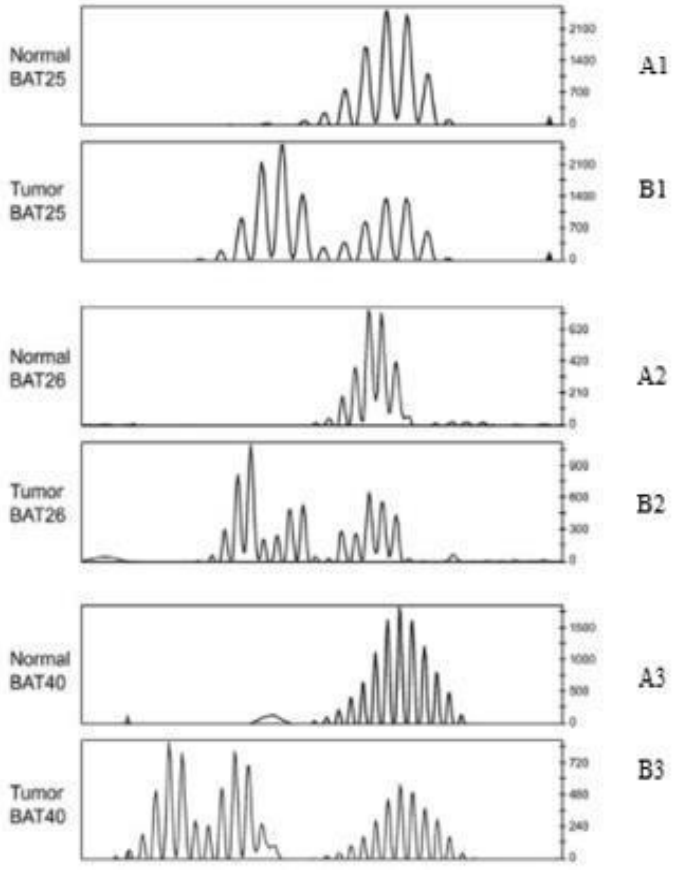
non-tumor tissues are also required, and any normal tissue from the hysterectomy specimen can be used, including the cervix, fallopian tube, or benign lymph nodes. The slides of both tissues are stained with hematoxylin-eosin (H&E). Approximately 5 to 10 slides with normal and tumor tissue are required to provide enough DNA to perform polymerase chain reaction (PCR)-based MSI analysis.

A panel of 7 markers recommended by the National Cancer Institute - NCI (BAT25, BAT26, BAT40, D2S123, D5S346, D173250 and TGF-R2) is used to detect changes in the number of microsatellite repeats in the tumor compared to normal tissue. The amplified DNA is analyzed in the ABI (Applied Biosystems) Genetic Analyzer by capillary electrophoresis.

Tumors with allelic deviation in 2 or more microsatellites in the panel are considered MSI-high. Tumors without allelic deviation in all 7 microsatellites are considered stable microsatellites. Tumors with allelic deviation in only 1 microsatellite are considered MSI-low. The significance of MSI-low in endometrial and ovarian tumors is not known.

A representative MSI chromatogram for the BAT25, BAT26, and BAT40 microsatellites is shown in Figure 3. Tumor DNA (represented by the bottom trace for each microsatellite) demonstrates an increased number of spikes compared to DNA extracted from non-neoplastic tissue from the same patient (top trace for each microsatellite). Therefore, allelic displacement is present for these 3 microsatellites, so the tumor is considered high MSI.

Figure 3 – Representative MSI chromatogram for BAT25, BAT26 and BAT40 microsatellites



Source: BROADDUS et al. (2006)

Tumor DNA (B1, B2, and B3 for each microsatellite) has a higher number of spikes compared to DNA from normal tissue from the same patient (A1, A2, and A3 for each microsatellite). Therefore, allelic displacement is present for these 3 microsatellites. If a tumor exhibits such allelic deviation in 2 or more of the 7-microsatellite panel, the tumor is considered MSI-high.

Broaddus et al. (2006) performed specific PCR in the proximal promoter region, in relation to the transcription initiation site of the MLH1 gene, -248 to -178 to detect possible methylation of this region.[5] Methylation of this region correlates with loss of expression of MLH1.Se methylation is present, the patient is likely to have a sporadic carcinoma rather than a tumor associated with LS. The MLH1 methylation assay can be performed using the same DNA extracted for the MSI analysis.

5.1.1 Genetic testing of at-risk individuals

If a hereditary cancer is identified based on family history, personal history, studies of the tumor, or a combination of both, genetic testing is important. Referral to genetic counseling may be useful for pre-test counseling and to gain insight into the implications of genetic testing (STRAFFORD, 2012).

Genetic testing categorically diagnoses individuals with LS. However, there are families that meet the clinical criteria for LS, but certain specific mutations cannot be identified (WEISSMAN et al., 2012). Genetic testing for LS is only available for mutations in hMLH1, hMSH2, or hMSH6 and is costly. Since the prevalence of LS does not exceed 5%, it may not be economically reasonable to test all patients with CS.

After tissue testing, a targeted approach to genetic testing can be performed. For example, a patient with a high MSI tumor and loss of hMSH2 by IHC analysis may have tests focused only on the hMSH2 gene. If a specific germline mutation in one of the DNA MMR genes is identified, at-risk family members can also be evaluated for the same mutation, which reduces the cost (STRAFFORD, 2012).

Several guidelines related to surveillance and screening of familial CRC have been proposed, such as the National Comprehensive Cancer Network (NCCN) guidelines. Gene mutations germline lesions are detected in up to 80% of LS cases, despite meeting the Amsterdam criteria and showing high MSI/loss of MMR protein expression (COHEN, 2014).

6 THE CE IN SL

6.1 IDENTIFICATION OF LS IN PATIENTS WITH EC

Diagnosing individuals with LS is very important, as cancer patients with a germline mutation in one of the genes in the MMR system associated with LS are at risk of developing a second primary

[5] Fixed location of the gene along the chromosome.

malignancy. In addition, once a specific mutation has been identified, family members of affected individuals can be tested. Thus, identifying a specific genetic mutation in a patient with CE would allow family members to undergo predictive genetic testing targeting the same mutation (WOLF et al., 2013).

In a series of 117 women from families with LS and a history of CRC and CE or CO, 16 had a synchronous diagnosis of CRC with SC or with CO and 49% were first diagnosed with CRC. This underscores the need for gynecologic gynecologists and oncologists to take an active role in identifying LS among their patients (WOLF et al. 2013).

Because proctologists, oncologists, and gastroenterologists have historically identified individuals with LS, the previous emphasis on establishing guidelines to assist specialists in identifying patients with LS has focused on patients with CRC. The Bethesda criteria define criteria to aid in the identification of patients with LS (KAYA et al., 2017). As more evidence accumulates, it is becoming increasingly clear that professionals dealing with patients with SC need to understand the importance of LS.

6.1.1 Clinical and Pathological Outcomes in LS-Associated FB

There are no concrete data comparing the prognosis among women with associated FB SL with Sporadic Cancer (CESP). Banno et al. (2013) reported a series of 125 women with CE who met the Amsterdam I or II criteria. The mean age at diagnosis of FB was 48 years, ranging from 27 to 72 years, and 57% of the cases occurred in women under 50 years of age, and 98% in women under 65 years of age. The overall survival rate was high, with only 12% of patients dying as a result of their FB. However, 61% developed a second primary cancer, and the majority (54 out of 75) were carriers of CRC. In 15% of these women, more than two primary cancers were also diagnosed.

Another survival analysis performed in a case-control study of 50 women with LS-associated CE (based on mutation analysis or meeting criteria Amsterdam II) matched to sporadic cases by age at diagnosis and FIGO6 stage showed no significant difference in tumor histology. Most tumors were endometrioid adenocarcinoma (92% for the study group and 88% for the control group). The overall cumulative 5-year survival rate was 88% for patients with LS-associated FB and 82% for patients with sporadic FB ($p = 0.59$) (TANGJITGAMOL; KITTISIAM; TANVANICH, 2017).

Although there is consensus that CRCs with high MSI are associated with a more favorable prognosis, the clinicopathologic impact of MSI in CE is unclear. The implication for tumors with high MSI resulting from LS is even less clear, as most studies are conducted in patients with sporadic tumors with high MSI (POWELL, 2017).

A retrospective study in 473 patients with CE classified 93 (20%) of the tumors as MSI-high. Disease-free survival was better compared to MSI-negative tumors (hazard ratio [HR] = 0.3; 95%

confidence interval [CI] = 0.2–0.7) (CUI et al., 2020). Li et al. (2020), in a small series of 65 cases of stage I and II sporadic endometrioid-type FB, found 11 of the 65 cases with high MSI.

There are conflicting reports on the association of SC with high MSI in relation to grade, stage, and clinical outcome. While some studies do not associate disease-free survival, MSI status, or negative prognosis for women with tumors with high MSI, 19 studies nevertheless showed better survival (KANOPIENE et al., 2014)

When compared with microsatellite-stable (MS) cases, tumors with high MSI were significantly more likely to be poorly differentiated (50% vs 9%; p = 0.003). The 5-year disease-free survival rate of high MSI cases was 63% compared to 96% for MS controls (p = 0.0004). Arabi et al. (2019) analyzed 446 cases of CE prospectively collected and found no association between endometrioid-like CE with high MSI and disease-free survival (HR = 0.951; 95% CI = 0.554–1.635) or overall survival (HR = 1.011; 95% CI = 0.688–1.48).

For individuals with documented hMLH1 and hMSH2 germline mutations, the lifetime risk of EC is estimated to be between 40 to 60%. One study specifically evaluated the risk of cancer in women with hMSH[6] mutations. Cumulative risk of endometrial cancer was 71% at 70 years of age. The risks of other cancers in LS are lower and include cancers of the renal pelvis, ovarian, stomach, small intestine, and ureter (VASEN et al., 2013).

6.2 COMPARING THE CESP WITH THE CE OF THE SL

6.2.1 Clinical and Histological Comparison of LS of high MSI versus CESP

Most research on CE with high MSI has focused on sporadic tumors, so the relevance to LS has not been well established. Broaddus et al. (2006) compared 3 groups with different pathological characteristics: (A) 26 cases of CESP with high MSI; (B) 42 cases of CESP diagnosed under the age of 50 years and (C) 50 cases of associated CE à SL and with high MSI. In the series (C) with LS, 78% were diagnosed as stage I, 10% as stage II, and 12% with stage III or IV disease.

Compared to CESP with high MSI and CESP cases under 50 years of age, groups (A) and (B) there was no significant difference in myometrial invasion, presence of lymphovascular space invasion and staging.

The histological subtype of the tumors proved to be the most striking difference between these three groups. Two groups—(B) the sporadic group of women under 50 years of age and (A) the group of sporadic MLH1 methylation—were almost entirely composed of tumors with endometrioid histology (41/42, 97.6%, and 25/26, 96.2%, respectively). However, the endometrioid type in CS associated with LS (C) accounted for only 43/50 (86%), with the remainder distributed in serous

[6] International Federation of Gynecology and Obstetrics (FIGO): surgical staging of FB that includes study of the extent of disease in the uterus, depth of myometrial invasion, cytology of peritoneal fluid and pelvic and para-aortic lymph nodes.

papillary carcinoma, clear cell carcinoma, and malignant mixed Müllerian tumors.

Although in the general population, non-endometrioid FB is typically diagnosed in older women, with a mean age of 65 to 68 years, the mean age of diagnosis of non-endometrioid tumors in patients with LS in this study was 46.4 years, similar à mean age at diagnosis of all FBs in LS (46.8 years). Interestingly, all of the non-endometrioid tumors in this study occurred in patients with hMSH2 mutations. Together, almost 25% of patients with LS had pathological findings for which radiotherapy or adjuvant chemotherapy would be indicated (BROADDUS et al., 2006).

7 SCREENING AND PREVENTION FOR INDIVIDUALS WITH LS

The diagnosis of LS in cancer patients and their relatives who have not yet developed a malignancy is important so that screening and individual prevention can be performed. Lindor et al. (2016) compiled a review of recommendations for the care of individuals with LS (Chart 4).

Table 4 – Recommended screening and prevention options for women with LS

INTERVENTION	RECOMMENDATION	*FOLLOW-UP*
Colonoscopy	From 20–25 years or 10 years earlier the age of the youngest individual with Diagnosis of cancer in the family. For MSH6 families, start at 30 Years	Every 1–2 years
Endometrial sample	From 30–35 years old	Annual
Transvaginal Ultrasonography (UTV)	From 30–35 years old	Annual
Urinalysis with cytology	From 25–35 years old	Every 1–2 years
History and examination	From the age of 21	Annual
Hysterectomy with Salpingoophorectomy bilateral (SOB)	Discuss as a prophylactic option after Full offspring	*

Source: LINDOR et al. (2016).

* Author's note: In this case, patients undergoing hysterectomy and prophylactic SOB should be followed up according to the needs linked to the remaining organs and that follow-up is already indicated.

Patients with LS-associated cancer are at high lifetime risk for a second malignancy and should be counseled as to available screening and preventive measures. For example, survivors of LS-associated CE should undergo CRC screening. Similarly, women with LS who present with CRC as a

sentinel tumor should be guided by FB screening.

UTV, endometrial biopsy, or hysterectomy with prophylactic SOB may be offered if fertility is no longer desirable. Family members who have not yet been diagnosed with cancer should undergo screening for CE and CRC, and may also benefit from hysterectomy with prophylactic SOB (LINDOR et al., 2016).

7.1 CE SCREENING

The data for FB screening are not as convincing for several reasons: low prevalence of the disease in the general population; presence of early symptoms, such as vaginal bleeding; and high survival rates for early disease. There are no CE screening programs for the general population, so basic data on sensitivity and specificity for screening in the general population are not available (MEYER; BROADDUS; LU, 2009). As an example, Cornou et al. (2016) evaluated UTV and endometrial thickness measurement in high-risk populations and reported that screening had a high rate of false-positives.

Meyer et al. (2019) looked at 41 women (35 premenopausal and 6 postmenopausal) diagnosed with LS by genetic mutation or meeting the Amsterdam criteria. The study analyzed annual UTVs and serum CA-125 level for screening for gynecologic malignancies. After a mean follow-up of 5 years, 17 out of 179 UTVs (9.5%) suggested further evaluation by endometrial sampling. From this, only 3 premalignant lesions were discovered (17.6%). An incidental FB was detected after the manifestation of clinical symptoms (MEYER; BROADDUS, LU, 2009).

Similarly, Helder-Woolderink et al. (2013) conducted a UTV screening study in women with LS or descendants of families with criteria for LS. The study period included 825.7 years of risk. Only two cases of EC have been reported; both with symptoms, as opposed to that identified in the triage UTV. We did not find a study evaluating the efficacy of prospective endometrial biopsy as an isolated screening tool for women with LS.

However, Lu & Daniels (2013) conducted a study on the combination of endometrial and ultrasound sampling in 175 women with germline mutations in MLH1, MSH2 or MSH6. Although there was no significant difference in long-term outcomes – in the 11 patients with CE detected by screening compared to 83 women from the same families who were diagnosed with CS detected by symptoms – the study revealed a reduction in stage at diagnosis, with 7% of women in the surveillance group having stage III/IV disease vs 17% of women who had symptoms.

In summary, despite the lack of evidence from current screening methods for CS, women with LS have an increased risk of CS and usually develop it at a younger age, at which stage it may be more difficult to recognize bleeding as a warning sign.

In addition, UTV can be useful in identifying ovarian abnormalities since these women also

have a lifetime risk of CO of 6 to 12%.

As such, tracking is a reasonable option. For these reasons, UTV and endometrial biopsy are currently offered for women with LS and recommended annually for women aged 30 to 35 years. This recommendation is based on expert consensus, but given the scarcity of data, further studies evaluating ultrasound, endometrial biopsy, or studies evaluating the possibility of including new screening techniques for CE are needed (HELDER-WOOLDERINK et al., 2013).

7.2 CRC SCREENING

Colonoscopy is the best screening method for CRC. Perrod, Rahmi, & Cellier (2021) reported that individuals from families with LS who underwent prospective screening (colonoscopy or barium enema) had a 62% reduction in the incidence of invasive CRC compared to individuals from the same families who did not receive routine screening. Subsequent follow-up showed that the group with prospective CRC screening also reduced mortality by approximately 65%.

Current recommendations for screening for CRC in individuals with known or suspected mutations is colonoscopy every 1 to 2 years, starting at the age of 20 to 25 years (or 30 years in families with known hMSH6 mutations) (WELLS; WISE, 2017). The age to start screening is higher for families with hMSH6 mutations. Evidence suggests that the age of onset of such individuals is, on average, 10 years later than with mutations in the other genes associated with LS (PERROD; RAHMI; CELLIER, 2021). In addition, most of the data on the incidence of CRC and the reduction in mortality after screening in this high-risk population are collected using colonoscopy for screening, which justifies the consolidation of this test (WELLS; WISE, 2017).

8 PROPHYLACTIC SURGERY

Schmeler et al. (2006) confirmed the efficacy of prophylactic hysterectomy in reducing the incidence of CE in a cohort of women with documented germline mutation in one of the DNA mismatch repair genes associated with LS. In this study, 61 women who underwent prophylactic hysterectomy were matched with 210 women who did not undergo risk-reduction surgery. None of those who underwent prophylactic hysterectomy developed FB compared with 33% of the women in the comparison group. Thus, women with LS should undergo hysterectomy and prophylactic SOB as a reasonable prevention strategy.

The mean age of CE diagnosis in patients with LS is 50 years. Because individuals with LS are at higher risk of CE at a younger age than the general population, it is recommended that prophylactic surgery be performed after the woman no longer desires fertility (ETCHEGAY et al., 2015). After the pregnancy is complete, women can have a traditional laparotomy (abdominal hysterectomy) or a laparoscopic one. (SCHMELER et al., 2006). In addition, LS-positive women with CRC may choose

to have this procedure in combination with colon surgery (KALAMO et al., 2020).

Because of the risk of occult malignancy in the endometrium or ovaries, at the time of prophylactic surgery, preoperative endometrial biopsy should be performed and, if necessary, staging, surgical support with an oncological surgeon should be arranged. In addition, intraoperative pathological analysis of the endometrium and ovaries is considered advantageous (Schmeler et al., 2006).

9 DISCUSSION

Although FB is less prevalent in our country, unlike countries with a high HDI, there is a trend towards an increase in new cases on a global scale, largely due to the increasing increase in obesity and sedentary lifestyle in the population, which are marked risk factors that have been proven to be important and linked to the disease. However, these factors have a greater association with CESP, whose pathophysiology is associated, in most cases, with hyperestrogenism, resulting from the peripheral conversion of androstenedione into estrone, which in obese women comes, on a large scale, from adipose tissue.

Contrary to the prevalence of CESP, LS CS corresponds to 3% of all EC cases. Its pathogenesis results from the mutation of germline genes, inherited in an autosomal dominant manner, whose function is to encode enzymes responsible for the error repair system of genetic sequencing. As a result, the function of correcting the modified DNA is lost, not eliminating the formation of atypical cells, which multiply with errors and generate several primary tumors. The most common are SCC and CRC and, in turn, the least prevalent are OC, renal pelvis, and stomach.

Women with LS are at high risk for SC in addition to other primary tumors throughout their lives. Thus, it is essential that in patients with FB there is reasonable suspicion when obtaining information from personal and family history when evaluating, so that an adequate and timely diagnosis can be made. The opposite should also be considered, women in usual gynecological follow-up should undergo a detailed anamnesis to evaluate suspicions worthy of investigation.

Although the prevalence of LS in patients with SC is small, 6 out of 10 patients with LS will have SC. This highlights the importance of the need for active surveillance in patients with a diagnosis or family history of tumors that meet the criteria for LS. The relative prevalence of CRC is higher than that of CE. On the other hand, CS, as it is a pathology exclusively related to the female sex, its absolute proportion is slightly lower. However, some studies have already shown that this proportion exceeds that of CRC in LS in female patients.

In addition, unlike CESP, LS FB is more frequent in women at an earlier age. Lynch's SCC often behaves like a sentinel tumor in individuals under 50 years of age, in more than half of the cases, a phase in which the woman may be still in the menacme. Therefore, abnormal uterine bleeding, one

of the main signaling symptoms of FB, may not be noticed or even confused with other causes more frequent in this age group, unlike the postmenopausal woman, in which the appearance of vaginal bleeding leads her to seek medical attention. This disturbs the diagnosis, as it makes it more difficult or delayed, increasing the chance of disease progression, leading to a late staging at the time of diagnosis, which aggravates the condition and prognosis.

It should be noted that although endometrioid FB, or type 1, is the most prevalent in ESCs, in LS it greatly reduces in proportion, to the detriment of more aggressive subtypes, such as serous and clear cell subtypes, which increase slightly in prevalence in this population, especially in those with hMSH2 mutations. The increase in the more aggressive histological subtypes and the difficulty of diagnosis in the face of confounding factors, due to the precocity of the age (mean of 46 years) at the onset of LS in relation to other types of LS cancers, leads to and corroborates the need to implement consistent protocols regarding screening, screening and the implementation of prophylactic measures of FB in patients with LS.

Some prophylaxis and screening measures evaluated in the literature and determined in some protocols based on expert consensus (level D) consider surgical prophylaxis after complete offspring (HTA and SOB); in the screening, there are UTVs alone or associated with endometrial biopsy. Studies have shown that screening with UTV plus endometrial biopsy, although there is no significant long-term difference, reduces the stage of FB at the time of diagnosis. Thus, comparatively, UTV with additional biopsy may be useful means for early diagnosis, which would allow, in addition to increasing life expectancy, less invasive and aggressive treatments. This data contributes to the reduction of severity and consequent surgical complications. In addition, it reduces the need for adjuvant therapy (chemotherapy and radiotherapy) - a treatment that is current in the most advanced endometrioid stages and in type 2 subtypes (serous and clear cell) - therefore, with harmful effects that are known to add physical sequelae and reduce quality of life, including sexual quality. UTV alone was not efficient for the early screening of asymptomatic FB, although it showed acceptable detection of premalignant lesions. Endometrial biopsy alone has not been shown to be effective in screening.

In spite of this, studies related to SC in LS are scarce, limited, and often have a small "n" compared to the number of studies and evidence in the literature regarding CRC in LS, especially with regard to screening, prevalence, and histopathological characteristics in LS SC. Regarding CRC screening, colonoscopy is consolidated, first because it has been shown to be effective and because most studies have focused on this screening method. Similar to CRC screening, the prospective analysis of CE screening can be a useful tool. However, studies that indicate the best form of evaluation need to be carried out looking for a considerable 'n' in spite of the other current studies.

The diagnosis of LS is well established in the literature and has well-established guidelines to aid the diagnosis of suspicion. The most recent are the Amsterdam II and Bethesda criteria, which

consist of the evaluation of the familial pedigree, the latter considering the histological study of the tumor. These tests provide an intermediate step before performing germline mutation analysis in the evaluation of individuals with LS-related malignancies. They can rule out LS in these patients, simplify and reduce the costs of genetic testing by targeting specific genes in individuals with positive results. Identifying a specific genetic mutation in the index case would allow your family members to undergo predictive genetic testing targeting the same mutation, which makes the process less costly.

In addition, because it behaves like a sentinel tumor in more than 50% of LS cases, confirmation of LS at the time of FB diagnosis may be a cost-effective approach in clinical management. Notably, because the mortality of CRC is much higher than that of CE.

The diagnosis of LS offers the opportunity to use screening and prevention strategies that can decrease the incidence and mortality of associated cancers. Further research is needed to indicate prevention strategies and to evaluate, as mentioned above, the effect of prophylactic surgery on survival. In the meantime, we should recommend that individuals diagnosed with LS be advised to follow current screening recommendations, based on expert consensus, and have the option of prophylactic surgery.

Although studies by several international groups are focusing on LS-related ECs, research on this entity continues to seek the necessary knowledge in order to obtain the greatest efficiency in the screening, treatment, and follow-up of these patients. There is a real lag, with prejudice in the clinical-pathological diagnosis of CS in LS due to the information, apprehension of renewed and current genetic concepts, as well as the clinical-pathological characteristics of FB related to LS.

It is very likely that gynecological cancer will predominate in the near future. Therefore, this disease can no longer be seen as it has been until then.

10 CONCLUSION

Although LS and CRC in LS remain historically and permanently studied and well-evidenced diseases, their presence in the literature and the focus on CS research in LS is still in the embryonic phase. This is due to the small number of consistent studies and the low level of evidence of recommendations regarding optimal screening, and therefore conclusive early detection and treatment.

Studies should be encouraged for a better understanding of this entity. The discrepancy in the quality and quantity of information between CRC and CE in SL shows how far research in the field of gynecology oncology is. Consensuses already show a prognostic association of MSI in CRC, on the other hand, this information is not clear in the SC, which corroborates the need for more equitable studies.

Considering the high incidence rate, early age of presentation, in relation to other primary cancers in LS — which enables the early diagnosis of both SC itself and other cancers in LS as a

familial index case — identifying a specific genetic mutation in a patient with SC would allow family members to undergo predictive genetic tests directed to the same mutation.

Despite the lack of evidence in the literature, until a more consistent protocol is established, showing efficiency and cost-effectiveness, patients with LS need to be informed about the possible forms of screening and their limitations, as well as to be well informed about the role of prophylactic surgery. Although studies have described a high rate of false-positives in the isolated screening of endometrial thickness measurement in high-risk populations, UTV and endometrial biopsy associated with it showed a reduction in the stage of FB at the time of diagnosis. Although they are methods based on expert consensus, they are currently offered to women with LS and recommended annually in those aged 30 to 35 years.

In addition, so far, the synchronicity of CO and EC are not sufficient to justify genetic testing of LS, unless there is a positive family history.

Given the scarcity of data, further studies evaluating ultrasound, endometrial biopsy, or studies evaluating the possibility of including new screening techniques for CE are needed. The construction of these measures aims, above all, at the consolidation of public policies, in order to offer society a model capable of improving diagnosis by screening, treatment, and consequently, survival and quality of life for individuals affected by this condition.

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