3 Hereditary Cancers of the Endometrium: HNPCC Syndrome and Beyond

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Introduction

The incidence of endometrial cancer is increasing worldwide [1]. Identifying women who are at increased risk of endometrial cancer can help in the early diagnosis and prevention of the disease. Obesity, early menarche and late menopause, tamoxifen use, hereditary factors like hereditary nonpolyposis colorectal carcinoma (HNPCC) syndrome, diabetes mellitus, systemic hypertension, etc. are some of the high-risk factors associated with carcinoma of the endometrium. The lifetime risk for endometrial cancer increases from 2.6 % to about 60 % in HNPCC syndrome [2].

What Is HNPCC Syndrome?

Hereditary nonpolyposis colorectal carcinoma syndrome or Lynch syndrome (named after American oncologist Henry T. Lynch) is an autosomal dominant syndrome resulting from germline mutations in one of four DNA mismatch repair (MMR) genes, MLH1, MSH2, MSH6, or PMS2. In addition to the increased risk of endometrial carcinoma, women affected with Lynch syndrome have a 25–50 % lifetime risk of colorectal cancer; 10 % lifetime risk of pelvic epithelial (previously referred to as ovarian), ureter, renal pelvis, and stomach cancer; and also increased risk of small bowel cancer, skin cancer, glioblastomas, and biliary and pancreatic tumors [3]. Studies about Lynch syndrome have mainly centered on colorectal carcinomas and preventive strategies were developed for colorectal cancer prevention. But it has been noted that women affected with Lynch syndrome have an equal or increased risk of developing gynecological malignancies when compared to colonic cancer [4]. In fact more than half of the affected patients present with gynecologic cancer, mostly endometrial carcinoma as "sentinel cancer" [5].

Defining Criteria

Clinical and familial criteria have been used to identify patients with HNPCC. The Amsterdam criteria [6] and Bethesda [7] guidelines (Tables 3.1 and 3.2) focus mainly on patients with colorectal carcinomas. The Bethesda guidelines have better sensitivity than Amsterdam criteria with respect to identifying MMR gene mutation [8]. The Society of Gynecologic Oncology (SGO) guidelines focus on patients with gynecologic cancers

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Table 3.1 Amsterdam criteria for Lynch syndrome screening [6]

Amsterdam criteria I
Three or more family members with a confirmed diagnosis of colorectal cancer, one of whom is a first-degree (parent, child, sibling) relative of the other two
Two successive affected generations
One or more colon cancers diagnosed under age 50 years
Familial adenomatous polyposis (FAP) has been excluded
Amsterdam criteria II
Three or more family members with HNPCC-related cancers, one of whom is a first-degree relative of the other two
Two successive affected generations
One or more of the HNPCC-related cancers diagnosed under age 50 years
Familial adenomatous polyposis (FAP) has been excluded

Table 3.2 Revised Bethesda guidelines [7]

Diagnosed with colorectal cancer before the age of 50 years
Synchronous or metachronous colorectal or other LS/HNPCC-related tumors (which include stomach, bladder, ureter, renal pelvis, biliary tract, brain (glioblastoma), skin (sebaceous gland adenomas, keratoacanthomas), and small bowel (carcinoma)), regardless of age
Colorectal cancer with a high-microsatellite instability morphology that was diagnosed before the age of 60 years
Colorectal cancer with one or more first-degree relatives with colorectal cancer or other LS/HNPCC-related tumors. One of the cancers must have been diagnosed before the age of 50 years (this includes adenoma, which must have been diagnosed before the age of 40 years)
Colorectal cancer with two or more relatives with colorectal cancer or other LS/HNPCC-related tumors, regardless of age

along with colorectal cancers and identify patients in whom genetic risk assessment may be helpful [9] (Table 3.3). Yet 75 % of the patients affected with Lynch syndrome do not have a suggestive family or personal history and also do not fit into the Amsterdam or Bethesda criteria [10, 11]. A comparison of the various screening methods has shown that only 36 % of endometrial cancer

Table 3.3 Society of Gynecologic Oncology (SGO) guidelines [9]

SGO guidelines: patients with a >20–25 % chance of having an inherited predisposition to endometrial, colorectal, and related cancers for whom genetic risk assessment may be helpful
Patients with endometrial or colorectal cancer who meet the revised Amsterdam criteria
Patients with synchronous or metachronous endometrial and colorectal cancer with the first cancer diagnosed prior to age 50 years
Patients with synchronous or metachronous ovarian and colorectal cancer with the first cancer diagnosed prior to age 50 years
Patients with colorectal or endometrial cancer with evidence of mismatch repair defect (i.e., microsatellite instability or immunohistochemical loss of expression of MLH1, MSH2, MSH6, or PMS2)
Patients with first- or second-degree relative with a known mismatch repair gene mutation
SGO guidelines: patients with a >5–10 % chance of having an inherited predisposition to endometrial, colorectal, and related cancers for whom genetic risk assessment may be helpful
Patients with endometrial or colorectal cancer diagnosed prior to age 50 years
Patients with endometrial or ovarian cancer with a synchronous or metachronous colon or other LS/HNPCC-associated tumor at any age
Patients with endometrial or colorectal cancer and a first-degree relative with LS/HNPCC-associated tumor diagnosed prior to age 50 years
Patients with colorectal or endometrial carcinoma diagnosed at any age with two or more first- or second-degree relatives with LS/HNPCC-associated tumors, regardless of age

patients with Lynch syndrome met the revised Bethesda criteria while 58 % met the Amsterdam II criteria. The SGO guidelines gave better results by identifying 71 % of patients with the 20–25 % screening criteria and 93 % identified through the 5–10 % criteria [12].

Clinical Presentation

Patients affected with Lynch syndrome develop colorectal cancer before the age of 50 years, and in around one-third of the patients, another HNPCC-related malignancy occurs within 10 years [13]. Individuals affected with Lynch

syndrome have a 25–70 % lifetime risk of developing endometrial carcinoma [3]. Now, it is known that more than 50 % of the affected patients present with endometrial cancer as their sentinel cancer [5].

These patients usually do not have features of estrogen excess like obesity, diabetes mellitus, estrogen, tamoxifen use, or polycystic ovarian syndrome [14]. An association with low body mass index (BMI) has been suggested [15]. They can present with irregular menstrual bleeding but are less likely to be associated with endometrial hyperplasia. A clinical suspicion of Lynch syndrome should arise when a patient is presenting with endometrial cancer without the usual risk factors. A patient has 25 % chance of developing a second cancer in 10 years and 50 % chance at 15 years following the diagnosis of a Lynch syndrome-related endometrial carcinoma [14]. Therefore, a clinical suspicion and diagnosis will help in screening for other cancers and will also be beneficial for the patient and her family members.

Genetic Basis

Lynch syndrome is caused by germline mutations in the MMR genes MLH1, MSH 2, MSH 6, and PMS 2. Rarely patients can have deletions of the EPCAM gene upstream to the MSH2 gene causing Lynch syndrome [8]. The MMR genes provide stability to the DNA by correcting the mismatches that are produced during DNA replication. Any mutation in the MMR gene causes loss of function and microsatellite instability (MSI) leading to the formation of cancer [16]. MSI can also be caused by an epigenetic mechanism – hypermethylation of MLH1 promoter gene leading to gene silencing and MSI. This is seen in 20–25 % of patients with sporadic endometrial cancer [17]. Carcinogenesis in the presence of MSI appeared to be due to frame-shift mutations of microsatellite repeats within the coding regions of the genes. PTEN seems to be the candidate gene in endometrial carcinoma [18].

Frequency of mutations of MMR genes in Lynch syndrome-related endometrial carcinomas is 50–66 % for MSH2, 24–40 % for MLH1, 10–13 % for MSH 6, and less than 5 % for PMS2 [19, 20]. Even though MSH6 mutations are less frequent, they have an increased risk of endometrial cancer compared to individuals with MSH2 or MLH1 mutations [3].

Pathology

It has been noted that endometrial cancers due to Lynch syndrome arise predominantly in the lower uterine segment. Overall 10–15 % of the lower uterine segment tumors are associated with Lynch syndrome [11, 21]. Both endometrioid and non-endometrioid tumors occur in Lynch syndrome. The non-endometrioid varieties include clear cell carcinoma, serous carcinoma of the endometrium, carcinosarcoma, and also undifferentiated tumors of the endometrium [22, 23]. In a study by Honoré et al. [24], it was found that MSI correlates with high tumor grades in endometrioid adenocarcinoma. The MSI-related beta-catenin mutations cause the upregulation of Cmyc which in turn stimulates CDK4, leading to the inactivation of the retinoblastoma suppressor gene, thus activating the CDK4/cyclin complex and sequestering the cell cycle inhibitors like p16, p21, and p27. This is the probable mechanism behind the high tumor grade in MSI [24]. Honoré et al. also state that the MSI-related endometrioid adenocarcinoma arises in a background of atrophic endometrium and is associated with more myometrial invasion, lymphovascular space invasion, and nodal metastases, which are adverse prognostic factors in carcinoma of the endometrium.

There are several histological features that are linked to MSI and MMR protein deficiency in endometrioid adenocarcinomas. Most prominent among them are the undifferentiated and de-differentiated tumor patterns [3]. Other features that are thought to be suggestive of MSI are prominent peritumoral lymphocytes, dense tumor infiltrating lymphocytes (TIL), and tumor heterogeneity [3]. The undifferentiated tumor pattern was initially described by Altrabulsi et al. [25] as solid sheets of medium-sized,

monotonous epithelial cells with complete absence of glandular proliferation. The term dedifferentiated carcinoma is used when an undifferentiated tumor pattern is associated with a focus of well to moderately differentiated endometrioid adenocarcinoma [26]. Tumor-infiltrating lymphocytes are considered as a marker of MMR protein deficiency and are seen in both genetic and sporadic conditions. More than 42 TIL per 10 high power fields has been proposed as more suggestive of Lynch syndrome [27]. Peritumoral lymphocytes are defined as readily appreciable aggregates of lymphocytes around the tumor at scanning magnification [28]. Tumor heterogeneity is defined as a tumor having two or more morphologically separate patterns, each constituting at least 10 % of the tumor with each component being juxtaposed and not intimately admixed [28].

Pelvic epithelial tumors, previously referred to as "ovarian tumors" found in association with Lynch syndrome, are well to moderately differentiated endometrioid carcinomas and clear cell carcinomas. Pelvic epithelial clear cell ovarian carcinoma in a younger patient has a strong association with Lynch syndrome [15, 29]. There are reports of synchronous endometrioid carcinomas of uterus and pelvic clear cell carcinoma ovary in women with MMR protein defects [15, 29].

Which Patients with Endometrial Carcinomas Are to Be Tested for Lynch Syndrome?

In unselected endometrial cancer patients, 1.8–2.1 % MMR gene mutation rates have been found [10, 30]. These rates are similar to the MMR mutation rates found in colorectal carcinoma [31]. In patients below the age of 50 years affected by endometrial cancer, the rates of MMR gene mutations have been found to be as high as 9 % [32]. The identification of patients affected with these mutations is important as they have increased risk for synchronous and metachronous cancers. They themselves and their family members would benefit from surveillance methods to detect other related cancers and genetic counseling. Also there could be prognostic and therapeutic implications for the affected patients [27]. The Amsterdam criteria [6] and Bethesda guidelines [7] focus mainly on colorectal cancers. The SGO guidelines [9] focus on gynecologic cancers and give better screening results [12] but still underestimate these cancers.

Screening for Lynch syndrome in all patients of endometrial cancer has been advocated and also implemented by some centers [14]. But it is not practical to screen all patients with endometrial cancers for Lynch syndrome. Many criteria have been proposed based on the age, family history, and pathological factors for screening Lynch syndrome. Using 50 years as a cutoff age will cause underdetection, as many women (especially patients with MSH6 mutations) above the age of 50 years present with MMR protein-deficient endometrial cancer [33]. Using the tumor morphology – lower segment tumors, presence of TIL, peritumoral lymphocytes, and undifferentiated and dedifferentiated tumor patterns – has been suggested to increase the detection rates of endometrial cancer patients at risk of HNPCC [27].

Use of immunohistochemistry (IHC) to detect the four main MMR proteins is an easy procedure and can detect most mutations, at significant direct cost but potential high returns and value over the long run for both the patient and her family [34]. Kwon et al. compared various criteria for Lynch syndrome testing for women with endometrial cancer and found that IHC triage of women having endometrial cancer at any age having at least one first-degree relative with Lynch associated cancer is a cost-effective strategy for Lynch syndrome detection [34].

Detecting Lynch Syndrome

The definitive way to detect Lynch syndrome is mutational analysis of the MMR gene DNA. In view of the cost, it is suggested that mutational analysis be used only as a confirmatory test after screening with IHC, MSI analysis, and MLH1 methylation studies [3].

Modica et al. have reported a sensitivity of 91 % and a specificity of 83 % for IHC in detecting MSI phenotype in endometrial carcinoma when antibodies against all four MMR proteins were used [35]. As MLH1 dimerizes with PMS 2 and MSH2 dimerizes with MSH 6 in their functional state, mutations of MLH1 and MSH2 will lead to loss of PMS2 and MSH 6, respectively. Using antibodies only against MLH1 and MSH2 only provides 69 % sensitivity and 100 % specificity and can be used as an economical alternative to the four-antibody test [35]. IHC has the advantage being a simple and less expensive test and can direct the gene sequencing to one or more specific genes.

MSI analysis is by polymerase chain reaction (PCR) amplification of the National Cancer Institute reference loci (BAT25, BAT26, D2S123, D5S346, and D17S250) on tumor and normal tissue for each patient [36]. Tumor with no instability detected is termed as MSI stable, instability at one focus is termed MSI low, and instability at two loci is termed MSI high. MSH6 mutations may be MSI stable or MSI low, and if MSI is used as a screening test, some mutation carriers may not be detected [3].

All tumors showing inactivation of MLH1 by IHC or MSI analysis should be subjected MLH1 promoter methylation assay. This is because MLH1 inactivation can occur also due to an acquired mechanism – MLH1 promoter methylation resulting in loss of protein. Tumors showing MLH1 promoter methylation are likely to be associated with Lynch syndrome [3].

DNA MMR mutation test is the confirmatory test to establish the diagnosis of Lynch syndrome. This is usually performed when the abovementioned screening tests show a strong possibility of Lynch syndrome [3].

Surveillance and Risk Reduction for Endometrial Carcinomas

There is limited data on the efficacy of endometrial cancer screening in women with Lynch syndrome. Vasen et al. have recommended annual physical examination and transvaginal sonography along with endometrial biopsy from the age of 30 to 35 years [37]. NCCN still states that there is no clear evidence to support screening for endometrial cancer in Lynch syndrome [38]. This may stem from the fact that screening for endometrial cancer had not produced improved outcomes, as well as reports of interval carcinomas not detected by screening [39]. But Renkonen-Sinisalo et al. showed that screening with endometrial biopsies in women affected with Lynch syndrome detected endometrial cancers at an early stage and there were more frequent detection of premalignant lesions which enabled prophylactic hysterectomy in the screened group. Compared with the unscreened group presenting with mutation-positive endometrial cancer, the surveillance group presented with a more favorable stage distribution and there were no deaths due to endometrial cancer [40].

The study by Lécuru et al. showed that ultrasonography showed 100 % sensitivity and 100 % NPV when used to screen patients with HNPCC/Lynch syndrome for atypical hyperplasia and endometrial cancer. But in this study endometrial cancers were diagnosed in women who presented with abnormal vaginal bleeding [41]. NCCN also stresses the fact that all women with Lynch syndrome must be made aware that abnormal uterine bleeding needs evaluation [38].

Little is known about the role of oral contraceptives in preventing endometrial carcinomas in women affected with Lynch syndrome. Prophylactic hysterectomy and bilateral salpingo-oophorectomy once childbearing is complete [38] or after the age of 35 years [42] can prevent the development of endometrial cancer in women with Lynch syndrome. Compared to gynecological surveillance, risk-reducing surgery is a comparatively less expensive option [43]. But the disadvantages of surgical menopause (if ovaries are also removed) and surgical complications must be explained. There is a chance of occult malignancy in the endometrium/ovary; hence, patients must consent for staging should there be intraoperative evidence of malignancy [3].

Other Hereditary Syndromes Associated with Endometrial Carcinomas

Endometrial carcinomas are also associated with breast-ovarian cancer syndrome and rarely with Cowden syndrome (PTEN hamartoma tumor syndrome).

Some isolated studies from Israel have associated uterine papillary cancers with BRCA germline mutations [44, 45]. These findings in the Ashkenazi Jewish population, in whom BRCA mutations are high, remain to be confirmed. Kwon et al. reported prolonged survival in advanced-stage endometrial carcinomas associated with BRCA mutations. The improved prognosis may be due to a difference in the tumor biology making these tumors more susceptible to radiation and chemotherapy [46]. This association of uterine serous cancers to the BRCA-related tumors has implications in the management of unaffected BRCA1 and 2 mutation carriers. Whether a hysterectomy is to be recommended as well in addition to a risk-reducing bilateral salpingo-oophorectomy will need to be further investigated [44].

PTEN hamartoma syndrome is an autosomal dominant syndrome characterized by the development of multiple gastrointestinal hamartomas, mucocutaneous lesions, and increased risk of certain malignancies. A number of disorders including Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, and Proteus syndrome come under this [47]. NCCN recommends patient education and prompt response to symptoms in an affected patient for endometrial cancer screening, and risk-reducing hysterectomy must be discussed with the patient [38].

Conclusion

HNPCC syndrome is the most common hereditary syndrome associated with endometrial cancer which is caused by germline mutations in the MMR genes MLH1, MSH 2, MSH 6, and PMS 2 leading to microsatellite instability and development of cancer. Women affected with HNPCC syndrome have 60 % lifetime risk of endometrial cancer, and more than half of the affected patients present with gynecologic cancer, mostly endometrial carcinoma as their "sentinel cancer." SGO guidelines for screening HNPCC syndrome can identify 93 % of affected women. Currently NCCN does not recommend screening for endometrial cancer in affected women, but studies have shown that screened cohort had detection of more premalignant lesions at early stage of diagnosis. Other syndromes associated with endometrial cancer are BRCA mutations and PTEN hamartoma syndrome. Women affected with hereditary syndromes should be educated to seek prompt evaluation in case of abnormal uterine bleeding and advised that prophylactic hysterectomy after completion of childbearing/after 35 years can prevent endometrial cancer.

Key Points

1. HNPCC syndrome or Lynch syndrome is the most common cause of hereditary cancer of the endometrium providing a 40-fold increased chance of endometrial cancer in affected when compared to general population.
2. Other hereditary syndromes associated with endometrial cancer are breast-ovarian cancer syndrome and Cowden syndrome.
3. SGO guidelines can identify 93 % of patients affected with Lynch syndrome.
4. In diagnosed Lynch syndrome patients without endometrial cancer, annual screening with sonography and endometrial biopsy and prophylactic hysterectomy after completion of childbearing can reduce the risk of endometrial cancer.
5. A clinical suspicion of Lynch syndrome should arise when a patient is presenting with endometrial cancer without the usual risk factors or endometrial hyperplasia.

6. Pathological factors like lower segment tumors, presence of TIL, peritumoral lymphocytes, undifferentiated and dedifferentiated tumor patterns, increase detection of Lynch syndrome.
7. In suspected women IHC testing, MSI analysis, and MLH1 methylation studies should be done followed by the definitive test "mutational analysis of the MMR gene DNA" to confirm Lynch syndrome.

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