Endometrial cancer and Lynch syndrome: similarities and genetic determinism

Abstract

Introduction. *Lynch syndrome (LS), which was formerly referred to as hereditary nonpolyposis colorectal cancer (HNPCC), is a type of inherited disease that is autosomal dominant in nature. This condition is caused by the presence of germline pathogenic variants (PVs) in the mismatch repair (MMR) genes. MMR's primary function is to maintain genomic stability by repairing mismatches that arise during DNA replication. The malfunction of MMR can lead to changes in the length of a microsatellite DNA called microsatellite instability (MSI) and increase susceptibility to tumors. There are two types of Lynch syndromes: type I Lynch syndrome and type II Lynch syndrome, based on the location of the tumors. The most prevalent extraintestinal sentinel cancer of LS is referred to as Lynch syndrome-associated endometrial cancer (LS-EC). Women with Lynch syndrome have a likelihood of 40-60% of developing endometrial cancer as their initial malignancy. LS-EC is a sentinel cancer of Lynch syndrome, indicating the possibility of the development of other LS-associated cancers in the future. Therefore, early screening and preventative strategies are necessary to reduce the morbidity and mortality caused by cancer. This article presents an overview of the research progress on LS-EC, encompassing genetic alterations, clinicopathological features, screening, diagnosis, surveillance, prevention and therapy.* ***Materials and method.*** *A review of the literature was performed regarding the current status of knowledge of Lynch syndrome-associated endometrial cancer, along with methods for diagnosis, screening and prevention of cancers.* ***Results.*** *For women who have Lynch syndrome, the estimated lifetime cumulative risk of developing endometrial cancer is between 40% and 60%. There is no existing evidence that indicates an advantage in survival for individuals who are at equal or higher risk of developing colorectal cancer, compared to those who have other forms of cancer. When comparing these cases, there is a connection between Lynch syndrome and an increased risk of endometrial cancer. The provision of sporadic cases can be achieved through a combination of medical history that pertains to both the family and the individual, as well as tumor testing. The current state of gynecologic cancer research has provided an effective foundation for the diagnosis of Lynch syndrome in women who have been diagnosed with endometrial cancer. The guidelines for screening women with Lynch syndrome entail a yearly procedure of endometrial sampling and transvaginal testing. It is recommended to begin ultrasonography screenings between the ages of 30 and 35 years old.* ***Conclusions.*** *The clinical implications of diagnosing Lynch syndrome in patients with endometrial cancer are significant. Decreasing the probability of certain outcomes can be achieved through screening and prevention practices for both individuals and their families.*

Keywords: *Lynch syndrome, endometrial cancer, prevention, screening*

Rezumat

Introducere. *Sindromul Lynch (SL), denumit anterior cancer colorectal ereditar nonpolipozic (HNPCC), este un tip de boală ereditară care este de natură autozomal dominantă. Această afecțiune este cauzată de prezența variantelor patogene ale liniei germinale (PV) în genele de reparare a nepotrivirii (MMR). Funcția principală a MMR este de a menține stabilitatea genomică prin repararea greșelilor care apar în timpul replicării ADN-ului. Funcționarea defectuoasă a MMR poate duce atât la modificări ale lungimii unui ADN-microsatelit, denumit instabilitate microsatelitară (MSI), cât și la creșterea susceptibilității la tumori. Există două tipuri de sindrom Lynch: sindrom Lynch de tip I și sindrom Lynch de tip II, în funcție de localizarea tumorilor. Cel mai răspândit cancer extraintestinal santinelă al SL este reprezentat de cancerul endometrial asociat sindromului Lynch (LS-EC). Femeile cu sindrom Lynch au o probabilitate de 40-60% de a dezvolta cancer endometrial ca malignitate inițială. LS-EC este un cancer santinelă al SL, indicând posibilitatea dezvoltării altor tipuri de cancer asociate sindromului Lynch în viitor. Prin urmare, screeningul precoce și strategiile preventive sunt necesare pentru a reduce morbiditatea și mortalitatea cauzate de cancer. Acest articol reprezintă o privire de ansamblu asupra progresului cercetării privind LS-EC, cuprinzând modificări genetice, caracteristici clinicopatologice, screening, diagnostic, supraveghere, prevenire și terapie.* ***Materiale și metodă.*** *A fost efectuată o trecere în revistă a literaturii de specialitate cu privire la stadiul actual al cunoștințelor despre cancerul endometrial asociat sindromului Lynch și la metodele de diagnostic, screening și prevenire a cancerelor. Strategia a implicat folosirea unor cuvinte-cheie precum sindrom Lynch, cancer endometrial, prevenire și screening, cu selecția articolelor, descrierea narativă a datelor obținute și citarea articolelor studiate.* ***Rezultate.*** *Pentru pacientele cu sindrom Lynch, riscul cumulat estimat pe parcursul vieții de a dezvolta cancer endometrial se situează între 40% și 60%. Nu există dovezi existente care să indice un avantaj în supraviețuire pentru persoanele care prezintă un risc egal sau mai mare de a dezvolta cancer colorectal, în comparație cu cei care au alte forme de cancer. Când se compară aceste cazuri, există o legătură între sindromul Lynch și un risc crescut de cancer endometrial. Furnizarea de cazuri sporadice poate fi realizată printr-o combinație a istoricului medical, care se referă atât la familie, cât și la individ, precum și prin testarea tumorii. Nivelul actual al cercetării cancerului ginecologic a oferit o bază eficientă pentru diagnosticul sindromului Lynch la femei care au fost diagnosticate cu cancer endometrial. Ghidurile pentru screeningul pacientelor cu sindrom Lynch presupun o procedură anuală de prelevare a probelor endometriale și o ecografie transvaginală. Se recomandă începerea examinărilor ecografice între 30 și 35 de ani.* ***Concluzii.*** *Implicațiile clinice ale diagnosticării sindromului Lynch la pacienții cu cancer endometrial sunt semnificative. Scăderea probabilității anumitor rezultate poate fi obținută prin screening și practici de prevenire, atât pentru pacienți, cât și pentru familiile acestora.*

Cuvinte-cheie: *sindrom Lynch, cancer endometrial, prevenire, screening*

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Submission date: 26.09.2023
Acceptance date: 7.10.2023

Cancerul endometrial și sindromul Lynch: asemănări și determinism genetic

Suggested citation for this article: Botea R, Suciu N, Piron-Dumitrașcu M, Iacoban SR, Crețoiu D, Suciu ID. Endometrial cancer and Lynch syndrome: similarities and genetic determinism. Ginecologia.ro. 2023;41(3):31-36.

Introduction

Lynch syndrome (LS) is an autosomal dominant disorder that is inherited and caused by pathogenic germline (PV) variants in mismatch repair (MMR) genes[1]. Lynch syndrome-associated endometrial cancer (LS-EC) is the most common extraintestinal sentinel cancer caused by germline PVs in the MMR genes, which include MSH2, MLH1, PMS2 and MSH6[1]. The clinicopathological features of LS-EC consist of early onset, endometrioid carcinoma, lower BMI, and lower uterine segment involvement[1]. The detection, diagnosis, surveillance, prevention and treatment of LS-EC have made significant progress[1].

Several studies recommend universal LS screening for endometrial cancer (EC) patients, and the screening is based on a combination of traditional clinical criteria and molecular techniques[1]. These techniques include MMR-immunohistochemistry (MMR-IHC), gene sequencing, microsatellite instability (MSI) testing, and MLH1 promoter methylation testing[1]. Prevention strategies include hysterectomy and bilateral salpingo-oophorectomy and chemoprevention with exogenous progestogens or aspirin[1]. Recent studies have demonstrated the benefits of immunotherapy for LS-EC[1]. NCCN guidelines recommend pembrolizumab and nivolumab for patients with high microsatellite instability (MSI-H)/mismatch repair deficiency (dMMR).

In 1913, Warthin initially identified Lynch syndrome or hereditary nonpolyposis colorectal cancer in a family that was more prone to develop colon, stomach and endometrial cancers[1,2]. In 1966, Lynch reported similar findings in two large families[1,3]. Lynch syndrome is an autosomal dominant disorder that results from the presence of germline inactivating mutations in one of four DNA mismatch repair (MMR) genes: MLH1 (mutL 1 homolog), MSH2 (mutS 2 homolog), MSH6 (mutS 6 homolog), and PMS2 (postmeiotic segregation increased 2)[1,4,5]. Another cause of LS is thought to be the deletion of the 3' end of the EPCAM (epithelial cell adhesion molecule) gene, which is upstream of MSH2 and leads to an epigenetic silencing of MSH2[1,6,7]. The absence or malfunction of MMR mechanisms can lead to an increase in microsatellite instability (MSI) due to an error-prone DNA replication process[1].

According to statistics from 2013, cancer diagnoses will exceed 1.6 million in the United States of America, with more than 500,000 individuals succumbing to the disease[1,8]. Among the most frequently diagnosed cancers there are colorectal cancer (CRC) and endometrial cancer, with over 100,000 and 50,000 new cases, respectively, resulting in 50,000 and 8000 cancer-related deaths[1,8]. In the United States, CRC is the second most common cause of cancer-related mortality[1,9]. Roughly 30% of CRCs are believed to have a hereditary component, which can manifest as one of the well-known colon cancer susceptibility syndromes. Lynch syndrome, one of these genetic disorders, is responsible for 3-5% of all CRCs and 2-3% of ECs[1,10].

The most frequent type of cancer that LS patients experience is colorectal cancer, and this high incidence rate has necessitated the screening of all CRCs for LS[1,5]. Lynch syndrome is also typified by extracolonic cancers, with endometrial and ovarian cancers being the most prevalent[1,5]. Women diagnosed with LS have a higher chance of experiencing EC as their initial cancer, with a 40% to 60% probability, and a greater cumulative lifetime risk of developing endometrial cancer than colorectal cancer[1,5,6]. The incidence of LS in unselected groups of patients with EC is around 2% to 3%, although this could be an underestimation, because certain populations may possess varying mutation frequencies, and some mutations' clinical significance is still uncertain[1,10]. The incidence of mutations in MMR genes for EC is 50% to 66% in MSH2, 24% to 40% in MLH1, 10% to 13% in MSH6, and under 5% in PMS2[1,10].

Lynch syndrome, formerly known as hereditary nonpolyposis colorectal cancer (HNPCC), is a genetic disease that is inherited in an autosomal dominant manner[11]. The disease is caused by pathogenic germline (PV) variants that are present in mismatch repair (MMR) genes[11]. MMR is responsible for maintaining genome stability by repairing mismatches generated by DNA replication[11]. When MMR does not work properly, it can lead to changes in the length of microsatellite DNA, which is called microsatellite instability (MSI)[11]. This instability can increase the susceptibility to tumors.

Lynch syndrome is divided into two types, depending on the location of the tumor. In Lynch syndrome type I, tumors are confined to the colon or rectum, while in Lynch syndrome type II, tumors may occur in extraintestinal tissue[11]. These tumors may include endometrial cancer, ovarian cancer (OC), breast cancer, cancers of the urinary tract, stomach, hepatobiliary tract, small intestine, and brain[11]. The risk of endometrial cancer in women with hMSH6 mutations, evaluated in a dedicated study, revealed a cumulative risk of 71% by the age of 70 years old[38]. People with Lynch syndrome have a lower risk of developing other cancers, such as stomach, small bowel, ovarian, renal pelvis and ureteral cancers, in addition to colorectal cancer, especially after the age of 50 years old[38].

The cause of Lynch syndrome can be attributed to mutations in DNA. Genes responsible for mismatch repair, namely hMLH1, hMSH2 and hMSH6, are crucial in maintaining genomic stability[38]. Lynch syndrome is inherited in an autosomal dominant pattern, in which

individuals receive a nonfunctional allele[12]. Loss of the corresponding allele results in a deficiency in genetic DNA repair in the affected tissue[12]. Most cases of Lynch syndrome (more than 90%) are attributed to inherited germline mutations of the hMLH1 and hMSH2 genes[38].

Before specific gene mutations were identified, Lynch syndrome was diagnosed based on clinical criteria, with the Amsterdam I criteria being the initial set of criteria used[38]. Amsterdam I criteria: multiple relatives with Lynch syndrome-associated cancer[12], at least one of whom is a first-degree relative of the other two[13], at least one case of Lynch syndrome-associated cancer diagnosed before the age of 50[14], ruling out familial adenomatous polyposis[15] and confirming the diagnosis by molecular genetic testing[38]. The criteria are widely used to identify individuals who should undergo genetic testing for Lynch syndrome. According to research, individuals may be at a higher risk of Lynch syndrome-related cancers if they have multiple family members who have been diagnosed with such cancers[13,16], two relatives who have been affected in consecutive generations[14], or one or more relatives who were diagnosed with Lynch syndrome-related cancer before the age of 50[38].

Clinicopathological characteristics

Patients with Lynch syndrome have a substantial possibility of developing a second metachronous cancer[11]. According to the study by Wang et al.[20], 33.3% (9/27) of LS-EC patients had a second primary tumor associated with Lynch syndrome, which was significantly higher than 5.1% (17/331) found in sporadic cases[11].

Second primary cancer sites in LS-EC patients included colorectal cancer (4/9), ovarian cancer (2/9), breast cancer (1/9), lip cancer (1/9) and vulvar cancer (1/9)[11]. In a study by Post et al., the cumulative incidence of LS-associated second primary tumor was 11.1% (4/36) among LS-EC patients, three of whom had colorectal cancer and one with ureteral cancer[11]. This risk was higher than in non-LS patients with mismatch repair deficient EC (dMMR)[11]. Despite differences in diagnostic methods (Amsterdam II criteria used by Wang et al., molecular methods used by Post et al.) and races, both studies indicate that patients with LS-EC are more likely to develop a second primary cancer[11].

Patients with LS-EC are usually diagnosed at a younger age compared to those with sporadic EC. In addition, the age of onset varies depending on the type of pathogenic germline (PV) present. In a recent study, MSH6 gene carriers showed a later onset of endometrial cancer compared to MSH2 or MLH1 gene carriers[11]. Patients with MLH1 and MSH2 gene mutations developed EC at a mean age of 39-49.5 years old, while those with MSH6 gene mutation developed EC at a mean age of 50.6-59.5 years old[11]. These findings provide a basis for creating personalized preventive measures.

Obesity is a widely recognized risk factor for endometrial cancer. It is recognized that obesity increases the tendency to develop EC in premenopausal women affected by Lynch syndrome, due to the local pro-estrogenic environment[11]. The study by Staff et al. showed a correlation between type 2 diabetes and an increased risk of LS-EC[11]. Diabetic LS patients were also found to be more likely to be overweight than non-diabetic LS patients. However, no association between BMI and an increased risk of LS-EC was established[11]. In addition, two research studies reported no substantial differences in BMI between microsatellite stable (MSS) and MSI patients[11]. Most studies suggested that patients with dMMR or MSI-H or germline MMR PVs had a lower BMI[11]. These studies indicated that, although obesity was a risk factor for LS-EC, patients with LS-EC had a lower BMI compared with EC patients[11].

Lynch syndrome is associated with germline PV in genes belonging to the MMR group, namely MSH2, MSH6, MLH1 and PMS2[11-13]. The EPCAM gene, which precedes MSH2, comprises nine exons. In colorectal cancer, 3' deletion of EPCAM has been shown to significantly reduce MSH2 gene activity by hypermethylating its promoter region, leading to the suppression of both EPCAM and MSH2 protein expression[11,14,15]. Conversely, in endometrial cancer, EPCAM 3'-end deletion can span the first exon of MSH2, including the promoter region, resulting in suppression of both EPCAM and MSH2 protein expressions[11]. However, this is not associated with MSH2 hypermethylation[11,16]. MLH1 and MSH2 gene expressions in endometrial cells that are normal and estrogen receptor (ER)-positive Ishikawa[18] cells are known to be upregulated positively by estradiol. The researchers also observed that cases with a deficiency of MMR protein expression have a lower expression of the estrogen receptor (ER) and the progesterone receptor (PR)[11,18]. It was also found that ER α/β bound to MSH2 through the MSH3/MSH6 interaction domain of MSH2 and, in turn, MSH2 potentiated the transactivation function of ER α ligand[11,19]. This may be related to the pathogenesis of LS-EC. Despite this, there are few reports on the impact of estrogen and progesterone on the pathogenesis of LS-EC. Therefore, further research is needed.

According to the Prospective Lynch Syndrome Database (PLSD), the cumulative risk of endometrial cancer in women aged 75 years old who have MLH1, MSH2, MSH6 or PMS2 mutations is estimated to be 37%, 48.9%, 41.1% and 12.8%, respectively[11,20]. A study by Marques-de-Sá et al. found that the highest percentage of individuals with LS-EC inherited the MSH2 mutations (48%), while 32%, 15% and 5% of individuals inherited MLH1 mutations, MSH6 and PMS2, respectively[11,21]. Another study, by Bonadona et al., indicated that MLH1 gene carriers had a significantly higher risk of developing EC by the age of 70 compared to MSH2 gene carriers, which is consistent with the findings of Quehenberger et al.[11,21,22] Furthermore, MSH6 mutations have been shown to cause a sex-restricted trait with a high risk of EC, but only a modestly increased risk of CRC in both sexes[11]. Women with MSH6 mutations have a 26-fold increased risk of EC and a six-fold increased risk of other LS-related cancers. Furthermore,

the risk of EC in 70- and 80-year-old women with MSH6 mutations was 26% and 44%, respectively, while the risk of CRC at the same age was 10% and 20%[11,24]. Endometrioid carcinoma is universally recognized as the most prevalent form of LS-EC[11,25,26]. Patients possessing the MSH2 mutation show a tendency to develop non-endometrioid carcinoma tumors, ultimately leading to a more diverse histological spectrum, different from LS-EC[11,27]. The International Federation of Gynecology and Obstetrics (FIGO) criteria for the staging and grading of LS-EC have been controversial. While some studies[26,28,29] suggested that intermediate/high FIGO stage and higher grades are more common among patients with LS-EC, Wang et al.[30] found that in China there was a higher rate of LS-EC cancers than sporadic EC[11]. Broaddus et al.[28] noted that 78% of LS-EC (composed mainly of MSH2 gene carriers) were in the early stages[11]. Race variation, types of mutations among the patients studied, as well as pathological tissue analysis methods explained the variation in stage and grade results between LS-EC and sporadic EC[11]. LS-EC is more likely to occur in the lower uterine segment (LUS) compared with sporadic EC[11].

According to Westin et al.[33], 14.2% of LUS-EC patients with MSH2 mutations were diagnosed with Lynch syndrome, which is significantly higher than the general EC population (1.8%)[11]. Masuda et al.[34] showed that the incidence of Lynch syndrome in the LUS-EC cohort was 11.1% (1/9) and that the age and BMI of LUS-EC patients were considerably lower than those of non-LUS-EC patients, which is in accordance with the clinical features of LS-EC[11]. Lower uterine segment involvement was determined to be a risk factor for lymph node metastasis[35], which had a negative impact on prognosis[11]. Tumors arising from MSI/dMMR EC have been observed to display increased numbers of neoantigens, leading to an increased presence of tumor-infiltrating lymphocytes (TILs), which in turn results in a better prognosis[11]. However, despite this, immune checkpoint proteins such as PD-1 and PD-L1 were found to be upregulated in EC TILs with MSI/dMMR, which may negate the positive effect of increased number of TILs[11]. LS-EC were found to have a higher level of immune cell infiltration at the invasive margin and an increased antitumor immune response compared with sporadic MSI-H EC[11]. While sporadic MSI-H EC significantly increased PD-L1 expression in both tumor epithelium and stroma, LS-EC had a significant decrease in PD-L1 expression in tumor epithelium and no difference in PD-L1 expression in stroma compared to MSS CE[11]. For this reason, it is suggested that LS-EC may be less responsive to single anti-PD-L1 treatment compared to sporadic EC, therefore other immune checkpoint blocking agents or combined use should be explored in LS-EC separately[11].

In addition, Ramchander et al.[36] observed a significant increase in PD-1+, CD8+ and CD45RO+ immune cells at the invasive margin in LS-EC compared with sporadic dMMR EC. Pakish et al.[37] reported that LS-EC had significantly more CD8+ cells and activated cytotoxic T lymphocytes in the stroma compared with sporadic MSI-H EC, indicating an increased antitumor immune response[11].

However, there is no consensus on the prognosis of LS-EC, and more large population studies are needed to investigate this further[11].

Screening and prevention for people with Lynch syndrome

It is imperative to diagnose Lynch syndrome in those who have cancer, as well as their relatives who have not yet developed malignancy, in order to provide personalized screening and preventive measures. Cancer patients with Lynch syndrome are at an increased risk of developing secondary malignancies throughout life and should be counseled regarding screening options and preventive measures[12]. For example, women who have survived Lynch-associated endometrial cancer should be screened for colorectal cancer[38]. Women with colorectal cancer associated with Lynch syndrome may be counseled about limited screening options for endometrial cancer, but they are offered screening ultrasound and endometrial biopsy in the office or prophylactic hysterectomy and bilateral salpingo-oophorectomy if no longer taken, considering the birth[38].

Family members who have not yet developed any cancer should be screened for both endometrial and colorectal cancer, and they may benefit from prophylactic hysterectomy and bilateral salpingo-oophorectomy if they do not plan to have any more children[38].

Endometrial cancer screening

The reasons behind the lack of evidence for endometrial cancer screening data are numerous. Due to the low prevalence of the disease in the general population and the absence of visible early symptoms such as vaginal bleeding, there are no screening programs for the general population[38]. This has also resulted in a lack of baseline data on screening sensitivity and specificity[38]. Two studies were conducted to evaluate the effectiveness of transvaginal ultrasound (TVU) and endometrial mucosal measurement in high-risk populations[38]. Both studies found that screening had a high false-positive rate and was ineffective[38]. In one study, 41 women (35 premenopausal and six postmenopausal) diagnosed with Lynch syndrome by genetic mutation or fulfilling the Amsterdam criteria underwent annual TVU and serum CA-125 tests to detect gynecologic malignancies. After a median follow-up of five years, only 17 of 179 ultrasounds (0.9%) suggested that further evaluation by endometrial sampling should be performed[38]. Of this, only three premalignant lesions were discovered. After clinical symptoms became apparent, only one case of endometrial cancer was identified[38].

A study by Dove-Edwin et al.[39] examined the effectiveness of TVU screening in 269 women who were either diagnosed with Lynch syndrome or came from families with a similar history[38]. During the study period, only two cases of endometrial cancer occurred; both were discovered symptomatically and not by screening

ultrasound[38]. No research has been conducted to date on the effectiveness of endometrial biopsy in the office as a screening tool for women with Lynch syndrome[38]. However, a Finnish study[40] evaluated the combination of endometrial sampling and ultrasound in 175 women with germline mutations in MLH1, MSH2 or MSH6[38]. Although there was no significant difference in the long-term outcomes between the 11 patients with endometrial cancer detected by screening and the 83 women from the same families who were diagnosed with endometrial cancer detected by symptoms, this study highlighted a stage of migration[38]. Seven percent of patients in the surveillance group had stage III/IV disease, compared with 17% of patients who presented symptomatically[38].

Although current screening methods for endometrial cancer have not yet provided conclusive data, women with Lynch syndrome face an increased risk of developing endometrial cancer throughout their lives, and may develop it at an earlier age, which makes recognizing bleeding as a warning sign much more challenging[38].

Moreover, for this group of women with a lifetime risk of ovarian cancer ranging from 6% to 12%, TVU may be useful in identifying ovarian abnormalities[38]. For these reasons, consideration of screening is warranted[38]. As of now, patients with Lynch syndrome are offered TVU and endometrial biopsy in the office, which are recommended annually for women aged 30 to 35 or older, due to expert consensus[38]. Based on expert consensus, it is important to note that further research is needed to evaluate endometrial ultrasound and biopsy, as well as new screening methods for endometrial cancer, due to the lack of adequate data[38].

Conclusions

Patients with Lynch syndrome have an approximately 40-60% lifetime risk of developing endometrial cancer, which is the most common extraintestinal sentinel cancer and occurs at a younger age[11].

This makes doctors treating patients with endometrial cancer alert to the possibility of Lynch syndrome existence, when collecting personal and family history information. Tumor studies serve as a valuable resource for clinicians to evaluate patients with Lynch syndrome-related malignancies before performing germline mutational analysis. These studies can eliminate the possibility of Lynch syndrome in these patients and make genetic testing simpler by focusing on specific genes in positive patients[38].

The detection of Lynch syndrome provides an opportunity to use screening and prevention techniques that can reduce the incidence and mortality rates of colorectal cancer[38]. Research is ongoing to determine the effectiveness of screening methods compared with prophylactic surgery in reducing the morbidity and mortality rates of endometrial cancer in women with Lynch syndrome.

Further investigation is needed to determine prospective methods for chemoprevention and to assess the impact of prophylactic surgery on gynecologic cancer survival and mortality[38]. Until then, it is suggested that individuals diagnosed with Lynch syndrome receive guidance from their healthcare providers regarding adherence to current screening guidelines[41,42] and be presented with the option of prophylactic surgery[38]. ■

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CONFLICT OF INTERESTS: none declared.

FINANCIAL SUPPORT: none declared.