

## Screening and diagnosis of endometrial cancer in Lynch syndrome

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### 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 CA125 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 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

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**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.

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## 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<sup>[1]</sup>. 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<sup>[2-4]</sup>.

If the risk of colorectal cancer was initially estimated at 80% at the age of 80 years, and 60% for endometrial cancer<sup>[5]</sup>, 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%<sup>[6]</sup>. 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<sup>[7]</sup>, 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<sup>[8,9]</sup>. 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<sup>[8]</sup>. However, the transition hyperplasia-cancer is faster than in the general population. Complex and atypical hyperplasia

emerge as premalignant lesions in LS<sup>[10]</sup>.

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<sup>[11]</sup>. 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<sup>[12]</sup>.

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<sup>[13]</sup>.

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%)<sup>[7]</sup>, 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<sup>[11]</sup>.

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%<sup>[3,4,6,14]</sup>. Moreover, Watson *et al*<sup>[4]</sup> 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)<sup>[1]</sup>. Four MMR genes have been identified: *hMLH1*, *hMSH2*, *hMSH6* and *PMS2*<sup>[15-21]</sup>. 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<sup>[2-4,22]</sup>.

## 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<sup>[1]</sup>.

If the risk of colorectal cancer was initially estimated at 80% at the age of 80 years, and 60% for endometrial cancer<sup>[5]</sup>, 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%<sup>[6]</sup>. The ERISCAM study, which is a prospective multicentre French cohort on patients with MMR gene mutation<sup>[7]</sup>, 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<sup>[8]</sup>.

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<sup>[8]</sup>. Complex and atypical hyperplasia emerge as premalignant lesions in LS<sup>[10]</sup>.

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<sup>[11]</sup>. 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<sup>[12]</sup>. 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<sup>[23]</sup>.

## OVARIAN CANCER IN LS

Bonadona *et al*<sup>[7]</sup> 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<sup>[24,25]</sup>.

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<sup>[26]</sup>.

Ketabi *et al*<sup>[26]</sup> 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<sup>[13]</sup>. Therefore, in 1997, the less stringent Bethesda Guidelines were developed. These criteria consider medical and familial history of LS-associated tumors<sup>[27]</sup>. In 2004, these guidelines were revised in order to achieve higher specificity<sup>[28]</sup>. Few studies had described these criteria but had limited sample sizes and focused only on *hMLH1* and *hMSH2* mutations<sup>[29,30]</sup>.

In 2011, Kwon *et al*<sup>[31]</sup> 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.

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

## 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<sup>[33]</sup>, 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 CA125 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<sup>[34]</sup>. They defined that patients with high risk of endometrial cancer should include women with genetic mutation of HNPCC, those showing a substantial likelihood 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<sup>[32,34]</sup>.

### Screening by pelvic ultrasound

The accuracy of ultrasonography was analyzed by three main studies.

Dove-Edwin *et al*<sup>[35]</sup> 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*<sup>[36]</sup> observed 41 women with identified mutation or fulfilling the Amsterdam criteria II. An annual clinical examination was associated with a transvaginal ultrasound and CA125 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 4 mm in postmenopausal women without hormone replacement treatment or 6 mm in other cases. Endometrial biopsy was performed at the same time. With a median of 51 mo (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)<sup>[37]</sup>.

### Screening by endometrial biopsy

The value of endometrial biopsy has been reported in three conflicting studies<sup>[38-40]</sup>. Renkonen-Sinisalo *et al*<sup>[38]</sup> 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 mo after a normal screening, and 1 at the time of prophylactic



hysterectomy. In addition, 14 hyperplasia were found<sup>[38]</sup>. Gerritzen *et al.*<sup>[39]</sup> 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<sup>[40]</sup>.

### Screening by hysteroscopy

Diagnostic hysteroscopy has also been proposed as a screening tool in LS<sup>[41-43]</sup>. 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<sup>[42]</sup>. 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 mo 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<sup>[43]</sup>.

### 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<sup>[44,45]</sup>. Ichikawa *et al.*<sup>[8]</sup> 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<sup>[46,47]</sup>. 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<sup>[48,49]</sup>. In this case, it is interesting to investigate by immunohistochemistry a loss of expression of the corresponding MMR protein. Ketabi *et al.*<sup>[50]</sup> 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.*<sup>[35]</sup> reported that pelvic ultrasound failed to detect ovarian cancer. Similarly, pelvic ultrasound associated with CA125 assay showed no evidence of ovarian cancer through screening<sup>[36,38]</sup>, while Renkonen-Sinisalo *et al.*<sup>[38]</sup> found 4 interval cancers. Gerritzen *et al.*<sup>[39]</sup> 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<sup>[51]</sup>. Ketabi *et al.*<sup>[52]</sup> 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<sup>[33]</sup>).

## 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<sup>[34,50]</sup>.

The INCa and ESMO recommends prophylactic surgery in women with an identified mutation or a significant risk of cancer, when they have no more desire of pregnancy<sup>[34]</sup>. 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<sup>[7,34]</sup>. Minimally invasive approach should be preferably used<sup>[34]</sup>.

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

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<sup>[53]</sup>. But Karamurzin *et al.*<sup>[54]</sup> 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<sup>[55]</sup>. Nevertheless, Schmeler *et al.*<sup>[53]</sup> 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.*<sup>[56]</sup> described on short period (3 mo) 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.

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