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Hereditary Endometrial Cancer: Lynch Syndrome

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Abstract Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC]), Cowden syndrome (CS), and Peutz-Jeghers syndrome (PJS) are hereditary diseases with an increased risk for endometrial cancer. Lynch syndrome is the most frequent disease associated with hereditary endometrial cancer. Lynch syndrome is autosomal dominant disorder caused by germ-cell mutation of DNA mismatch repair genes. Patients with Lynch syndrome have a higher risk of endometrial cancer compared with the general population. Thus, these patients and their families may develop malignant tumors, including colon and endometrial cancers. The lifetime risk of endometrial cancer in females with Lynch syndrome is particularly high (28-60 %). Lynch syndrome is a typical hereditary tumor associated with endometrial cancer, and elucidation of the oncogenic mechanism is important to understand the characteristics of endometrial cancer, including sporadic endometrial cancer. The Amsterdam II Criteria are used for screening for Lynch syndrome, but some cases of hereditary endometrial cancer do not meet these criteria (masked Lynch syndrome); therefore, patients with a suspected hereditary predisposition, including juvenile-onset and double cancer, should undergo genetic tests in addition to taking of a family history.

Keywords Endometrial Cancer · Lynch syndrome · Revised Amsterdam Criteria · DNA mismatch repair gene · hMLH1 · hMSH2 · hMSH6 · Lower uterine segment · Epimutation · Gynecological cancer

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Introduction

Most cases of endometrial cancer result from multistep carcinogenesis after changes from a normal endometrium to atypical endometrial hyperplasia, which is a precancerous lesion in type 1 endometrial cancer. This process is thought to be due to accumulation of mutations in cancer-related genes, including oncogenes, tumor-suppressor genes, and DNA mismatch repair (MMR) genes. The cancer thus develops in a multistage process. In contrast, if aberrant cancer-related genes are already present in germ cells, the lifetime risk for endometrial cancer increases, and approximately 5 % of cases of endometrial cancer are thought to be caused by a genetic predisposition.

Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC]), Cowden syndrome (CS), and Peutz-Jeghers syndrome (PJS) are hereditary diseases with an increased risk for endometrial cancer. Lynch syndrome is the most frequent disease associated with hereditary endometrial cancer. Lynch syndrome also is associated with aberrant expression of MMR genes, which is important for understanding the carcinogenic mechanism and biological characteristics of sporadic endometrial cancers. Furthermore, patients with Lynch syndrome have a high risk of developing other diseases, including colon cancer. Therefore, screening and preventive measures are important for these patients and their family. In this review, we focus on Lynch syndrome and describe the latest findings for this disease, including the carcinogenic mechanism and screening methods.

Lynch syndrome and endometrial cancer

Lynch syndrome is a typical familial tumor with autosomal dominant inheritance. Female patients with Lynch syndrome complicate with endometrial cancer at a high incidence. In the revised 1999 Amsterdam II Criteria (ACII), endometrial cancer was included as a cancer similar to colon, small intestine, ureteral, and kidney cancers (Table 1) [1]. The prevalence of Lynch syndrome is 0.9-2.7 % [2], and approximately 2.3 % of cases of endometrial cancer occur due to Lynch syndrome [3]. The lifetime risk of endometrial cancer is 28-60 % in females with aberrant genes associated with Lynch syndrome (Table 2) [4].

Lynch syndrome is caused by germ-cell mutation of DNA MMR genes. Six MMR genes have been cloned: *hMLH1, hMSH2, hMSH3, hMSH6, PMS1,* and *PMS2*. *hMLH1, hMSH2,* and *hMSH6* mutations are particularly important in families of patients with Lynch syndrome (Table 3). Most mutations occur in *hMLH1* and *hMSH2* in patients with colon cancer [5], whereas *hMHS6* mutations are important role in tumorigenesis in patients with endometrial cancer [6, 7•]. Aberrations in these MMR genes prevent correct repair of mismatched bases, resulting in DNA strands with different lengths (Figure 1). This phenomenon occurs in microsatellite regions of the human genome and is referred to as microsatellite instability (MSI). Most short-tandem repeats (STRs), such as microsatellites, are present in noncoding regions and do not produce proteins with mutations. However, some STRs can occur in regions coding genes for which mutation is involved in carcinogenesis, including BAX, which is related to apoptosis induction, and *TGFRII*, which is associated with inhibition of cell proliferation [7•].

Clinicopathological characteristics of endometrial cancer in patients with Lynch syndrome

Broaddus et al. [8] described the clinicopathological characteristics of 50 patients with Lynch syndrome-related endometrial cancer with an *hMSH1* or *hMSH2* mutation (Group A), 42 patients with sporadic endometrial cancer aged <50 years with no aberrant mutation (Group B), and 26 patients with loss of hMLH protein expression and MSI-positive sporadic endometrial cancer due to *hMLH* promoter hypermethylation (Group C). The mean ages in Groups A, B, and C were 46.8, 39.9, and 61.1 years, with a significant difference between Groups A and C. There was a slightly more frequent occurrence of nonendometrioid adenocarcinoma (clear cell adenocarcinoma, serous adenocarcinoma, and carcinosarcoma) in Group A (14 %). Regarding differentiation, G2 and G3 endometrial cancer cells were frequently detected in Group C and vascular invasion also was found in Group C. The International Federation of Gynecology and Obstetrics (FIGO) surgical stage III and IV advanced cancer was more common in Group B compared with Group A [8]. Thus, cases of MSI-positive sporadic endometrial cancer due to *hMLH1* promoter methylation had less differentiation and most were advanced cancer; in contrast, Lynch syndrome-related endometrial cancer due to *hMLH1* or *hMSH2* mutation was clinicopathologically similar to endometrial cancer with onset at an early age.

The cases of Lynch syndrome-related endometrial cancer in Broaddus et al. [8] included multiple histological types, including nonendometrioid adenocarcinoma, and had different characteristics from those of sporadic endometrial cancer. However, most patients with Lynch syndrome had *hMSH2* mutations and the clinicopathological characteristics may differ from those of patients with *hMLH1* mutations. In addition,

Table 2 Risks of patients with hereditary diseases developing endometrial cancer throughout life

Disease	Risk throughout life
Lynch syndrome	42 % (diseased until 70 years old)
	61 % (MSH2 mutation)
	42 % (MLH1 mutation)
Cowden syndrome	5-10 %
Peutz-Jeghers syndrome	9 %

Table 1 Amsterdam Criteria in 1990 and 1999

Amsterdam Minimum Criteria (1990)
1. Al least 3 cases of colorectal cancer in relatives (verified pathologically)
2. One is a first degree relative to the other two
3. At least two successive generations should be affected
4. One case of colorectal cancer diagnosed before the age of 50 years old
5. FAP should be excluded
Revised Amsterdam Criteria II (1999)
1. At least 3 relatives with an HNPCC-associated cancer (cancer of the colorectum, endometrium, small bowel, ureter or renal pelvis)
2–5: As for the minimum criteria

Table 3 MMR genes related to Lynch syndrome

Gene	Chromosomal position	cDNA size	Exon size	Gene size
MSH2	2p21	2.8 kb	16	73 kb
MLH1	3p21-p23	2.3 kb	19	58-100 kb
MLH3	14q24.3	4.3 kb	12	37 kb
MSH6	2p21	4.2 kb	10	20 kb
PMS1	2q31	2.8 kb	12	93 kb
PMS2	7q22	2.6 kb	15	16 kb

the prognosis of Lynch syndrome-related endometrial cancer does not differ from that of sporadic endometrial cancer [9], but the onset age of sporadic endometrial cancer has been found to be 60 years, whereas that of Lynch syndrome-related endometrial cancer is only 48 years [10].

The Committee for Gynecologic Cancer of the Japan Society of Obstetrics and Gynecology (JSOG) evaluated the patient background, clinicopathological factors, and the incidence and type of double cancer in 34 patients with Lynch syndrome-related endometrial cancer meeting ACII, through comparison with 873 of 2,457 Japanese patients with sporadic endometrial cancer as controls. The mean ages of the patients with Lynch syndrome-related and sporadic endometrial cancer were 49.9 and 56.9 years, respectively, with a significantly younger age and juvenile onset in Lynch syndrome-related cancer. Regarding tissue type, non-endometrioid adenocarcinoma was not found in patients with Lynch syndrome-related cancer, which differs from reports outside Japan. The differentiation rates in the Lynch syndrome-related and sporadic endometrial cancer patients were 73.5 % and 59.3 % in G1, 8.8 % and 24.2 % in G2, and 17.7 % and 15.1 % in G3, respectively, indicating greater occurrence of the well-differentiated type in the Lynch syndrome-related group. The FIGO surgical stage was Stage I in 85.3 % of the patients with Lynch syndrome-related endometrial cancer and 66.5 % in those with sporadic endometrial cancer group, showing a greater occurrence of Stage I cases in Lynch syndrome-related endometrial cancer. The incidences of double cancer in the Lynch syndrome-related and sporadic endometrial cancer patients were 38.2 % and 5.8 %, respectively, with a significantly higher incidence in Lynch syndrome-related cancer. Regarding the type of double cancer, colon cancer was present in 69.2 % of the cases of Lynch syndrome-related endometrial cancer, whereas ovarian cancer, colon cancer, and breast cancer were found in 35.3 %, 25.5 %, and 23.5 % of the cases of sporadic endometrial cancer, respectively [11]. These reports suggest that the characteristics of Lynch syndrome in Asia may differ from those in Europe and the United States. International accumulation of cases and analyses are needed to resolve this issue [7•].

Hereditary endometrial cancer not meeting the Amsterdam II Criteria (ACII)

The revised 1999 Amsterdam II Criteria (ACII) is used for clinical screening of Lynch syndrome. However, the results

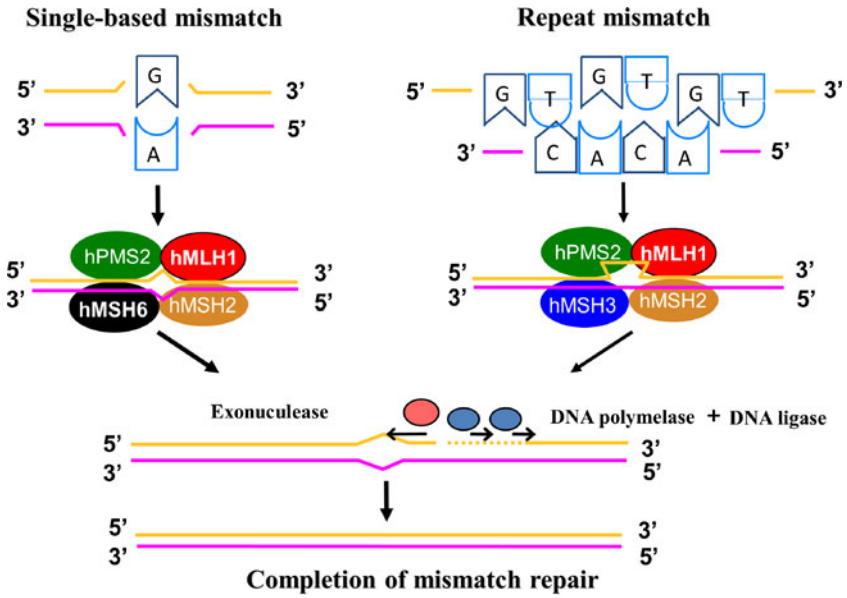

Fig. 1 Clinical criteria of Lynch syndrome

of germline MMR gene mutations show that some patients with a mutation do not meet ACII. These cases are referred to as cryptic Lynch syndrome. Thus, the incidence of Lynch syndrome-related endometrial cancer may actually be higher. Hampel et al. conducted a genetic analysis of MMR genes in 543 patients with endometrial cancer and detected a mutation in ten (1.8 %) of these cases (1 with *hMLH1*, 2 with *hMSH2*, and 6 with *hMSH6*), of which seven did not meet ACII [12]. ACII does not include Lynch syndrome-related cancers, such as gastric, breast, and ovarian cancers, and therefore these diagnostic criteria alone cannot detect all cases of familial endometrial cancer.

Hirai et al. performed mutation analysis of germline genes in patients with frequent familial onset of Lynch syndrome-related tumors (Group A) and double cancer (Group B). The multicenter collaborative study included patients with at least two first-degree relative probands (including themselves) with Lynch syndrome-related tumors (colon, endometrial, small intestinal, ureteral, renal pelvic, gastric, breast, and ovarian cancers) and in whom the age at onset of at least one tumor was ≤50 years in Group A, and patients with synchronous or metachronous double Lynch syndrome-related tumors who met the criteria in the revised Bethesda Guidelines for Lynch syndrome (2004) regardless of the onset age in Group B. Peripheral blood leukocyte-derived DNA was obtained from 120 patients (Group A: 57; Group B: 48; and Groups A+B: 15) and germline mutations in 3 MMR genes *(hMLH1*, *hMSH2* and *hMSH6*) were analyzed by direct sequence analysis. Gene mutations were found in 18 (15 %) of the 120 patients: 9 (15.8 %) in Group A; 4 (8.3 %) in Group B; and 5 (33.3 %) in Groups A+B. Of 18 patients with genetic mutations, 5 (27.8 %) had a mutation in *hMLH1*, 4 (22.2 %) in *hMSH2*, and 9 (50 %) in *hMSH6*. Of patients with mutations in *hMSH6*, eight had mutations mainly in exons 4–6 and most were frameshift mutations. Two of four patients who met ACII criteria (1 in Group A and 3 in Groups A+B) had *hMLH1* and *hMSH2* mutations, respectively. Among patients with double cancer who had genetic mutations, of six patients with double cancer, including colon cancer, five and one had mutations in *hMLH1* and *hMSH2*, respectively. In contrast, all three patients with double cancer, including breast or ovarian cancer, had mutations in *hMSH6*. All of the double cancers developed simultaneously with or before development of endometrial cancer [13, 14]. These results suggest that there may be many cases of Lynch syndrome-related endometrial cancer and that genetic analyses for MMR genes are useful in patients with endometrial or double cancer showing a familial cluster of cancer. Furthermore, mutation of the *hMSH6* gene appears to be particularly strongly associated with carcinogenesis of endometrial cancer.

Screening and surveillance for Lynch syndrome-related endometrial cancer

In general, hereditary tumors tend to be characterized by juvenile onset, multiple organ double cancer, and bilateral occurrence. The guidelines of the Gynecologic Oncologists (SGO) are useful for specific diagnosis of Lynch syndrome. These guidelines suggest that patients with endometrial and colon cancers who meet ACII, those who simultaneously or metachronously developed endometrial and colon cancers at age <50 years, those who simultaneously or metachronously develop ovarian and colon cancers at age <50 years, and those with a first or second-degree relative with aberrant MMR genes have a >20-25 % probability of hereditary predisposition for endometrial and colon cancers. Therefore, hereditary risks should be evaluated by genetic analysis in these patients. It has been shown that in patients diagnosed with endometrial and colon cancers at age <50 years, those with endometrial and ovarian cancers who simultaneously or metachronously complicate with a Lynch syndrome-related tumor, those with endometrial and colon cancers with at least two first- or second-degree relatives who developed a Lynch syndrome-related tumor, and those with a first- or second-degree relative who met the above criteria have a >5-10 % probability of hereditary predisposition for endometrial and colon cancers; therefore, evaluation of hereditary risks by genetic analysis is useful in these patients [15].

MSI analysis and immunohistochemical staining are useful for secondary screening to identify subjects who should undergo a mutation test for Lynch syndrome. The National Cancer Institute (NCI) recommends five satellite markers (BAT25, BAT26, D2S123, D5S346, and D173250) for MSI analysis [16]. A case with an allelic shift in at least two markers is defined as MSI-high and that with only one marker as MSI-low. However, most MSI reflects inactivity due to epigenetic changes in MMR genes and particularly *MLH1* promoter methylation, which occurs in sporadic endometrial cancer at a rate of approximately 20 % [17]. Therefore, MSI for screening for Lynch syndrome may not always be useful in patients with endometrial cancer. Immunohistochemical staining of MMR proteins may be less expensive and more effective for identifying aberrant MMR genes [18].

Patients with Lynch syndrome and persons from a family with Lynch syndrome have a high risk of other cancers. Therefore, appropriate screening and preventive measures for cancer are needed. Thus, Lindor et al. proposed that females with Lynch syndrome should undergo colonoscopy (every 1–2 years from age 20–25 years), transvaginal ultrasonography (once a year from age 30–35 years), urine cytology (every 1–2 years from age 25–35 years), and history taking and physical examination, including genetic counseling and a system review (every year from age 21 years), with hysterectomy and adnexectomy considered

if a patient does not want a child [19]. However, the effectiveness of these surveillance methods is unclear [20]. Preventive hysterectomy and ovariectomy have been discussed for risk reduction in colon cancer surgery for patients with Lynch syndrome who are older than reproductive age, but a consensus has not been reached.

Lynch syndrome and endometrial cancer in the lower uterine segment

Pathologically, the endometrium includes two regions: the uterine corpus (UC) and the lower uterine segment (LUS) [21]. Endometrial cancer usually develops in the mucosa of the UC and the uterine fundus but occasionally in the uterine isthmus in the LUS. If tumors are observed macroscopically to develop in the LUS and expand from the lower uterine corpus to the upper cervix, the disease is defined as carcinoma of the LUS. Cancer spreading from the uterine body to the internal cervix is excluded from this definition because the initial site is uncertain [22]. The LUS is located between the uterine body and cervix and has both endometrial and cervical characteristics in the grandular epithelium and stroma. The mucosal layer of the LUS is thinner compared with the uterine body, making the mucosal layer unlikely to respond to hormone stimulation [21]. Only a few cases have been described due to the rarity of endometrial cancer in the LUS; however, these cases have been shown to have clinicopathological characteristics that differ from those in normal endometrial cancer.

Westin et al. showed that 5 (14.2 %) of 35 patients with carcionma of the LUS met ACII criteria and had Lynch syndrome. All five patients had *hMSH2* mutation and also MSI, with decreased expression of hMSH2 protein shown by immunostaining. Among patients who did not meet ACII criteria, decreases in hMSH2 and hMSH6 protein levels were found in immunohistochemical staining and ten patients (29 %) were considered to have Lynch syndrome, including four who were strongly suspected to have a *hMSH2* mutation due to high MSI and one who had a decreased expression of hMLH1 protein, but no aberrant methylation [23]. These results show an incidence of Lynch syndrome in carcinoma of the LUS of 14.2 % based on the five patients with a definitive diagnosis of Lynch syndrome and an extremely high incidence based on the 1-2 % incidence of Lynch syndrome in patients with general endometrial cancer. Using immunological staining, Garg et al. showed that 5 of 32 patients with decreased expression of MMR proteins (hMLH1, hMSH2, hMSH6, and PMS2) had carcinoma of the LUS, whereas only 1 of 39 patients without abnormal protein expression had this disease, indicating a relationship between Lynch syndrome and carcinoma of the LUS [24]. Masuda et al. examined nine patients with carcinoma of the LUS and found that the onset age was significantly younger than that in cases of non-LUS carcinoma, although there were no significant differences in tissue type, FIGO surgical staging and MSI. One of the nine patients (11 %) with carcinoma of the LUS met ACII criteria and had Lynch syndrome. These patients had mutations of *hMLH1*, but not of *hMLH2*, and also had MSI and decreased hMLH1 protein in immunostaining. These results show a strong relationship of Lynch syndrome with carcinoma of the LUS [25•].

Epimutation and Lynch syndrome

Epimutation is defined as abnormal transcriptional repression of active genes caused by epigenetic abnormalities in germ cells. Epimutation is thought to be a direct cause of oncogenesis. Methylation has been shown recently in DNA from normal tissues and peripheral blood in cases of sporadic colorectal cancer, and many studies have shown epimutation in cancers, including epimutation of the DNA MMR genes *hMLH1* and *hMSH2*. These results have led to a focus on epimutation as a novel oncogenic mechanism [26•].

Epimutation affects one or both alleles of a gene and effectively reduces the level of the gene product by preventing transcription of the affected allele. Germline epimutation is an event in which epigenetic changes, such as aberrant methylation, occur at the stage of germ cells and are maintained in fertilization and embryonic development, resulting in persistence in adult somatic cells. Epigenetic characteristics can be transmitted over generations, but epimutation is not always inherited and may have a hereditary form that does not follow Mendelian inheritance [26•, 27–30]. Epimutation also may completely disappear in spermatogenesis [31], but epimutation inherited from the mother alone is unlikely to disappear during oogenesis [30, 31].

The relationship between epimutation and cancer has mainly been analyzed in colon cancer. Gazzoli et al. first showed that *hMLH1* may be methylated in peripheral blood, as well as in tumor tissue, in patients with colorectal cancer [32], based on a study in 14 patients with suspected Lynch syndrome with MSI. None of these patients had methylation of MMR genes, but hypermethylated *hMLH1* (approximately 50 %) was found in normal blood DNA in one 25-year-old female patient. Allele methylation in tissues derived from the embryologically discrete germ layer in this patient suggested that the methylation pattern may be constitutional or germline methylation. Because no mutation was found in specimens from her parents, hereditary evidence for epimutation was not obtained; however, it is notable that methylation occurred in such a young patient.

Patients with multiple cancers also have been shown to have *hMLH1* epimutation [33]. *hMLH1* methylation was

found in a phenotype derived from a triploblastic organism in two patients with multiple cancer. Tissues from the parents of these patients were not examined, but no methylation was found in tissues in four of their five children. Much controversy exists regarding constitutional epimutation, including whether this is transmitted from a mother or father or occurs de novo in early embryonic development. Miyakura et al. found methylation in the *hMLH1* promoter region in peripheral blood lymphocytes in 4 of 30 patients with juvenile-onset sporadic colon cancer or multiple cancer, and one of the four patients had multiple cancer, including endometrial cancer [34]. Methylation was found only in one allele. Although it is unknown whether methylation is inherited, MSI was found in all patients and methylation also was detected in normal tissues of the large intestine, digestive mucosa, endometrium, and bone marrow in three patients. It is of interest that this finding and loss of heterozygosity (LOH) in both alleles of *hMLH1* in colon cancer are consistent with the mechanism of carcinogenesis by germline epimutation proposed by Suter et al., based on Knudson's "two hit" hypothesis (Figure 2).

Thus, a new type of Lynch syndrome has been found in patients with clinically suspected Lynch syndrome. This new type has no pathologic mutations in MMR genes but is characterized by epimutation in the promoter region of *hMLH1* [35]. This finding suggests that germline epimutation in MMR genes is a cause of Lynch syndrome. Additionally, in families with *hMSH2* methylation, germline mutation of *epithelial cell adhesion molecule (EPCAM)* is a cause of epimutation [36]. *EPCAM* is highly expressed in epithelial tissues and cancer, and a 3' end deletion in *EPCAM* causes read through with *hMSH2*, which causes hypermethylation of CpG islands in the *hMSH2* promoter [37]. Furthermore, methylation of *hMSH2* in Lynch syndrome kindreds has been shown to be transmitted genetically [35] and to follow Mendelian inheritance, in contrast to epimutation of *hMLH1*. To date, only two families have been found to have hereditary epimutation of MMR genes; however, it is possible that epimutation of MMR genes is a factor in onset of hereditary endometrial cancer, similarly to colon cancer, and further studies are required to investigate this possibility.

Cowden syndrome and endometrial cancer

Cowden syndrome (CS) is a rare disease with autosomal dominant inheritance that is characterized by formation of multiple hamartomas in various tissues. The prevalence of CS is estimated to be 1 per 200,000-250,000 population [38]. Patients with CS have increased morbidity risks for various malignant tumors, particularly breast, thyroid, and endometrial cancers. The *PTEN* (*phosphatase and tensin homologue deleted on chromosome 10*) gene is associated with onset of CS [39] and approximately 80 % of patients with CS have a *PTEN* mutation [40]. The lifetime risk of endometrial cancer is 5 % to 10 % in patients with CS compared with 2 % to 4 % in the general population [41].

PTEN codes for a protein with tyrosine kinase activity and acts as a tumor suppressor gene. PTEN also is a phosphatidylinositol phosphatase that regulates the reverse reaction of PI3K and inhibits activation of Akt via PI3K. Akt is a serine/threonine kinase that activates or inactivates downstream factors, with resulting transmission of signals related to cell growth, survival, differentiation, and glucose metabolism [42]. Akt is related to cell survival through inactivation of apoptosis executioners and transcription factors related to apoptosis-inducing factors. Therefore, if PTEN regulation of Akt activation is lost, the PI3K-Akt pathway is activated, and this leads to malignant

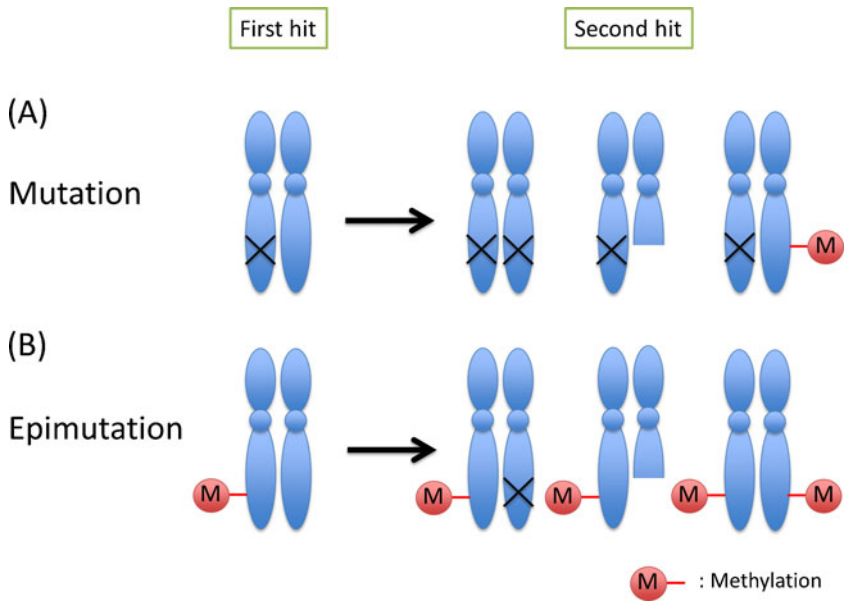

Fig. 2 Based on Knudson's "two hit" hypothesis

transformation of cells. Regarding surveillance for endometrial cancer in patients with CS, cytology for women in their late 30s and transvaginal ultrasonography for postmenopausal women have been proposed; however, the effectiveness of these surveillance methods remains unclear.

Peutz-Jeghers syndrome and endometrial cancer

Peutz-Jeghers syndrome (PJS) is characterized by multiple hamartomatous polyps in the gastrointestinal tract and mucocutaneous pigmentation. Patients with PJS have a higher risk of developing a malignant tumor in the gastrointestinal tract and other organs compared with the general population. *LKB1/STK11* has been identified as a disease-related gene with autosomal dominant inheritance. *LKB1* mutation is found in 80-94 % of patients with PJS [43, 44]. The incidence of PJS is estimated to be 1 per 50,000-250,000 population [45]. Patients with PJS are at risk for gynecological cancers and have a 9 % lifetime risk of developing endometrial cancer [46]. *LKB1/STK1* codes for a serine/threonine kinase that directly phosphorylates AMPK and has functions including regulation of glucose, lipid metabolism, cell proliferation, and cell polarity. PJS has less risk for endometrial cancer compared to Lynch syndrome and no specific surveillance is required.

Conclusions

Lynch syndrome, CS, and PJS are hereditary diseases associated with endometrial cancer, and Lynch syndrome is particularly important with regard to the prevalence and risk for developing endometrial cancer. In most patients with Lynch syndrome, endometrial cancer is likely to be a sentinel cancer; therefore, it is important to suspect Lynch syndrome if juvenile endometrial cancer is diagnosed. ACII criteria are used for surveillance of Lynch syndrome, but genetic analysis is important in high-risk patients with familial accumulation, even if they do not meet diagnostic criteria. For patients with a hereditary predisposition, screening and preventive measures are recommended, but the efficacy of these approaches is currently unknown. Surveillance for endometrial cancer also is recommended in patients with CS and PJS, but the risk of developing endometrial cancer is lower than that in Lynch syndrome and screening may be less effective. An investigation of the benefits of current screening and preventive measures is required, with establishment of new diagnostic criteria and surveillance methods for hereditary endometrial cancer.

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