Hereditary Cancers

7

Lorenzo Ceppi, Don S. Dizon, and Michael J. Birrer

7.1 Introduction

Every year, epithelial endometrial cancer (EC) incidence accounts for 7% of all cancers in women worldwide, representing the fourth most common malignancy arising in women. In the United States alone, over 61,800 new cases are expected and over 12,160 women will die of this disease in 2019 [1].

According to the Division of Cancer Prevention and Control, the incidence of endometrial cancer in the United States is likely to increase more than for many other types of cancers [2]: the number of cases per year will rise from 48,301 in 2010 to 63,119 in 2020 (+30.7%). Much of this increase is likely as a result of an aging population and more sedentary behaviors and the associated impact from obesity. However, there is a subset of patients (up to 5% [3]) in whom endometrial cancer is a manifestation of a familial syndrome, due to a genetic predisposition.

Familial risk for endometrial cancer is classically seen in patients impacted by Lynch Syndrome (formerly known as the Hereditary Non-polyposis Colorectal Cancer [HNPCC] syndrome), which has an estimated prevalence of 2–5% of newly diagnosed EC [4] and Cowden Syndrome, which is associated with a PTEN

L. Ceppi
Center for Cancer Research, The Gillette Center for Gynecologic Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Department of Medicine and Surgery, Milano-Bicocca University, ASST-Monza, Desio Hospital, Monza, Italy

D. S. Dizon
Center for Cancer Research, The Gillette Center for Gynecologic Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

M. J. Birrer (✉)
Center for Cancer Research, The Gillette Center for Gynecologic Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

O'Neal Cancer Center, Birmingham, AL, USA
e-mail: mbirrer@uab.edu

M. R. Mirza (ed.), *Management of Endometrial Cancer*,
https://doi.org/10.1007/978-3-319-64513-1_7

Table 7.1 Familial syndromes classically associated with endometrial cancer

Syndrome	Gene	Chromosome
Lynch		
Mismatch repair genes	MSH2 MLH1 MSH6 PMS2	2p21 3p21.3 2p16 7p22.2
Other genes	EPCAM	2p21
Cowden	PTEN	10q23.3

mutation. Although some reports suggest that mutations in BRCA1 or BRCA2, which are associated with Hereditary Breast Ovarian Cancer Syndrome (HBOCS), increase the risk of endometrial cancer, the data are controversial at best and no conclusive evidence is available to inform this question (Table 7.1).

The mutations in these syndromes are grounded in the germline inheritance of a single mutated allele of a tumor-suppressor gene. As one allele is inherited as mutated, the patient is more likely to develop a mutation or a loss of the function in the remaining allele. The loss of function of a cellular control is the basis of cancer development through lifetime [5].

In this chapter, we review the familial syndromes associated with an increased endometrial cancer risk.

7.2 Lynch Syndrome (LS)

Lynch syndrome, named after Dr. Henry Lynch, is a familial cancer syndrome manifest by cancers affecting patients at an early age. In the general population, LS is present in about 1–600 to 1–3000 individuals [6]. Classically, it is associated with colorectal cancer although it is recognized now that EC is also a common manifestation among women affected. LS is the most common cause of hereditary endometrial cancer [7] and accounts for 2–5% of all EC diagnoses. While HNPCC was used interchangeably with LS, it is no longer used [8] because of the heterogeneity on which it was applied to families who may or may not have had evidence of microsatellite instability on genomic testing.

The major phenotype of LS is colorectal cancer (CRC), and patients with LS have an estimated cumulative risk by age of 70 years of up to 55% of being affected. Beyond this, women with LS face a 30–45% lifetime risk of developing EC and a 4–20% risk of ovarian cancer (OC), highlighting the importance of gynecologic screening in these patients [9–11]. Indeed, several datasets indicate that for women, the risk of EC may exceed the risk of colorectal cancer [12]. Beyond these tumors, patients with LS are also at increased risk of other tumors compared to the general population, including tumors of the stomach, urinary tract, pancreatic or hepatobiliary tract, small bowel, brain, and skin (Table 7.2). Even though LS screening diagnostics and therapeutics are also related to other cancers (colorectal and ovarian cancer mainly), the discussion of these other associations are beyond the scope of the present review and will not be discussed.

Table 7.2 Cumulative risks of cancer by age 70 years in Lynch syndrome

Cancer	Risk in general population, %	Risk in LS, %	Mean age at diagnosis, years
Colon	5.5	35–55%	69
MLH1/MSH2		Female: 22–53	27–46
MSH6		Female: 10	54–63
PMS2		Female: 15	47–66
Endometrium	2.7	30–45%	65
MLH1/MSH2		14–54	48–62
MSH6		17–71	54–57
PMS2		15	49
Stomach	<1	0.2–13	49–55
Ovary	1.6	4–20	43–45
Hepato-biliary tract	<1	0.02–4	54–57
Urinary tract	<1	0.2–25	52–60
Small bowel	<1	0.4–12	46–49
Brain/central nervous system	<1	1–4	50
Sebaceous neoplasm	<1	1–9	NA
Pancreas	1.5	0.4–4.0	63–65

7.3 Genetics

LS is characterized by germline mutations in mismatch repair (MMR) genes: every individual that inherits the mutation is at an increased risk of developing cancer during their lifetime. The function of MMR system is to maintain genomic integrity by correcting base substitution mismatches and small insertion–deletion mismatches that are generated by errors in base pairing during DNA replication. The reported distribution of specific mutations in LS is 32, 39, 15, and 14% for MLH1 (MutL homolog 1), MSH2 (MutS homolog 2), MSH6 (MutS homolog 6), and PMS2 (post-meiotic segregation 2) [13]. Recently, mutation in EPCAM (formerly known as TACSTD1) was associated with Lynch syndrome. EPCAM 3′ end deletions act through a mechanism of tissue-specific epigenetic silencing causing MSH2 gene primer hypermethylation and loss of expression [14].

Mismatch repair deficiency leads to an accumulation of genetic mutations and genomic instability. The most common event is base-pair mismatch in the microsatellite regions, represented of repetitive nucleotide sequences (microsatellites) throughout the whole genome in coding and noncoding regions. This occurrence is known as microsatellite instability (MSI), a characteristic feature of LS-associated cancers. Mismatch repair can affect cell growth genes (TGFβR2 [15]) and of the DNA MMR genes themselves (hMSH3, hMSH6) that possibly drive the tumorigenesis in Lynch-related tumors.

Table 7.2 shows cumulative lifetime risk to age 70 of EC described in published reports.

The largest published dataset to date shows higher EC risk for mMLH1 carriers (54%) rather than for mMSH2 [16] (21%), with lower risk for mMSH6 carriers (16%). Even a much lower EC risk is related to PMS2 mutations [17]. EPCAM mutation carriers yield a very low EC risk compared to mMSH2 patients [18].

7.4 Clinical Features

LS-associated EC has a mean age of incidence in the late fourth decade, approximately 10 years earlier than the age of onset of sporadic EC [19]. For this reason, women with young onset EC (i.e., before 50) should be evaluated for LS, which impacts up to 10% of cases [20]. When such a tumor is diagnosed before 50 years it should be considered as a sentinel event [21], which often predates other cancer diagnoses by a decade.

Despite this younger age at diagnosis, there are few features to distinguish LS-associated and sporadic EC. Broaddus [22] compared 50 women with LS-associated EC to 42 women with sporadic EC diagnosed at a young age (<50 years) and 26 women who had EC with MSI associated with MLH1 promoter methylation (not Lynch-related genetic alteration). Among women with LS-associated EC, only three carried a mutation in MLH1, 94% of these cancers were associated with an MSH2 mutation. LS-associated EC appeared to have less endometrioid histology tumors, compared to women with sporadic EC and those with disease associated with MLH1 promoter methylation (86% versus 98 and 96%, respectively), were less likely to have tumor associated with lymph-vascular invasion (24% versus 40 and 52%, *P*, 0.005), were more likely to be stage I at diagnosis (78% versus 67 and 60%) and less likely to be stage III/IV at diagnosis (12% versus 26 and 36%). In addition, there appeared to be a trend among LS patients to have non-endometrioid histology. However, undifferentiated histology was only observed in EC associated with an MLH1 methylation. These reported differences had no statistical significance, if not otherwise reported, but they represent the only available comparison to date.

Some data suggest that the disease may arise from the lower uterine segment. In a study by Westin, et al. 29% of patients with LS-associated disease arose in the lower uterine segment, compared to only 1.8% in those with sporadic disease [23]. Finally, there does not appear to be any prognostic impact of EC based on whether or not it is associated with LS. This was illustrated by Boks et al. [24] who reported not only a similar distribution of histologic subtypes but also similar 5 years overall survival between the groups.

7.5 Genetic Risk Assessment

The purpose of a genetic risk assessment is to identify unaffected women at an elevated risk of cancer related to LS and to identify patients with EC who may be at increased risk of second malignancies. Multiple organizations have developed

criteria to identify patients at an increased risk based on history and clinical factors (Table 7.3).

The International Collaborative Group on Hereditary Non-polyposis Colorectal Cancer established criteria to identify HNPCC families in 1991 first (known as the Amsterdam I criteria) [25]. These criteria were developed for research purpose and included history of three cancer cases involving relatives with at least one first relative of the other two, cancer diagnoses in at least two generations, and one cancer diagnosed before 50 years. The specificity of these criteria was high, but the sensitivity was low as colonic malignancies only were considered.

The original criteria were broadened to include also extra colonic cancer diagnoses in an attempt to make identification of patients more sensitive in 1999 (Amsterdam II) [26], although these criteria were criticized as because in several studies, only 13–36% of mutation carrier families met these criteria [27, 28]. In addition, sensitivity remained low (0.22, range 0.13–0.67), though it was associated with high specificity (0.98, range 0.97–1.0).

In 1997, the Bethesda guidelines [29] were developed as an alternative to Amsterdam criteria and were revised to incorporate all cancer types seen with LS in

Table 7.3 Comparison between Revised Amsterdam and Bethesda criteria for Lynch Syndrome screening

Revised Amsterdam criteria for diagnosis of hereditary non-polyposis colorectal cancer	Revised Bethesda guidelines
1. Three or more relatives with histologically verified HNPCC-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis), one of which is a first-degree relative of the other two. Familial adenomatous polyposis should be excluded	1. CRC diagnosed at younger than 50 years
2. Cancer involving at least two generations	2. Presence of synchronous or metachronous CRC or other LS-associated tumors
3. One or more cancer cases diagnosed before the age of 50 years	3. CRC with MSI-high pathologic-associated features (Crohn-like lymphocytic reaction, mucinous/signet cell differentiation, or medullary growth pattern) diagnosed in an individual younger than 60 years old
	4. Patient with CRC and CRC or LS-associated tumor a diagnosed in at least one first-degree relative younger than 50 years old
	5. Patient with CRC and CRC or LS-associated tumor at any age in two first-degree or second-degree relatives
	a: LS-associated tumors include tumor of the colorectum, endometrium, stomach, ovary, pancreas, ureter, renal pelvis, biliary tract, brain, small bowel, sebaceous glands, and kerotoacanthomas

2004 [30]. Features were added to the original Amsterdam criteria, including age of diagnosis, tumor features, and personal and family cancer history. These guidelines have less strict criteria used to identify potential patients who might carry LS, but result in a higher sensitivity of 0.82 (0.78–0.91) although specificity is lower at 0.77 (0.75–0.79) [31]. Despite the different criteria, neither appears able to identify all patients with mismatch repair gene mutations. Revised Amsterdam criteria and Bethesda guidelines are listed in Table 7.3.

In 2007, the Society of Gynecologic Oncologists (SGO) aimed to provide further guidance on the role of genetic risk assessment based on clinical criteria (Table 7.4) [32]. In contrast to the Amsterdam I and Bethesda criteria, the SGO sought to stratify at-risk individuals into those in whom there is a 20–25% versus 5–10% chance of having LS, for whom testing would be recommended or helpful, respectively. The society listed cancer affected patients, but also not affected high risk patients. The proposed approach is to offer genetic testing to women with a first- or second-degree relative with a known mismatch repair gene mutation, secondly to women with a first- or second-degree relative with a LS-related tumor, regardless of age.

Table 7.4 SGO Education Committee statement on risk assessment for inherited gynecologic cancer predispositions

Patients with greater than approximately 20–25% chance of having an inherited predisposition to endometrial, colorectal, and related cancers and for whom genetic risk assessment is recommended	Patients with greater than approximately 5–10% chance of having an inherited predisposition to endometrial, colorectal, and related cancers and for whom genetic risk assessment may be helpful
1. Patients with endometrial or colorectal cancer who meet the Amsterdam II criteria	1. Patients with endometrial or colorectal cancer diagnosed prior to age 50
2. Patients with synchronous or metachronous endometrial and colorectal cancer with the first cancer diagnosed prior to age 50	2. Patient with endometrial or ovarian cancer with a synchronous or metachronous colon or other Lynch/HNPCC-associated tumor[a] at any age
3. Patients with synchronous or metachronous ovarian and colorectal cancer with the first cancer diagnosed prior to age 50	3. Patients with endometrial or colorectal cancer and a first-degree relative with a Lynch/HNPCC-associated tumor[a] diagnosed prior to age 50
4. Patients with colorectal or endometrial cancer with evidence of a mismatch repair defect (i.e. microsatellite instability (MSI) or immunohistochemical loss of expression of MLH1, MSH2, MSH6, or PMS2)	4. Patients with colorectal or endometrial cancer diagnosed at any age with two or more first- or second-degree relatives[b] with Lynch/HNPCC-associated tumors[a], regardless of age
5. Patients with a first- or second-degree relative with a known mismatch repair gene mutation	5. Patients with a first- or second-degree relative[b] that meets the above criteria[a]

[a]Lynch/HNPCC-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome) tumors, sebaceous gland adenomas and keratoacanthomas in Muir–Torre syndrome, and carcinoma of the small bowel

[b]First- and second-degree relatives are parents, siblings, aunts, uncles, nieces, nephews, grandparents, and grandchildren

7.6 Computational Models

In addition to clinical criteria, computational models are also available. These use algorithms that take into account clinical features to calculate individual risk for having an LS gene mutation. They are most often employed if clinical criteria suggest the presence of LS. Commonly used models are described below.

MMR predict model [33] uses sex and age at diagnosis of CRC, location of tumor (proximal vs. distal), multiple CRCs (synchronous or metachronous), diagnosis of EC in any first-degree relative, and age at diagnosis of CRC in first-degree relatives. http://hnpccpredict.hgu.mrc.ac.uk/.

MMRpro model [34] uses personal and family history of colorectal and endometrial cancer age at diagnosis and molecular testing results for MMR genes, if available. This calculator determines the risk divided for germline mutation and also indicated the risk for future cancer in presymptomatic gene carriers and other unaffected individuals. http://bcb.dfci.harvard.edu/bayesmendel/software.php.

PREMM$_{1,2,6}$ *model* [35] uses sex, personal, and family history of colorectal, endometrial, or other LS cancers. This calculator estimates for germline mutation risk. This model can be found at: http://premm.dfci.harvard.edu/.

It has been published that this model would be cost-effective improving health outcomes as primary screening of individuals between the ages of 25 and 35, followed by genetic testing of those whose risk exceeds 5% [36].

These models, developed with different methods for different purposes and with the primary aim to distinguish patients at risk for LS-related CRC, included also LS-related EC risk assessment. Mercado [37] assessed the area under the curve, sensitivity and specificity of the abovementioned prediction models among 563 population-based and 129 clinic-based endometrial cancer cases. Although the models were able to detect affected population (AUCs of 0.77, 0.76, and 0.77, respectively), in the clinic-based cohort the accuracy was lower (AUCs of 0.67, 0.64, and 0.54, respectively). The conclusion was that computational models have limited clinical utility in determining which patients with endometrial cancer should undergo genetic testing for Lynch syndrome. Immunohistochemical analysis and microsatellite instability testing may be the best currently available tools to screen for Lynch syndrome in endometrial cancer patients.

7.7 Tumor Testing

For affected patients in whom LS risk is strongly suspected, genomic testing of the tumor should be performed [38] to identify MMR system mutations, and to guide the next germline mutation genetic test.

Immunohistochemistry (IHC) can recognize mismatch repair deficiency through the test of MMR panel (MLH1, MSH2, MSH6, PMS2) on endometrial or colorectal tumor tissue, showing protein loss of expression. As a complementary tool, microsatellite instability can be tested through a polymerase chain reaction (PCR) assay [39]. Depending on the distribution of DNA fragments between tumor and normal

tissue, samples can be identified as MSI-high, -low, or stable, if no difference is shown. MSI-H is defined as instability in ≥30% of the examined microsatellites. Both MMR IHC and MSI testing have a high accuracy performance. IHC is preferred as a diagnostic tool, MSI testing can be considered in rare cases were no protein expression loss is shown in an individual with LS likely familiar history. Cases like that are when missense mutations occurs were a not functional MMR protein is produced. Indeed it is reported for MMR IHC and MSI testing [40] a sensitivity of 0.83 (0.75–0.89) and 0.85 (0.75–0.93), and a specificity of 0.89 (0.68–0.95) and 0.90 (0.87–0.93) respectively.

It is important to note that MLH1 loss with or without PMS2 protein loss can be the result of MLH1 promoter methylation, which occurs in 20–30% of endometrial cancers and up to 20% of colorectal cancers. This is not an hereditary mutation and the differential diagnosis must be ruled out. Several available tools for testing methylation based on fluorescence-based real-time PCR [41, 42], or on gene sequencing methods (pyrosequencing) [43] are available to perform such an analysis.

For patients with colorectal or endometrial cancer, a practice bulletin endorsed by the SGO suggests that testing of all affected women irrespective of age of diagnosis is perhaps the most sensitive approach to the identification of women with LS [44]. However, it is also acknowledged this would increase the patients' number tested by a factor of 3–4. Therefore, acknowledging that most women with either of these LS-related cancers present at a younger age, they ultimately recommend molecular screening of every CRC and EC diagnosed before age 60 years for LS when resources are available [45], and at least one subsequent report found that it was cost-effective [46]. SGO in a clinical practice statement [47] recommends universal screening to overcome lack of familiar history diagnoses, considering for screening also women older than 60 years.

To confirm the diagnosis, germline DNA mutation represent the definitive test. Also for unaffected patients where clinical suspect has to be confirmed, MMR and/or MSI testing can be performed on peripheral blood, which can be used to screen for large rearrangements.

In all cases where genetic testing is concerned, careful pre- and posttest counseling is critical and full informed consent should be given. This includes resources to provide psychosocial support, information regarding financial repercussions, and frank discussions regarding ethical implications of testing (e.g., testing of minors), and options for cancer prevention (including the role of risk-reducing surgeries). In the US, the Genetic Information Non-discrimination Act (GINA) (http://frwebgate.access.gpo.gov/cgibin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ233.110.pdf) bars discrimination from employment or medical insurance coverage on the basis of genetic risk. However, this protection does not yet extend to other insurance types, including life and long-term care insurance.

7.8 Screening and Prevention

For patients with LS, screening is focused on gastrointestinal and gynecologic cancer. In one study, gastrointestinal screening with colonoscopy or sigmoidoscopy and barium enema every 3 years resulted in a lower incidence of colorectal cancer incidence

and death due to disease compared to a population that did not undergo screening [48]. These results were corroborated by a subsequent systematic review [49].

Although methods for screening for endometrial cancer are available, none have shown benefits in either earlier detection or survival. Dove-Edwin et al. [50] evaluated the role of transvaginal ultrasound in women from one of 292 LS families over a period of 13 years. Only two cases of endometrial carcinoma were reported and neither was detected by surveillance screening. Renkonen-Sinisalo et al. [51] reported their experience involving 175 women with MMR mutations using pelvic exam with endometrial biopsy. EC occurred in 14 cases, 11 of which were diagnosed by surveillance, 8 by intrauterine biopsies. Transvaginal ultrasound detected only 4 EC patients but missed 6 other cases. Intrauterine sampling detected 14 cases of potentially premalignant hyperplasia. Because of the potential for endometrial biopsy to detect disease, current guidelines suggest that this be performed every 1–2 years, starting at age 30–35 years [44].

7.9 Prophylactic Surgery

For women, hysterectomy is reasonable option for cancer prevention. If performed, a bilateral salpingo-oophorectomy should also be done as women with LS are also at risk for ovarian cancer.

The benefit of prophylactic pelvic surgery was shown in one study where women with documented MMR mutations underwent prophylactic hysterectomy and bilateral salpingo-oophorectomy were matched with controls without any surgery performed. The reduction of risk was substantial: no tumor occurred in the surgery group (61 patients) versus 69 cases of EC among 210 patients. A comparable risk reduction was demonstrated for ovarian cancer occurrence, where no ovarian or primary peritoneal tumor occurred versus 12 cases among 223 patients [52]. The incidence of endometrial in those who did not undergo prophylactic surgery was 33%. Of note, as discussed before, there are reports of intraoperative diagnoses of EC during prophylactic surgery in this population [51, 53].

A modeling study evaluated different screening strategies with risk reducing surgery and concluded that annual screening starting at age 30 years followed by prophylactic surgery at age 40 years was the most effective gynecologic cancer prevention strategy, but incremental benefit over prophylactic surgery at age 40 years alone was attained at substantial cost [54]. Patients should be counseled telling that the substantial increase of cancer risk occurs after 40s, and that the prophylactic approach before then is the most effective.

7.10 Chemoprevention

Chemoprevention against endometrial cancer may be provided by progestin-based oral contraceptives. These agents have a known impact on the overall incidence of EC [55] and are effective in preventing endometrial hyperplasia and early endometrial cancer treatment [56]. Studies demonstrated an increased breast cancer risk

related to combined hormonal replacement therapy (estrogens and progestins), but this evidence is not related to combined OCP.

Lu et al. reported evidence of effect of progestin-containing OCPs or depomedroxyprogesterone acetate (depoMPA) on endometrial proliferation in LS women [57], but the impact on subsequent cancer risk has not been adequately evaluated.

Although the data are limited, SGO/ACOG guidelines suggest the use of progestin-based contraception for chemoprevention in LS patients based on expert opinion.

NSAIDs and Cox-2 inhibitors have been tested as potential chemo preventative options in LS patients although most data come from studies to prevent colorectal cancer. For example, the CAPP2 [58] trial enrolled patients with LS and randomly assigned them to treatment with aspirin 600 mg per day or Novelose (resistant starch) for 4 years. The long-term analysis [59] showed a survival advantage for patients completing at least 2 years of aspirin treatment with a hazard ratio of 0.41 (95% CI, 0.19–0.86, $P = 0.02$). In addition, there was a trend towards a lower incidence of cancers, including those of the endometrium and ovary. Finally, there were no differences in adverse events reported and no protection for patients who underwent chemoprevention for less than 2 years was evident.

Currently, no sufficiently indication should be made to extend this treatment to LS population [60] to decrease cancer risk. There is a recommendation to discuss an individual patient treatment choice, taking into account risks and benefits [61].

7.11 Other Cancer Syndromes Associated with an Increased Risk of Endometrial Cancer

7.11.1 Muir-Torre Syndrome

Muir-Torre Syndrome is an autosomal-dominant inherited skin condition characterized by sebaceous skin adenoma, epithelioma or and carcinoma, multiple keratoacantomas, and visceral diseases such as colorectal, endometrial, urological, and upper gastrointestinal cancers. It is considered a Lynch variant due to the same underlying mutations that drive these tumors as LS: MSH2 and MLH1 [62, 63]. As such, the cancer risk in this population is the same as LS. However, given the risk of skin carcinomas, screening for Muir-Torre syndrome-associated skin lesions among LS patients is recommended.

7.11.2 Cowden Syndrome

Cowden Syndrome is associated with an autosomic germline mutation in PTEN gene, and it is part of the PTEN hamartoma tumor syndrome. As its description,

individuals with Cowden Syndrome are at increased risk for benign and malignant neoplasias including skin and mucosal hamartomas, as well as intestine polyps. The greatest risk for women with CS is breast cancer with a lifetime risk of 85%, followed by thyroid 35%, kidney 33%, endometrial 28%, and colorectal 9% cancers, and melanoma 6% [64, 65]. It is estimated that CS affects 1 in 20,000 individuals. The median occurrence of these diseases is 20–30 years. While general cancer screening is recommended [66], there are none specific to endometrial cancer. Instead, patients who develop abnormal uterine bleeding (menorrhagia or any bleeding other than normal period) should be referred for further evaluation.

7.11.3 Hereditary Breast Ovarian Cancer Syndrome

At this time, whether patients with hereditary breast and ovarian cancer syndrome (HBOCS), most commonly associated with mutations in BRCA genes, have an increased risk of endometrial cancer is controversial. Levine et al. studied a consecutive series of 199 Ashkenazi Jewish population with EC. He found that among this population, only three EC cases had BRCA1 or 2 mutations [67]. Notably, not even the 17 cases of papillary serous endometrial carcinoma were associated with a BRCA mutation. A separate prospective study showed that only 6 of 857 BRCA1 and BRCA2 mutation carriers developed EC after an average follow-up time of 3.3 years and in 4 of these cases, EC was also associated with tamoxifen use [68]. The low incidence of EC in BRCA carriers was underscored in a separate study which reported 17 cases of EC among 4456 women with a BRCA mutation after a mean follow-up of 5.7 years [69]. In this study, the Standardized Incidence Ratio (SIR) for BRCA1 carriers was 1.91 (95% CI: 1.06–3.19, $p = 0.03$) and for BRCA2 carriers was 1.75 (95% CI: 0.55–4.23, $p = 0.2$). The SIR for women who received tamoxifen was 4.14 (95% CI: 1.92–7.87) and was 1.67 (95% CI: 0.81–3.07) for women who did not. The authors concluded that the higher endometrial cancer risk in BRCA1 mutation carriers was attributable to a history of tamoxifen use. For this reason hysterectomy at the time of prophylactic BSO may be a reasonable option, but only if subsequent treatment with tamoxifen is being considered. At present, there is no guidance on the role of hysterectomy or the risk management for EC in women with a BRCA mutation.

7.11.3.1 Recommendations for Lynch Syndrome, from SGO/ACOG Guidelines [43]

Limited or Inconsistent Scientific Evidence (Level B)

1. Genetic risk assessment should be considered for unaffected women who have a first-degree relative affected with endometrial or colorectal cancer who was either diagnosed before age 60 years or who is identified to be at risk of Lynch syndrome by one of the systematic clinical screens that incorporates a focused personal and family medical history.
2. Whenever possible, molecular evaluation for Lynch syndrome should begin with tumor testing.

3. Obstetric and gynecologic physicians and practices should adopt one of the following three approaches for assessing the possibility of Lynch syndrome in a woman personally affected with colorectal or endometrial cancer:
   (a) Perform tumor testing on any endometrial or colorectal tumor from a woman identified to be at risk of Lynch syndrome through a systematic clinical screen that includes a focused personal and family medical history.
   (b) Perform tumor testing on all endometrial or colorectal tumors irrespective of age of diagnosis.
   (c) Perform tumor testing on all endometrial or colorectal tumors diagnosed before age 60 years.

Consensus and Expert Opinion (Level C)

– Progestin-based contraception, including oral contraceptives, may be considered for chemoprevention of endometrial cancer in women with Lynch syndrome.

References

1. Siegel RL, et al. Cancer statistics, 2015. CA Cancer J Clin. 2015;65:5–29.
2. Weir HK. The past, present, and future of cancer incidence in the United States: 1975 through 2020. Cancer. 2015;121:1827.
3. Gruber SB, Thompson WD. A population-based study of endometrial cancer and familial risk in younger women. cancer and steroid hormone study group. Cancer Epidemiol Biomark Prev. 1996;5(6):411–7.
4. Watson P, Lynch H. Extracolonic cancer in hereditary non poliposis colon rectal cancer. Cancer. 1993;71:677.
5. Knudson AG Jr. Hereditary cancer, oncogenes, and antioncogenes. Cancer Res. 1985;45:1437–43.
6. Dunlop MG, Farrington SM, Nicholl I, et al. Population carrier frequency of hMSH2 and hMLH1 mutations. Br J Cancer. 2000;83(12):1643–5.
7. Hendriks YM, De Jong AE, Morreau H, et al. Diagnostic approach and management of Lynch syndrome (hereditary nonpolyposis colorectal carcinoma): a guide for clinicians. CA Cancer J Clin. 2006;56:213–25.
8. Jass JR. Hereditary non-polyposis colorectal cancer: the rise and fall of a confusing term. World J Gastroenterol. 2006;12:4943–50.
9. Dunlop MG, Farrington SM, Carothers AD, et al. Cancer risk associated with germline DNA mismatch repair gene mutations. Hum Mol Genet. 1997;6(1):105–10.
10. Barrow E, Alduaij W, Robinson L, Shenton A, Clancy T, Lalloo F, Hill J, Evans DG. Colorectal cancer in HNPCC: cumulative lifetime incidence, survival and tumour distribution. A report of 121 families with proven mutations. Clin Genet. 2008;74(3):233–42.
11. Stoffel E, Mukherjee B, Raymond VM, et al. Calculation of risk of colorectal and endometrial cancer among patients with Lynch syndrome. Gastroenterology. 2009;137(5):1621–7.
12. Barrow E, Hill J, Evans DG. Cancer risk in Lynch syndrome. Familial Cancer. 2013;12(2):229–40.
13. Palomaki GE, et al. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. Genet Med. 2009;11(1):42–65.

14. Ligtenberg MJ, Kuiper RP, Chan TL, et al. Heritable somatic methylation and inactivation of MSH2 in families with Lynch syndrome due to deletion of the 3′ exons of TACSTD1. Nat Genet. 2009;41:112–7.
15. Kim TM, Laird PW, Park PJ. The landscape of microsatellite instability in colorectal and endometrial cancer genomes. Cell. 2013;155(4):858–68.
16. Bonadona V, Bonaiti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2 and MSH6 genes in Lynch syndrome. JAMA. 2011;305:2304.
17. Senter L, Clendenning M, Sotamaa K, et al. Th e clinical phenotype of Lynch syndrome due to germ-line PMS2 mutations. Gastroenterology. 2008;135:419–28.
18. Ligtenberg MJ, Kuiper RP, Geurts van Kessel A, Hoogerbrugge N. EPCAM deletion carriers constitute a unique subgroup of Lynch syndrome patients. Familial Cancer. 2013;12(2):169.
19. Aarnio M, et al. Clinicopathological features and management of cancers in lynch syndrome. Pathol Res Int. 2012:350309.
20. Lu KE, Schorge JO, et al. Prospective determination of prevalence of Lynch syndrome in young women with endometrial cancer. J Clin Oncol. 2007;25(33):5158–64.
21. Lu KH, Dinh M, Kohlmann W, et al. Gynecologic malignancy as a "sentinel cancer" for women with HNPCC. Obstet Gynecol. 2005;105:569–74.
22. Broaddus RR, Lynch HT, Chen LM, et al. Pathologic features of endometrial carcinoma associated with HNPCC: a comparison with sporadic endometrial carcinoma. Cancer. 2006;106:87.
23. Westin SN, Lacour RA, Urbauer DL, Luthra R, Bodurka DC, Lu KH, Broaddus RR. Carcinoma of the lower uterine segment: a newly described association with Lynch syndrome. J Clin Oncol. 2008;26:5965.
24. Boks DE, Trujillo AP, Voogd AC, et al. Survival analysis of endometrial carcinoma associated with hereditary nonpolyposis colorectal cancer. Int J Cancer. 2002;102(2):198–200.
25. Vasen HFA, Mecklin JP, Meera Khan P, et al. The international collaborative group on hereditary non-polyposis colorectal cancer. Dis Colon Rectum. 1991;34:424–5.
26. Vasen HFA, Watson P, Mecklin JP, et al. New criteria for hereditary non-polyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative Group on HNPCC (ICG-HNPCC). Gastroenterology. 1999;116:1453–6.
27. Hampel H, Frankel WL, Martin E, Arnold M, Khanduja K, Kuebler P, et al. Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). N Engl J Med. 2005;352:1851–60.
28. Lindor NM, Rabe K, Petersen GM, et al. Lower cancer incidence in Amsterdam-I criteria families without mismatch repair deficiency: familial colorectal cancer type X. JAMA. 2005;293:1979–85.
29. American Gastroenterological Association. American Gastroenterological Association medical position statement: hereditary colorectal cancer and genetic testing. Gastroenterology. 2001;121(1):195.
30. Umar A, et al. Revised Bethesda guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst. 2004;96:261–8.
31. Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-society Task Force on colorectal cancer. Am J Gastroenterol. 2014;109(8):1159–79.
32. Lancaster JM, et al. SGO Committee statement Society of Gynecologic Oncologists Education Committee statement on risk assessment for inherited gynecologic cancer predispositions. Gynecol Oncol. 2007;107:159–62.
33. Green RC, Parfrey PS, Woods MO, et al. Prediction of Lynch syndrome in consecutive patients with colorectal cancer. J Natl Cancer Inst. 2009;101:331–40.
34. Barnetson RA, Tenesa A, Farrington SM, et al. Identification and survival of carriers of mutations in DNA mismatch-repairs genes in colon cancer. N Engl J Med. 2006;354:2751–63.
35. Kastrinos F, Steyerberg EW, Mercado R, et al. The PREMM(1,2,6) model predicts risk of MLH1, MSH2, and MSH6 germline mutations based on cancer history. Gastroenterology. 2011;40:73–81.

36. Dinh TA, Rosner BI, Atwood JC, et al. Health benefits and cost-effectiveness of primary genetic screening for Lynch syndrome in the general population. Cancer Prev Res. 2010;4:9–22.
37. Mercado RC, Hampel H, Kastrinos F, et al. Performance of PREMM1,2, 6, MMRpredict, and MMRpro in detecting Lynch syndrome among endometrial cancer cases. Genet Med. 2012;14(7):670–80.
38. Backes FJ, Leon ME, Ivanov I, et al. Prospective evaluation of DNA mismatch repair protein expression in primary endometrial cancer. Gynecol Oncol. 2009;114:486–90.
39. Umar A, Boland CR, Terdiman JP, et al. Revised Bethesda guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst. 2004;96(4):261–8.
40. Palomaki GE, McClain MR, Melillo S, et al. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. Genet Med. 2009;11:42–65.
41. Eads CA, Danenberg KD, Kawakami K, Saltz LB, Blake C, Shibata D, Danenberg PV, Laird PW. MethyLight: a high-throughput assay to measure DNA methylation. Nucleic Acids Res. 2000;28:E32.
42. Nygren AO, Ameziane N, Duarte HM, Vijzelaar RN, Waisfisz Q, Hess CJ, Schouten JP, Errami A. Methylation-specific MLPA (MS-MLPA): simultaneous detection of CpG methylation and copy number changes of up to 40 sequences. Nucleic Acids Res. 2005;33:e128.
43. Newton K, Jorgensen NM, Wallace AJ, et al. Tumour MLH1 promoter region methylation testing is an effective prescreen for Lynch syndrome (HNPCC) et al. J Med Genet. 2014;51:789–96.
44. American College of Obstetricians and Gynecologists. Lynch syndrome. Practice Bulletin No. 147. Obstet Gynecol. 2014;124:1042–54.
45. Society of Gynecologic Oncology. SGO clinical practice statement: screening for Lynch syndrome in endometrial cancer. Chicago: SGO; 2014. https://www.sgo.org/clinical-practice/guidelines/screeningfor-lynch-syndrome-in-endometrial-cancer/. Retrieved 22 July 2014.
46. Resnick KE, Hampel H, Fishel R, et al. Lynch syndrome screening strategies among newly diagnosed endometrial cancer patients. Gynecol Oncol. 2009;114(1):128–34.
47. Society of Gynecologic Oncology. SGO clinical practice statement: screening for Lynch syndrome in endometrial cancer. Chicago: SGO; 2014. https://www.sgo.org/clinical-practice/guidelines/screeningfor-lynch-syndrome-in-endometrial-cancer/. Retrieved May 2015.
48. Jarvinen HJ, Aarnio M, Mustonen M, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterology. 2000;118(5):829.
49. Lindor NM, et al. Lower cancer incidence in Amsterdam-I criteria families without mismatch repair deficiency: familial colorectal cancer type X. JAMA. 2005;293:1979–85.
50. Dove-Edwin I, Boks D, Goff S, et al. 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.
51. Renkonen-Sinisalo L, Bützow R, Leminen A, et al. Surveillance for endometrial cancer in hereditary nonpolyposis colorectal cancer syndrome. Int J Cancer. 2007;120(4):821.
52. Schmeler KM, Lynch HT, Chen LM, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med. 2006;354(3):261–9.
53. Chung L, Broaddus R, Crozier M, Luthraa R, Levenback C, Lu K. Unexpected endometrial cancer at prophylactic hysterectomy in a woman with hereditary nonpolyposis colon cancer. Obstet Gynecol. 2003;102(5 Pt 2):1152–5.
54. Kwon JS, Sun CC, Peterson SK, et al. Cost-effectiveness analysis of prevention strategies for gynecologic cancers in Lynch syndrome. Cancer. 2008;113:326–35.
55. Weiss NS, Sayvetz TA. Incidence of endometrial cancer in relation to the use of oral contraceptives. N Engl J Med. 1980;302:551–4.
56. Baker J, Obermair A, Gebski V, Janda M. Efficacy of oral or intrauterine device-delivered progestin in patients with complex endometrial hyperplasia with atypia or early endometrial adenocarcinoma: a meta-analysis and systematic review of the literature. Gynecol Oncol. 2012;125:263–70.

57. Lu KH, Loose DS, Yates MS, Nogueras-Gonzalez GM, Munsell MF, Chen LM, et al. Prospective, multi-center randomized intermediate biomarker study of oral contraceptive vs. Depo-Provera for prevention of endometrial cancer in women with Lynch syndrome. Cancer Prev Res. 2013;6:774–81.
58. Burn J, Bishop DT, Mecklin JP, et al. Effect of aspirin or resistant starch on colorectal neoplasia in the Lynch syndrome. N Engl J Med. 2008;359:2567–78.
59. Burn J, Gerdes AM, Macrae F, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomized controlled trial. Lancet. 2011;378:2081–7.
60. Rothwell PM, Fowkes FG, Belch JF, et al. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomized trials. Lancet. 2011;377:31–41.
61. National Comprehensive Cancer Network. Clinical practice guidelines in oncology genetic/familial high risk assessment: colorectal (Version 3.2019). https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf. Accessed June 2019.
62. Ponti G, Ponz de Leon M. Muir-Torre syndrome. Lancet Oncol. 2005;6:980.
63. South CD, et al. The frequency of Muir-Torre syndrome among Lynch syndrome families. J Natl Cancer Inst. 2008;100(4):277.
64. Gustafson S, Zbuk KM, Scacheri C, et al. Cowden syndrome. Semin Oncol. 2007;34(5):428–34.
65. Tan M-H, Mester JL, Ngeow J, Rybicki LA, Orloff MS, Eng C. Lifetime Cancer risks in individuals with germline PTEN mutations. Clin Cancer Res. 2012;18(2):400–7. https://doi.org/10.1158/1078-0432.CCR-11-2283.
66. National Comprehensive Cancer Network. Clinical practice guidelines in oncology genetic/familial high risk assessment: breast and ovarian (Version 2.2014). https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf. Accessed 22 June 2019.
67. Levine D, Lin O, Barakat R, et al. Risk of endometrial cancer associated with BRCA mutation. Gynecol Oncol. 2001;80(3):395–8.
68. Biener M, Fich A, Rosen B, et al. The risk of endometrial cancer in women with BRCA1 and BRCA2 mutations. A prospective study. Gynecol Oncol. 2007;104:7.
69. Segev Y1, Iqbal J, Lubinski J, et al. The incidence of endometrial cancer in women with BRCA1 and BRCA2 mutations: an international prospective cohort study. Gynecol Oncol. 2013;130(1):127–31.