**Name of Journal: *World Journal of Obstetrics and Gynecology***

**ESPS Manuscript NO: 27642**

**Manuscript Type: Minireviews**

**Screening and diagnosis of endometrial cancer in Lynch syndrome**

Caroline C *et al*. Endometrial cancer in LS

**Caroline Cornou, Anne Sophie Bats, Charlotte Ngo, Léa Rossi, Perrine Capmas, Pierre Laurent-Puig, Chérazade Bensaid, Claude Nos, Marie Aude Lefrère-Belda, Fabrice Lécuru**

**Caroline Cornou, Anne Sophie Bats, Charlotte Ngo, Léa Rossi, Perrine Capmas, Pierre Laurent-Puig, Chérazade Bensaid, Claude Nos, Marie Aude Lefrère-Belda, Fabrice Lécuru,** Department of Gynecologic Oncology, European Hospital Georges Pompidou, University of Paris Descartes, 75015 Paris, France

**Author contributions:** All the authors contributed to the manuscript.

**Conflict-of-interest statement:** There is no conflict of interest associated with any of the senior author or other coauthors contributed their efforts in this manuscript.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited manuscript

**Correspondence to: Caroline Cornou, MD**, Department of Gynecologic Oncology, European Hospital Georges Pompidou, University of Paris Descartes, 20 rue Leblanc, 75015 Paris, France. caroline.cornou@aphp.fr

**Telephone**: +33-1-56092565

**Fax**: +33-1-56092582.

**Received:** June 9, 2016

**Peer-review started:** June 14, 2016

**First decision:** July 11, 2016

**Revised:** September 15, 2016

**Accepted:** October 25, 2016

**Article in press:**

**Published online:**

**Abstract**

Lynch syndrome (LS) is an autosomal dominant inherited cancer predisposition syndrome caused by a mismatch of DNA repair (MMR system). Lifetime risk of developing endometrial and ovarian cancer in LS is higher than in the general population and gynecologic screening appears interesting. Screening is based on several tests: pelvic ultrasound, endometrial biopsy and hysteroscopy for endometrial cancer, pelvic ultrasound and ca 125 for ovarian cancer. Those tests appear efficient for the diagnosis of gynecologic cancers in LS. Nevertheless, screening tests have not proved clinical benefit until now, and potential problems of compliance, risk of false negative cases, and interval cancer associated with screening do justify offering prophylactic surgery to patients. Women with LS (LS) should be informed of the potential benefits and risks of screening and the importance of evaluation in case of gynecologic symptoms or abnormal bleeding. Chemoprevention by progestin-containing oral contraceptives and the treatment of premalignant lesion are available options for reducing the risk of endometrial cancer in LS population.

**Key words:** Lynch syndrome; Endometrial cancer; Ovarian cancer; Gynecologic screening; Prophylactic hysterectomy

**© The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Lynch syndrome (LS) is an autosomal dominant inherited cancer predisposition syndrome caused by a mismatch of DNA repair, lifetime risk of developing endometrial and ovarian cancer in LS is higher than in the general population. Gynecologic screening appears interesting for the diagnosis of gynecological cancers in LS although screening tests have not proved clinical benefit until now. The aim of this review was to describe the various forms of screening and the results in this population.

Cornou C, Bats AS, Ngo C, Rossi L, Capmas P, Laurent-Puig P, Bensaid C, Nos C, Lefrère-Belda MA, Lécuru F. Screening and diagnosis of endometrial cancer in Lynch syndrome. *World J Obstet Gynecol* 2016; In press

**INTRODUCTION**

Lynch syndrome (LS) is an autosomal dominant inherited cancer predisposition syndrome. Initially described by Whartin in 1913, Lynch proposed the first diagnostic criteria in 1966 made on the basis of a family’s cancer history[1]. That mutation increases woman lifetime risk of endometrial cancer, colorectal cancer and ovarian cancer. Furthermore, other tumours such as gastric, small bowel, urinary, and biliary tract have also been associated with LS[2-4].

 If the risk of colorectal cancer was initially estimated at 80% at the age of 80 years, and 60% for endometrial cancer[5], recent data report a lower prevalence. The risk of colorectal cancer for women is estimated at just over 20% at the age of 80 years. The risk of endometrial cancer reported in the northern European population with identified hMLH1 or hMSH2 mutation remains close to 40%[6]. The ERISCAM study (Estimation des Risques de Cancer chez les porteurs de mutation des gènes MMR), which is a prospective multicentre French cohort on patients with MMR gene mutation[7], found a cumulative risk of colorectal cancer at the age of 70 years of 31% for women, and 33% and 9% for endometrial cancer and ovarian cancer. For endometrial cancer, the cumulative risk at the age of 70 years was 54% in case of MLH1 gene mutation, 21% in MSH2 mutation, and 16% in MSH6 mutation. At the age of 40 years, the estimated cumulative risk was 2%, regardless of the mutation. Regarding ovarian cancer, it was respectively 20%, 24% and 1% at the age of 70 years and 1% at the age of 40 years, all mutations combined. The median age of onset of endometrial cancer was 49 years and 44 years for ovarian cancer. Thus, women with LS are at high risk of developing endometrial cancer, also called "sentinel" cancer, because it reveals the hereditary predisposition in 50% of cases.
Very few data are available on the natural history of endometrial cancer in LS. Clinical cases suggest that the onset of microsatellite instability precedes the loss of MMR protein expression[8,9]. A short phase of hyperplasia seems to precede cancer. This sequence seems to be observed not only for endometrial cancer, but also for LS -related ovarian cancer[8]. However, the transition hyperplasia-cancer is faster than in the general population. Complex and atypical hyperplasia emerge as premalignant lesions in LS[10].

Endometrial cancers are characterized by a higher proportion of advanced stage than in the general population (although the majority is stage I), more aggressive histologic types (clear cell carcinomas, papillary serous carcinoma and carcinosarcoma), and a location in the uterine isthmus[11]. When comparing tumours of patients with LS with those of sporadic cases before the age of 50 years, FIGO stage and grade, mitotic index, depth of invasion and lymphocytic infiltration are higher in case of genetic predisposition[12].

LS was defined by Amsterdam criteria. Initially, only colorectal cancer were described: at least three relatives with colorectal cancer, one should be a first degree relative to the other two, at least two generations affected, at least one diagnosed before 50 and adenomatous polyposis should be excluded. Subsequently, these ones integrate other cancers of spectrum (Amsterdam criteria 2). There should be at least three relatives with an owned restrictive spectrum Lynch cancer: one should be a first-degree relative to the other two, at least two successive generations should be affected, at least one should be diagnosed before 50, familial adenomatous polyposis should be excluded, tumors should be verified by pathological examination[13].

In female population with LS, endometrial cancer occurs at younger ages than in sporadic cases; moreover cumulative risk of endometrial cancer at the age of 70 is around 33%, higher than cumulative risk of colorectal cancer (31%)[7], and appears frequently as sentinel cancer (first cancer to occur). Furthermore, endometrial cancer characteristics are different: an earlier age of cancer at onset, tumour morphology (dedifferentiate or undifferentiate endometrial carcinoma), and presence of synchronous ovarian cancer (clear cell carcinoma) seems more frequent in LS[11].

 Because of this high risk of endometrial cancer, it is necessary to offer patients with LS gynecologic screening.

Lifetime risk for ovarian cancer in LS ranges between 9 and 12%, compared with 1.3% in the general population. The rate at the age of 70 is 9%[3,4,6,14] . Moreover, Watson *et al*[4] showed that MSH2 mutation had nearly twice the incidence rate compared to patients with MLH1 mutation.

Risk subject identification is indeed fundamental to offer a genetic counselling, a screening and a gynaecological management suitable for the proband and the relatives. This screening is thus an important tool in cancer prevention.

**PATHOGENESIS OF LS**

LS is an autosomal dominant inherited predisposition to cancer, caused by the mutation of a gene, involved in the DNA Mismatch Repair (MMR), leading to genome instability in tumour cells, particularly visible at microsatellite loci (MSI+ phenotype, for microsatellite instability)[1]. Four MMR genes have been identified: hMLH1, hMSH2, hMSH6 and PMS2[15-21]. Their respective proteins have the function to recognize DNA replication abnormalities, which occur during mitosis, and to perform excision and repair. MMR gene mutation makes the associated protein nonfunctional, *i.e.,* unable to correct matching errors. This is common in microsatellite loci, containing 2 to 5 base pairs repeat, particularly sensitive to matching errors. The newly synthesized DNA strand is abnormally long. The tumours are thus called “unstable” or MSI+. This results in a problem of compensation, causing inactivation of tumour suppressor genes and development of cancer, mainly colorectal and endometrial cancer.

 There are, at a lower risk level, tumours of the ovary, urinary excretory tract, small intestine, stomach, hepatobiliary tract, skin and brain[2-4,22].

**LS EPIDEMIOLOGY**

Initially, two clinical syndromes were described. Hereditary non-polyposis colorectal cancer site specific (HNPCCSS), described as association of colorectal cancer in the same family; and Cancer Family Syndrome (CFS). CFS associated colorectal cancer and another spectrum Lynch cancer, like endometrial[1].

If the risk of colorectal cancer was initially estimated at 80% at the age of 80 years, and 60% for endometrial cancer[5], recent data report a lower prevalence. The risk of colorectal cancer in women is estimated at just over 20% at the age of 80 years. The risk of endometrial cancer reported in the northern European population with identified hMLH1 or hMSH2 mutation remains close to 40%[6]. The ERISCAM study (Estimation des Risques de Cancer chez les porteurs de mutation des gènes MMR), which is a prospective multicentre French cohort on patients with MMR gene mutation[7], found a cumulative risk of colorectal cancer at the age of 70 years of 31% for women, and 33% and 9% for endometrial cancer and ovarian cancer. For endometrial cancer, the cumulative risk at the age of 70 years was 54% in case of hMLH1 gene mutation, 21% in hMSH2 mutation, and 16% in hMSH6 mutation. At the age of 40 years, the estimated cumulative risk was 2%, regardless of the mutation. Regarding ovarian cancer, it was respectively 20%, 24% and 1% at the age of 70 years and 1% at the age of 40 years, all mutations combined. The median age of onset of endometrial cancer was 49 years and 44 years for ovarian cancer.

**ENDOMETRIAL CANCER IN LS**

Women with LS are at high risk of developing endometrial cancer, which is often also called ”sentinel” cancer, because it reveals the hereditary predisposition in 50% of cases. Indeed, endometrial cancer occurs at younger age in LS. Very few data are available on the natural history of endometrial cancer in LS, especially molecular pathogenesis[8].

Indeed, a short phase of hyperplasia seems to precede cancer and this transition is faster than in the general population. This sequence seems also observed for LS -related ovarian cancer[8]. Complex and atypical hyperplasia emerge as premalignant lesions in LS[10].

Endometrial cancers seem characterized by a higher proportion of advanced stage than in the general population, more aggressive histologic types (clear cell carcinomas, papillary serous carcinoma and carcinosarcoma), and a location in the uterine isthmus[11]. Moreover, endometrial carcinoma appears earlier and frequently as sentinel cancer but few data is available and this cancer may differ according to patients’ age. Although the majority of endometrial carcinomas related to LS are type I cancers, the proportion of type II cancers seems to be higher than in the case of sporadic endometrial carcinoma. Before the age of 50 years, FIGO stage and grade, mitotic index, depth of invasion and lymphocytic infiltration in endometrial tumours are higher in case of genetic predisposition[12]. Conversely, women over 50 years present low-grade and stage tumour, which may be associated with ovarian tumour in 13% of cases. MSI+ endometrial cancers, combining high grade, presence of lympho-vascular emboli, deeper depth of invasion or higher stage, could have a worse prognosis[23].

**OVARIAN CANCER IN LS**

Bonadona *et al*[7] 2011 found a cumulative risk at the age of 70 years of 9% for ovarian cancer, mainly with MLH1 and MSH2 mutation. Synchronous ovarian and endometrial cancers are more often found in LS population[24,25].

 Compared to the general population, the rate of clear cell carcinoma and endometrioid adenocarcinoma is more frequent. A young age and an earlier stage could explain that these cancers have better prognosis than in general population[26].

Ketabi *et al*[26] in 2011 showed that typical ovarian cancer associated with LS presents at a young age, at an early stage and are often non-serous tumours.

**DIAGNOSTIC OF LS IN CASE OF GYNAECOLOGICAL CANCERS**

Clinical criteria for the detection of families with LS were first established in 1991. The so-called Amsterdam Criteria were originally designed to find families suitable for research projects aimed at identifying the genetic causes of hereditary colorectal cancers.In 1999, these were extended to extra-colonic cancers associated with LS. But they have a low sensitivity[13]. Therefore, in 1997, the less stringent Bethesda Guidelines were developed. These criteria consider medical and familial history of LS -associated tumors[27]. In 2004, these guidelines were revised in order to achieve higher specificity[28]. Few studies had described these criteria but had limited sample sizes and focused only on hMLH1 and hMSH2 mutations[29,30].

 In 2011, Kwon *et al*[31] estimated the costs and benefits of different testing criteria to identify LS in women with endometrial cancer. They compared six criteria for LS and found that immunohistochemistry in patient having at least one first degree relative with Lynch associated cancer, whatever the age was, is a cost effective strategy for detecting LS. Indeed, with Amsterdam II criteria, the proportion of women with endometrial cancer and Amsterdam II criteria may be as low as 30% when patients with endometrial cancer and LS who have at least one first degree relative with Lynch associated cancer at any age may be as high as 80 to 100%. Consequently, a better identification of patients with LS creates a better surveillance of those.

Morover, Vasen in 2013 found that investigation of all endometrial cancer in patients less than 70 years old by immunohistochemistry or MSI can improve identification[32].

**GYNAECOLOGICAL SCREENING**

The young age at onset, tumour characteristics and high risk of developing cancer of LS related-endometrial cancers seem to justify a gynaecological screening in this population. However, although colorectal screening has emerged in LS[33], gynaecological screening in LS is not established. The benefit of gynaecological surveillance is unclear and there is no consensus in surveillance modality. Screening is based on the detection of premalignant lesions (complex or atypical hyperplasia), endometrial cancer and ovarian cancer.

There are several screening tests: pelvic ultrasound, endometrial biopsy and hysteroscopy for endometrial cancer; pelvic ultrasound and Ca 125 assay for ovarian cancer, but any of these tests has yet proved its effectiveness.

***Guidelines for gynaecological screening***

Many studies have been raised about the modalities of gynaecological screening in LS. The French National Institute of Cancer (INCa) recommends screening of patient with LS starting at the age of 30 years. This includes pelvic ultrasound and endometrial biopsy, preferably by Pipelle de Cornier, at least every 2 years (INCA recommendations).

The other international agencies propose different screening protocols. In 2015, the European Society for Medical Oncology (ESMO), the European SocieTy for Radiotherapy and Oncology (ESTRO) and European Society of Gynaecological Oncology (ESGO) proposed new guidelines[34]. They defined that patients with high risk of endometrial cancer should include women with genetic mutation of HNPCC, those showing a substantial likehood of being mutated and those coming from families with suspected predisposition to colonic cancer but without genetic testing results. Although there is insufficient evidence for annual screening, gynaecological screening is recommended from the age of 35, due to the high risk of endometrial cancer. Screening is recommended with annual gynecological examination, transvaginal ultrasound and endometrial biopsy with or without hysteroscopy until hysterectomy. Prophylactic surgery should be considered at the age of 40, and is an option for prevention of ovarian and endometrial cancer. Women with LS should be informed of the potential benefits and risks of screening, and also that the recommendations are based on expert opinion in the absence of scientific evidence until now.

The application of local progesterone using the LNG-IUD and the treatment of premalignant disease (Atypical Endometrial Hyperplasia, Endometrial Intraepithelial Neoplasia) are available options in patient at high risk of endometrial cancer[32,34].

***Screening by pelvic ultrasound***

The accuracy of ultrasonography was analyzed by three main studies.

Dove-Edwin *et al*[35] reported 292 cases of women fulfilling the Amsterdam criteria, and having an annual ultrasound. No cancer was detected and two interval cancers occurred. The main limitations of this study are outdated methodology for ultrasound and inclusion of low-risk patients. In a prospective study, Rijcken *et al*[36] observed 41 women with identified mutation or fulfilling the Amsterdam criteria II. An annual clinical examination was associated with a transvaginal ultrasound and CA 125 assay. An endometrial biopsy was performed in case of abnormal bleeding or increased endometrial thickness. One hundred seventy-nine scans were performed, leading to propose 17 endometrial biopsies or curettage. Three atypical hyperplasia were diagnosed and an interval cancer occurred eight months after a normal scan. In the third study conducted in our center, 96 ultrasound/endometrial biopsy assessments were performed in 58 patients. With an average age of 42 years, 75% of patients fulfilled the Amsterdam criteria II and 25% had hMLH1 or hMLH6 gene mutation. The ultrasound was considered normal in the absence of polyp or abnormality with endometrial thickness less than 4mm in postmenopausal women without hormone replacement treatment or 6mm in other cases. Endometrial biopsy was performed at the same time. With a median of 51 months (246 years of exposure), two cancers occurred in this population, both diagnosed by ultrasound. The sensitivity of this review is therefore 100% but with a specificity of only 55%. It is noteworthy that both cancers were symptomatic (bleeding)[37].

***Screening by endometrial biopsy***

The value of endometrial biopsy has been reported in three conflicting studies[38-40]. Renkonen-Sinisalo *et al*[32] studied 175 mutated patients, who were annually monitored by ultrasound and endometrial biopsy. Five hundred and three examinations were performed during 759 years of follow-up. Fourteen cancers were diagnosed in the study: 11 by endometrial biopsy, 2 as interval cancer, respectively 3 and 31 months after a normal screening, and 1 at the time of prophylactic hysterectomy. In addition, 14 hyperplasia were found[38]. Gerritzen *et al*[39] reported a series of 100 patients fulfilling the Amsterdam criteria, screened by pelvic ultrasound, and endometrial biopsy in 64 patients. The endometrial biopsy revealed 3 atypical hyperplasia and endometrial cancer. The authors concluded that endometrial biopsy improves the detection of premalignant and malignant endometrial lesions. The third study assessed the additional value of endometrial biopsy coupled with pelvic ultrasound in the annual screening for endometrial lesions, comparing two periods (period 1: ultrasound alone and period 2: ultrasound coupled with endometrial biopsy). Seventy-five patients aged over 30 years with LS or a high risk first degree related were included in the study. Four premalignant lesions and 1 endometrial cancer were diagnosed during the first period of the study, and only 2 premalignant lesions were found in the second one, which would not have been missed in the absence of endometrial biopsy. The endometrial cancer was symptomatic. The authors conclude that the endometrial biopsy provides no benefit to annual pelvic ultrasound in the screening of LS. Nevertheless, the study population did not include only mutated patients, who are at higher risk for endometrial lesions[40].

***Screening by hysteroscopy***

Diagnostic hysteroscopy has also been proposed as a screening tool in LS[41-43]. This examination is done in outpatient clinic, without anaesthesia, and is well tolerated when using flexible hysteroscopy and uterine distension with saline. In addition, it allows targeted biopsies. Our team reported 62 women followed with hysteroscopy and endometrial biopsy at the same time. Three cancers were diagnosed. Hysteroscopy diagnosed the three lesions with a sensitivity of 100%. However, these three patients were symptomatic[42]. A second prospective cohort study evaluated the performance of hysteroscopy in the detection of endometrial cancer in LS compared with pelvic ultrasound. Forty- one patients received 69 annual screening visits. Four patients had endometrial cancer or atypical hyperplasia, five endometrial polyps and two endometrial hyperplasia, highlighted on hysteroscopy. Ultrasound detected 2 cancers or atypical endometrial hyperplasia. Hysteroscopy had a specificity of 89.8% comparable to ultrasound but was associated with a higher positive likelihood ratio and a lower negative likelihood ratio. No interval cancer occurred with a 22 months follow-up. The authors emphasized that hysteroscopy in gynaecological screening of LS is acceptable and has a high diagnostic accuracy for the detection of cancer and atypical endometrial hyperplasia[43].

***Screening by molecular technique***

Bladder cancer is a tumour also characterized by microsatellite instability. Several studies have evaluated the analysis of microsatellite instability in urine for the detection of urinary tract tumours and showed that this technique could not only detect recurrence but also early stage tumours[44,45]. Ishikawa *et al*[8] reported a case of endometrial hyperplasia without atypia associated with microsatellite instability and loss of expression of MMR protein. Seven months later, the patient developed an endometrial cancer, suggesting that failure in DNA repair appears early in the process of carcinogenesis.

Our team has reported the feasibility of detection of microsatellite instability in washings of the uterine cavity in patients with endometrial cancer in the context of LS[46,47]. MSI analysis in the uterine cavity washings could be a promising tool for early diagnosis of unstable tumours in patients with LS and thereby improve their prognosis. Microsatellite instability analysis can also be performed on endometrial biopsy.

It must be stressed that microsatellite instability analysis can sometimes be difficult, especially in case of hMSH6 gene mutation[48,49]. In this case, it is interesting to investigate by immunohistochemistry a loss of expression of the corresponding MMR protein. Ketabi *et al*[50] estimated the incidence rate of endometrial cancer in prospective cohort of 871 patients and they concluded that surveillance should only be targeted at MMR-mutation carriers.

***Screening for ovarian cancer***

Little is known on the benefit of screening for ovarian cancer in LS, and no study has specifically investigated this issue. The only available data are provided by studies investigating screening of endometrial lesions. Dove-Edwin *et al*[35] reported that pelvic ultrasound failed to detect ovarian cancer. Similarly, pelvic ultrasound associated with CA125 assay showed no evidence of ovarian cancer through screening[36,38], while Renkonen *et al*[38] found 4 interval cancers. Gerritzen *et al*[39] reported one borderline tumour and one malignant ovarian tumour, diagnosed because abnormal scan associated with increased CA125.

***Acceptability and compliance in gynaecological screening***

Acceptability of gynaecological screening has been assessed and the patients report that transvaginal ultrasound examination is the most well tolerated, followed by hysterosonography, diagnostic hysteroscopy, and finally endometrial biopsy[51]. Ketabi *et al*[52] showed that knowledge of endometrial cancer risk is the most important predictor of their compliance with gynecologic screening. Compliance in gynaecological screening of patients with LS appears crucial, and is fortunately often high (97.1% for Järvinen[33]).

**PROPHYLACTIC SURGERY**

Surveillance techniques have not shown clinical benefits and potential problems of compliance, risk of false negative cases, and interval cancer associated with screening do justify offering prophylactic surgery to patients[34,50].

The French National Institute of Cancer (INCa) and European society for Medical Oncology recommends prophylactic surgery in women with an identified mutation or a significant risk of cancer, when they have no more desire of pregnancy[34]. The reasonable age to offer this surgery is probably in premenopausal women *i.e.,* 40-45 years, given the median age of endometrial and ovarian cancer reported in the ERISCAM study[7,34]. Minimally invasive approach should be preferably used[34].

The indication has to be validated by a multidisciplinary meeting after psychological counselling. In preoperative consultation, the physicians should inform patients of the induced menopause, its side effects, as well as detail surgery[34].

Prophylactic hysterectomy and bilateral salpingo-oophorectomy seems to be the most effective and least expansive preventive measure in patients with LS. This procedure eliminates risk of endometrial and ovarian cancer and any specific gynaecological screening. In a published study of 210 patients with prophylactic surgery, no cases of endometrial cancer and ovarian cancer were recorded among women who did chose this option[53]. But Karamurzin *et al*[54] in 2013, analyzed a series of 25 patients and revealed incidental endometrial cancer or endometrial hyperplasia in 24% of cases. Moreover, a recent study suggests that prophylactic surgery does not impact on quality of life in premenopausal woman with LS and women tend not to worry about developing endometrial cancer[55]. Nevertheless, Schmeler *et al*[53] reported two cases of primary peritoneal cancer after prophylactic surgery.

**CHEMOPREVENTION OF ENDOMETRIAL CANCER**

Women with LS are at high risk for cancer and represent an ideal population for cancer chemoprevention. Epidemiologic studies have shown that progestin-containing oral contraceptives reduce the risk of endometrial cancer in general population. Stoffel *et al*[56] described on short period (3 months) the effects of progestin containing in oral contraceptive pills or depo-medroxyprogesterone (depo-MPV) on the endometrium of patient with LS. There results showed an endometrial response, suggesting that exogenous progestins may be reasonable chemoprotective agents in this high-risk patient population. But currently, a reduction in incidence of endometrial cancer in this group remains unknown. Research need to elucidate the molecular mechanisms that lead to endometrial carcinogenesis and the impact of hormonal treatment.

**CONCLUSION**

Currently, there is no scientific evidence to support gynaecologic screening in patients with LS. Screening is based on annual gynaecological examination, pelvic ultrasound, and endometrial biopsy.

 The recommendations are based on expert opinion and multimodal screening in LS seems justified because of high prevalence of endometrial cancer compared with the general population. The presence of premalignant lesions, abnormal bleeding almost always present at an early stage of the disease, and good prognosis of early stage suggest that patients should be informed about the importance of gynaecological closed surveillance.

Moreover, it seems reasonable to propose prophylactic hysterectomy and bilateral salpingo-oophorectomy at the age of 40-45 years, with or without colorectal surgery, in women with an identified mutation or a significant risk of cancer, when they have no more desire of pregnancy.

 Epidemiologic studies have shown that progestin-containing oral contraceptives reduce the risk of endometrial cancer in high-risk population. Research needs to elucidate the molecular mechanisms that lead to endometrial carcinogenesis and the impact of hormonal treatment.

A better histological and biological characterization of premalignant and malignant endometrial lesions as well as oncogenesis, including description of onset of microsatellite instability and loss of expression of MMR proteins in endometrial cells appears crucial for a better understanding of the disease and an effective screening.

**REFERENCES**

1 **Lynch HT**, Krush AJ, Larsen AL, Magnuson CW. Endometrial carcinoma: multiple primary malignancies, constitutional factors, and heredity. *Am J Med Sci* 1966; **252**: 381-390 [PMID: 5922484 DOI: 10.1097/00000441-196610000-00001]

2 **Lynch HT**, de la Chapelle A. Hereditary colorectal cancer. *N Engl J Med* 2003; **348**: 919-932 [PMID: 12621137 DOI: 10.1056/NEJMra012242]

3 **Aarnio M**, Sankila R, Pukkala E, Salovaara R, Aaltonen LA, de la Chapelle A, Peltomäki P, Mecklin JP, Järvinen HJ. Cancer risk in mutation carriers of DNA-mismatch-repair genes. *Int J Cancer* 1999; **81**: 214-218 [PMID: 10188721 DOI: 10.1002/(SICI)1097-0215(19990412)81:2<214::AID-IJC8>3.0.CO;2-L]

4 **Watson P**, Vasen HF, Mecklin JP, Bernstein I, Aarnio M, Järvinen HJ, Myrhøj T, Sunde L, Wijnen JT, Lynch HT. The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. *Int J Cancer* 2008; **123**: 444-449 [PMID: 18398828 DOI: 10.1002/ijc.23508]

5 **Vasen HF**, Wijnen JT, Menko FH, Kleibeuker JH, Taal BG, Griffioen G, Nagengast FM, Meijers-Heijboer EH, Bertario L, Varesco L, Bisgaard ML, Mohr J, Fodde R, Khan PM. Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. *Gastroenterology* 1996; **110**: 1020-1027 [PMID: 8612988 DOI: 10.1053/gast.1996.v110.pm8612988]

6 **Quehenberger F**, Vasen HF, van Houwelingen HC. Risk of colorectal and endometrial cancer for carriers of mutations of the hMLH1 and hMSH2 gene: correction for ascertainment. *J Med Genet* 2005; **42**: 491-496 [PMID: 15937084 DOI: 10.1136/jmg.2004.024299]

7 **Bonadona V**, Bonaïti B, Olschwang S, Grandjouan S, Huiart L, Longy M, Guimbaud R, Buecher B, Bignon YJ, Caron O, Colas C, Noguès C, Lejeune-Dumoulin S, Olivier-Faivre L, Polycarpe-Osaer F, Nguyen TD, Desseigne F, Saurin JC, Berthet P, Leroux D, Duffour J, Manouvrier S, Frébourg T, Sobol H, Lasset C, Bonaïti-Pellié C. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *JAMA* 2011; **305**: 2304-2310 [PMID: 21642682 DOI: 10.1001/jama.2011.743]

8 **Ichikawa Y**, Tsunoda H, Takano K, Oki A, Yoshikawa H. Microsatellite instability and immunohistochemical analysis of MLH1 and MSH2 in normal endometrium, endometrial hyperplasia and endometrial cancer from a hereditary nonpolyposis colorectal cancer patient. *Jpn J Clin Oncol* 2002; **32**: 110-112 [PMID: 11956307 DOI: 10.1093/jjco/hyf026]

9 **Zamecnik M**. Possible precursor of HNPCC-related endometrioid carcinoma of the uterus. *Am J Surg Pathol* 2004; **28**: 1667; author reply 1667 [PMID: 15577693]

10 **Huang M**, Djordjevic B, Yates MS, Urbauer D, Sun C, Burzawa J, Daniels M, Westin SN, Broaddus R, Lu K. Molecular pathogenesis of endometrial cancers in patients with Lynch syndrome. *Cancer* 2013; **119**: 3027-3033 [PMID: 23760948 DOI: 10.1002/cncr.28152]

11 **Garg K**, Soslow RA. Lynch syndrome (hereditary non-polyposis colorectal cancer) and endometrial carcinoma. *J Clin Pathol* 2009; **62**: 679-684 [PMID: 19638537 DOI: 10.1136/jcp.2009.064949]

12 **Walsh CS**, Blum A, Walts A, Alsabeh R, Tran H, Koeffler HP, Karlan BY. Lynch syndrome among gynecologic oncology patients meeting Bethesda guidelines for screening. *Gynecol Oncol* 2010; **116**: 516-521 [PMID: 20034658 DOI: 10.1016/j.ygyno.2009.11.021]

13 **Vasen HF**, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. *Gastroenterology* 1999; **116**: 1453-1456 [PMID: 10348829 DOI: 10.1016/S0016-5085(99)70510-X]

14 **Boilesen AE**, Bisgaard ML, Bernstein I. Risk of gynecologic cancers in Danish hereditary non-polyposis colorectal cancer families. *Acta Obstet Gynecol Scand* 2008; **87**: 1129-1135 [PMID: 18972272 DOI: 10.1080/00016340802443806]

15 **Fishel R**, Lescoe MK, Rao MR, Copeland NG, Jenkins NA, Garber J, Kane M, Kolodner R. The human mutator gene homolog MSH2 and its association with hereditary nonpolyposis colon cancer. *Cell* 1993; **75**: 1027-1038 [PMID: 8252616 DOI: 10.1016/0092-8674(93)90546-3]

16 **Leach FS**, Nicolaides NC, Papadopoulos N, Liu B, Jen J, Parsons R, Peltomäki P, Sistonen P, Aaltonen LA, Nyström-Lahti M. Mutations of a mutS homolog in hereditary nonpolyposis colorectal cancer. *Cell* 1993; **75**: 1215-1225 [PMID: 8261515 DOI: 10.1016/0092-8674(93)90330-S]

17 **Papadopoulos N**, Nicolaides NC, Wei YF, Ruben SM, Carter KC, Rosen CA, Haseltine WA, Fleischmann RD, Fraser CM, Adams MD. Mutation of a mutL homolog in hereditary colon cancer. *Science* 1994; **263**: 1625-1629 [PMID: 8128251 DOI: 10.1126/science.8128251]

18 **Bronner CE**, Baker SM, Morrison PT, Warren G, Smith LG, Lescoe MK, Kane M, Earabino C, Lipford J, Lindblom A. Mutation in the DNA mismatch repair gene homologue hMLH1 is associated with hereditary non-polyposis colon cancer. *Nature* 1994; **368**: 258-261 [PMID: 8145827 DOI: 10.1038/368258a0]

19 **Nicolaides NC**, Papadopoulos N, Liu B, Wei YF, Carter KC, Ruben SM, Rosen CA, Haseltine WA, Fleischmann RD, Fraser CM. Mutations of two PMS homologues in hereditary nonpolyposis colon cancer. *Nature* 1994; **371**: 75-80 [PMID: 8072530 DOI: 10.1038/371075a0]

20 **Kolodner RD**, Hall NR, Lipford J, Kane MF, Rao MR, Morrison P, Wirth L, Finan PJ, Burn J, Chapman P. Structure of the human MSH2 locus and analysis of two Muir-Torre kindreds for msh2 mutations. *Genomics* 1994; **24**: 516-526 [PMID: 7713503 DOI: 10.1006/geno.1994.1661]

21 **Akiyama Y**, Sato H, Yamada T, Nagasaki H, Tsuchiya A, Abe R, Yuasa Y. Germ-line mutation of the hMSH6/GTBP gene in an atypical hereditary nonpolyposis colorectal cancer kindred. *Cancer Res* 1997; **57**: 3920-3923 [PMID: 9307272]

22 **Colas C**, Coulet F, Svrcek M, Collura A, Fléjou JF, Duval A, Hamelin R. Lynch or not Lynch? Is that always a question? *Adv Cancer Res* 2012; **113**: 121-166 [PMID: 22429854 DOI: 10.1016/B978-0-12-394280-7.00004-X]

23 **Shia J**, Black D, Hummer AJ, Boyd J, Soslow RA. Routinely assessed morphological features correlate with microsatellite instability status in endometrial cancer. *Hum Pathol* 2008; **39**: 116-125 [PMID: 17949789 DOI: 10.1016/j.humpath.2007.05.022]

24 **Aysal A**, Karnezis A, Medhi I, Grenert JP, Zaloudek CJ, Rabban JT. Ovarian endometrioid adenocarcinoma: incidence and clinical significance of the morphologic and immunohistochemical markers of mismatch repair protein defects and tumor microsatellite instability. *Am J Surg Pathol* 2012; **36**: 163-172 [PMID: 22189970 DOI: 10.1097/PAS.0b013e31823bc434]

25 **Chui MH**, Ryan P, Radigan J, Ferguson SE, Pollett A, Aronson M, Semotiuk K, Holter S, Sy K, Kwon JS, Soma A, Singh N, Gallinger S, Shaw P, Arseneau J, Foulkes WD, Gilks CB, Clarke BA. The histomorphology of Lynch syndrome-associated ovarian carcinomas: toward a subtype-specific screening strategy. *Am J Surg Pathol* 2014; **38**: 1173-1181 [PMID: 25025451 DOI: 10.1097/PAS.0000000000000298]

26 **Ketabi Z**, Bartuma K, Bernstein I, Malander S, Grönberg H, Björck E, Holck S, Nilbert M. Ovarian cancer linked to Lynch syndrome typically presents as early-onset, non-serous epithelial tumors. *Gynecol Oncol* 2011; **121**: 462-465 [PMID: 21388660 DOI: 10.1016/j.ygyno.2011.02.010]

27 **Fidalgo PO**, Cravo ML, Nobre-Leitão C. Re: A National Cancer Institute Workshop on Hereditary Nonpolyposis Colorectal Cancer Syndrome: meeting highlights and Bethesda Guidelines. *J Natl Cancer Inst* 1998; **90**: 939-940 [PMID: 9637147 DOI: 10.1093/jnci/90.12.939]

28 **Umar A**, Boland CR, Terdiman JP, Syngal S, de la Chapelle A, Rüschoff J, Fishel R, Lindor NM, Burgart LJ, Hamelin R, Hamilton SR, Hiatt RA, Jass J, Lindblom A, Lynch HT, Peltomaki P, Ramsey SD, Rodriguez-Bigas MA, Vasen HF, Hawk ET, Barrett JC, Freedman AN, Srivastava S. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst* 2004; **96**: 261-268 [PMID: 14970275 DOI: 10.1093/jnci/djh034]

29 **Cohen SA**, Leininger A. The genetic basis of Lynch syndrome and its implications for clinical practice and risk management. *Appl Clin Genet* 2014; **7**: 147-158 [PMID: 25161364 DOI: 10.2147/TACG.S51483]

30 **Steinke V**, Holzapfel S, Loeffler M, Holinski-Feder E, Morak M, Schackert HK, Görgens H, Pox C, Royer-Pokora B, von Knebel-Doeberitz M, Büttner R, Propping P, Engel C. Evaluating the performance of clinical criteria for predicting mismatch repair gene mutations in Lynch syndrome: a comprehensive analysis of 3,671 families. *Int J Cancer* 2014; **135**: 69-77 [PMID: 24493211 DOI: 10.1002/ijc.28650]

31 **Kwon JS**, Scott JL, Gilks CB, Daniels MS, Sun CC, Lu KH. Testing women with endometrial cancer to detect Lynch syndrome. *J Clin Oncol* 2011; **29**: 2247-2252 [PMID: 21537049 DOI: 10.1200/JCO.2010.32.9979]

32 **Vasen HF**, Blanco I, Aktan-Collan K, Gopie JP, Alonso A, Aretz S, Bernstein I, Bertario L, Burn J, Capella G, Colas C, Engel C, Frayling IM, Genuardi M, Heinimann K, Hes FJ, Hodgson SV, Karagiannis JA, Lalloo F, Lindblom A, Mecklin JP, Møller P, Myrhoj T, Nagengast FM, Parc Y, Ponz de Leon M, Renkonen-Sinisalo L, Sampson JR, Stormorken A, Sijmons RH, Tejpar S, Thomas HJ, Rahner N, Wijnen JT, Järvinen HJ, Möslein G. Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. *Gut* 2013; **62**: 812-823 [PMID: 23408351 DOI: 10.1136/gutjnl-2012-304356]

33 **Järvinen HJ**, Renkonen-Sinisalo L, Aktán-Collán K, Peltomäki P, Aaltonen LA, Mecklin JP. Ten years after mutation testing for Lynch syndrome: cancer incidence and outcome in mutation-positive and mutation-negative family members. *J Clin Oncol* 2009; **27**: 4793-4797 [PMID: 19720893 DOI: 10.1200/JCO.2009.23.7784]

34 **Colombo N**, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, Marth C, Nout R, Querleu D, Mirza MR, Sessa C. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: Diagnosis, Treatment and Follow-up. *Int J Gynecol Cancer* 2016; **26**: 2-30 [PMID: 26645990 DOI: 10.1097/IGC.0000000000000609]

35 **Dove-Edwin I**, Boks D, Goff S, Kenter GG, Carpenter R, Vasen HF, Thomas HJ. The outcome of endometrial carcinoma surveillance by ultrasound scan in women at risk of hereditary nonpolyposis colorectal carcinoma and familial colorectal carcinoma. *Cancer* 2002; **94**: 1708-1712 [PMID: 11920532 DOI: 10.1002/cncr.10380]

36 **Rijcken FE**, Mourits MJ, Kleibeuker JH, Hollema H, van der Zee AG. Gynecologic screening in hereditary nonpolyposis colorectal cancer. *Gynecol Oncol* 2003; **91**: 74-80 [PMID: 14529665 DOI: 10.1016/S0090-8258(03)00371-8]

37 **Lécuru F**, Huchon C, Metzger U, Bats AS, Le Frère Belda MA, Olschwang S, Puig PL. Contribution of ultrasonography to endometrial cancer screening in patients with hereditary nonpolyposis colorectal cancer/Lynch syndrome. *Int J Gynecol Cancer* 2010; **20**: 583-587 [PMID: 20686377 DOI: 10.1111/IGC.0b013e3181d7283a]

38 **Renkonen-Sinisalo L**, Bützow R, Leminen A, Lehtovirta P, Mecklin JP, Järvinen HJ. Surveillance for endometrial cancer in hereditary nonpolyposis colorectal cancer syndrome. *Int J Cancer* 2007; **120**: 821-824 [PMID: 17096354 DOI: 10.1002/ijc.22446]

39 **Gerritzen LH**, Hoogerbrugge N, Oei AL, Nagengast FM, van Ham MA, Massuger LF, de Hullu JA. Improvement of endometrial biopsy over transvaginal ultrasound alone for endometrial surveillance in women with Lynch syndrome. *Fam Cancer* 2009; **8**: 391-397 [PMID: 19504173 DOI: 10.1007/s10689-009-9252-x]

40 **Helder-Woolderink JM**, De Bock GH, Sijmons RH, Hollema H, Mourits MJ. The additional value of endometrial sampling in the early detection of endometrial cancer in women with Lynch syndrome. *Gynecol Oncol* 2013; **131**: 304-308 [PMID: 23769810 DOI: 10.1016/j.ygyno.2013.05.032]

41 **Thorson AG**, Knezetic JA, Lynch HT. A century of progress in hereditary nonpolyposis colorectal cancer (Lynch syndrome). *Dis Colon Rectum* 1999; **42**: 1-9 [PMID: 10211513 DOI: 10.1007/BF02235175]

42 **Lécuru F**, Le Frère Belda MA, Bats AS, Tulpin L, Metzger U, Olschwang S, Laurent-Puig P. Performance of office hysteroscopy and endometrial biopsy for detecting endometrial disease in women at risk of human non-polyposis colon cancer: a prospective study. *Int J Gynecol Cancer* 2016; **18**: 1326-1331 [PMID: 18217965 DOI: 10.1111/j.1525-1438.2007.01183.x]

43 **Manchanda R**, Saridogan E, Abdelraheim A, Johnson M, Rosenthal AN, Benjamin E, Brunell C, Side L, Gessler S, Jacobs I, Menon U. Annual outpatient hysteroscopy and endometrial sampling (OHES) in HNPCC/Lynch syndrome (LS). *Arch Gynecol Obstet* 2012; **286**: 1555-1562 [PMID: 22865035 DOI: 10.1007/s00404-012-2492-2]

44 **Steiner G**, Schoenberg MP, Linn JF, Mao L, Sidransky D. Detection of bladder cancer recurrence by microsatellite analysis of urine. *Nat Med* 1997; **3**: 621-624 [PMID: 9176487 DOI: 10.1038/nm0697-621]

45 **Amira N**, Mourah S, Rozet F, Teillac P, Fiet J, Aubin P, Cortesse A, Desgrandchamps F, Le Duc A, Cussenot O, Soliman H. Non-invasive molecular detection of bladder cancer recurrence. *Int J Cancer* 2002; **101**: 293-297 [PMID: 12209982 DOI: 10.1002/ijc.10561]

46 **Bouquier J**, Blons H, Narjoz C, Lécuru F, Laurent-Puig P, Bats AS. Microsatellite instability analysis in uterine cavity washings as a screening tool for endometrial cancer in Lynch syndrome. *Fam Cancer* 2011; **10**: 655-657 [PMID: 21822721 DOI: 10.1007/s10689-011-9470-x]

47 **Bats AS**, Roussel H, Narjoz C, Le Frere-Belda MA, Chamming's F, Blons H, Laurent-Puig P, Lecuru F. Microsatellite instability analysis for the screening of synchronous endometrial and ovarian cancer in Lynch syndrome. *Anticancer Res* 2013; **33**: 3977-3981 [PMID: 24023337]

48 **Verma L**, Kane MF, Brassett C, Schmeits J, Evans DG, Kolodner RD, Maher ER. Mononucleotide microsatellite instability and germline MSH6 mutation analysis in early onset colorectal cancer. *J Med Genet* 1999; **36**: 678-682 [PMID: 10507723]

49 **Wu Y**, Berends MJ, Mensink RG, Kempinga C, Sijmons RH, van Der Zee AG, Hollema H, Kleibeuker JH, Buys CH, Hofstra RM. Association of hereditary nonpolyposis colorectal cancer-related tumors displaying low microsatellite instability with MSH6 germline mutations. *Am J Hum Genet* 1999; **65**: 1291-1298 [PMID: 10521294 DOI: 10.1086/302612]

50 **Ketabi Z**, Gerdes AM, Mosgaard B, Ladelund S, Bernstein I. The results of gynecologic surveillance in families with hereditary nonpolyposis colorectal cancer. *Gynecol Oncol* 2014; **133**: 526-530 [PMID: 24631699 DOI: 10.1016/j.ygyno.2014.03.012]

51 **Nutis M**, García KM, Nuwayhid B, Mulla Z, ElMasri W. Use of ultrasonographic cut point for diagnosing endometrial pathology in postmenopausal women with multiple risk factors for endometrial cancer. *J Reprod Med* 2008; **53**: 755-759 [PMID: 19004400]

52 **Ketabi Z**, Mosgaard BJ, Gerdes AM, Ladelund S, Bernstein IT. Awareness of endometrial cancer risk and compliance with screening in hereditary nonpolyposis colorectal cancer. *Obstet Gynecol* 2012; **120**: 1005-1012 [PMID: 23090516 DOI: http: //10.1097/AOG.0b013e31826ba2aa]

53 **Schmeler KM**, Lynch HT, Chen LM, Munsell MF, Soliman PT, Clark MB, Daniels MS, White KG, Boyd-Rogers SG, Conrad PG, Yang KY, Rubin MM, Sun CC, Slomovitz BM, Gershenson DM, Lu KH. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. *N Engl J Med* 2006; **354**: 261-269 [PMID: 16421367 DOI: 10.1097/01.ogx.0000216536.75662.99]

54 **Karamurzin Y**, Soslow RA, Garg K. Histologic evaluation of prophylactic hysterectomy and oophorectomy in Lynch syndrome. *Am J Surg Pathol* 2013; **37**: 579-585 [PMID: 23426126 DOI: 10.1097/PAS.0b013e3182796e27]

55 **Moldovan R**, Keating S, Clancy T. The impact of risk-reducing gynaecological surgery in premenopausal women at high risk of endometrial and ovarian cancer due to Lynch syndrome. *Fam Cancer* 2015; **14**: 51-60 [PMID: 25342222 DOI: 10.1007/s10689-014-9761-0]

56 **Stoffel EM**, Walsh C. Chemoprevention of endometrial cancer in Lynch syndrome: a step forward. *Cancer Prev Res (Phila)* 2013; **6**: 755-759 [PMID: 23842794 DOI: 10.1158/1940-6207.CAPR-13-0238]

**P-Reviewer:** Khajehei M, Wang PH, Yokoyama Y **S-Editor:** Qiu S **L-Editor: E-Editor:**