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Gynecologic cancers in Lynch syndrome/HNPCC

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Abstract

Recent studies have estimated that the lifetime risk of endometrial cancer in women with Lynch syndrome/hereditary non-polyposis colorectal cancer syndrome (Lynch/HNPCC) is 40–60%. This risk equals or exceeds their risk for colon cancer. While much research has been done to define the natural history and molecular features of Lynch/HNPCC associated colon cancer, there has been considerably less research defining Lynch/HNPCC associated endometrial cancer. This article will review current information regarding the clinico-pathologic features of Lynch/HNPCC associated endometrial cancer. In addition, current consensus guidelines for endometrial cancer screening and prevention for women with Lynch/HNPCC will be discussed. Given the increased risk of multiple cancers, changing the name of this syndrome from hereditary non-polyposis colorectal cancer syndrome to Lynch Syndrome may benefit both patients and clinicians. Clinicians caring for women with Lynch/HNPCC may stress colon cancer screening and prevention without reviewing endometrial cancer risks and symptoms or screening and prevention options. Perhaps more importantly, women with Lynch/HNPCC may focus on colon cancer risks and lack understanding of endometrial cancer risks. With increasing evidence that women with Lynch/HNPCC have significant risks for both colon and endometrial cancers, we believe a multi-disciplinary approach to the management of these individuals is crucial.

Introduction

For women with Lynch syndrome/hereditary non-polyposis colorectal cancer syndrome (Lynch/HNPCC), risk of endometrial cancer equals or exceeds risk of colon cancer [1, 2]. Despite this fact, very little is known about Lynch/HNPCC associated endometrial cancer [3]. Research regarding the natural history and molecular features of Lynch/HNPCC associated endometrial cancer has lagged behind research of Lynch/HNPCC-associated colon cancer. Perhaps more importantly, individuals with Lynch/HNPCC focus on colon cancer risk and may lack understanding of endometrial cancer risk. Clinicians caring for women with Lynch/HNPCC may stress colon cancer screening and prevention without reviewing endometrial cancer risks and symptoms, or screening and prevention options. Finally, while gastroenterologists, gastrointestinal surgeons and medical oncologists actively identify colon cancer patients as potentially having Lynch/HNPCC, the gynecologic community has been less pro-active in identifying women with endometrial cancer as Lynch/HNPCC probands.

The purpose of this article is to review current information regarding the clinico-pathologic features of Lynch/HNPCC-associated endometrial cancer. Current recommendations for endometrial cancer screening and prevention for women with Lynch/HNPCC will be discussed. In addition, the data regarding ovarian cancer risk in individuals with Lynch/HNPCC will be reviewed.

Lifetime risk of endometrial and ovarian cancer in women with Lynch/HNPCC

With the identification of *MLH1* and *MSH2*, the estimates of cancer risks for individuals with Lynch/HNPCC

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have become more precise. Recent studies by Aarnio et al. and Dunlap et al. estimate the risk of endometrial cancer in mutation positive women to be 40–60% [1, 2]. In fact, for mutation positive women, these two studies found that risk of endometrial cancer is higher than risk of colon cancer. Aarnio et al. reported a 60% lifetime risk for endometrial cancer in women with Lynch/HNPCC, as compared to a 54% lifetime risk for colon cancer. Dunlap et al. reported a 42% risk of endometrial cancer and a 30% risk of colon cancer in mutation positive women. Vasen et al. examined cancer risks in *MLH1* mutation carriers separate from *MSH2* mutation carriers [4]. They reported a 35–40% risk of endometrial cancer in women with *MSH2* mutations and a 25% risk for developing endometrial cancer in women with *MLH1* mutations. They also reported that the risk of developing colon cancer in women with either *MLH1* or *MSH2* germline mutations was 50–60%. Green et al. examined a large *MSH2* kindred in Newfoundland and found that, for women, the cumulative risk by age 70 of endometrial cancer was 79% and the cumulative risk of colon cancer was 64% [5]. Data from all of these studies was obtained from Lynch/HNPCC families that had documented germline mutations. The reported risks of endometrial cancer in these studies are higher than the previously reported risk of 20%, which was based on families that fulfilled Amsterdam criteria but had not undergone genetic testing [6]. Clearly, women with Lynch/HNPCC have a significant risk for endometrial cancer, and that risk may, in fact, exceed their colon cancer risk.

Wijnen et al. reported an excess of endometrial cancers in female carriers of *MSH6* germline mutations [7]. Truncating *MSH6* mutations were identified in 10 of 214 Lynch/HNPCC kindreds in which an *MLH1* or *MSH2* mutation had not been identified. The authors report that the frequency of endometrial cancer and hyperplasia was 73% in their cohort of female *MSH6* mutation carriers compared with 29% in *MSH2* mutation carriers and 31% in *MLH1* mutation carriers. Recently, Hendriks et al. examined a large number of individuals from 20 families with *MSH6* mutations [8]. They reported that women with *MSH6* mutations had a 71% cumulative risk of endometrial cancer by age 70, substantially higher than their risk for colon cancer. In addition, they found that the mean age of endometrial cancer in these women was 55 years, with a sharp increase in risk after age 50.

Risk of ovarian cancer in women with a Lynch/HNPCC mutation has been reported to be 12% [1]. Vasen et al. reported that the risk of ovarian cancer with an *MSH2* mutation was approximately 10%, while the risk of developing ovarian cancer with an *MLH1* mutation was lower at 3% [4]. Green et al. reported a 36% risk of ovarian cancer in a large kindred with an *MSH2* mutation [5]. With the availability of clinical genetic testing, future studies of mutation carriers will help to further define these cancer risks.

Endometrial and ovarian cancer phenotype in Lynch/HNPCC

While endometrial cancer is a significant risk for women with Lynch/HNPCC, little is known about the clinical and pathologic features of Lynch/HNPCC associated endometrial cancer. Vasen et al. identified 125 women with endometrial cancer from families fulfilling Amsterdam criteria from seven countries [9]. At the time of the study, genetic testing was not available. The median age of diagnosis of endometrial cancer in their cohort was 48 years, with a range of 27–72 years. Information on presenting symptoms, histology and grade of tumor was not reported. Interestingly, 61% of 125 cases had a second primary cancer, mostly colon, either before or after the diagnosis of endometrial cancer. They reported excellent survival with only 12% dying of their endometrial cancer. A study by Boks et al. also examined survival of endometrial cancer patients with Lynch/HNPCC [10]. They compared 50 patients with endometrial cancer and Lynch/HNPCC (based either on germline test results or revised Amsterdam criteria) with 100 age and stage matched women with sporadic endometrial cancer. The overall five year cumulative survival rates were similar: 88% for women with HNPCC and 82% for women with sporadic endometrial cancer.

In the cohort of women with Lynch/HNPCC, the majority (78%) had early stage disease and 92% had endometrioid histology. Among the 22% of women with Lynch/HNPCC and advanced stage disease, it was unclear whether prognosis was improved as compared to a sporadic population with advanced stage disease. In Lynch/HNPCC-associated colon cancer, overall survival appears to be more favorable as compared to sporadic colon cancer [11]. Additional studies will be needed to determine if this holds true for Lynch/HNPCC-associated endometrial cancer. Comparing outcomes in advanced stage patients may be important, as prognosis for early stage endometrial cancer is highly favorable.

van den Bos et al. recently performed a histopathologic review of a small series of endometrial cancers from patients with known Lynch/HNPCC mutations and reported an association with poorly differentiated tumors and lymphangioinvasive growth [12]. We are currently conducting a pathologic review of a series of endometrial cancers in known mutation carriers and have preliminarily noted a wide spectrum of endometrial cancer seen in women with Lynch/HNPCC, including tumors of all grades and histologies. The previously held notion that Lynch/HNPCC associated endometrial cancers are of endometrioid histology and low grade is likely to be re-examined as additional studies are reported.

Women with germline *MLH1* or *MSH2* mutations and endometrial cancer demonstrate loss of immunohistochemical staining in the tumor of the corresponding protein [13]. MSI is demonstrated in endometrial tumors, but differs from the pattern seen in Lynch/

HNPCC associated colon cancer [14]. Kuismanen et al. performed MSI in 44 Lynch/HNPCC associated colon cancers and 57 Lynch/HNPCC associated endometrial cancers. Lynch/HNPCC associated colon cancers demonstrated a higher proportion of unstable loci than Lynch/HNPCC associated endometrial cancers. Approximately 23% of these endometrial tumors showed no MSI, despite the use of an extended panel of 12 microsatellites. In addition, whereas the colon cancers displayed a more consistent pattern of microsatellite instability, with unstable loci predominantly in BAT loci, TGFβ RII and dinucleotide repeats, the endometrial cancers displayed a more heterogeneous pattern with different unstable loci in different tumors. Such unusual patterns of MSI have also been observed in other extra-colonic malignancies associated with Lynch/HNPCC [15].

Typical endometrioid endometrial cancer develops through a stepwise pathway from normal endometrium, to complex hyperplasia with atypia, to carcinoma. It is unclear whether Lynch/HNPCC-associated endometrial cancer follows this pattern. In one study, 2 patients with known mutations had endometrial hyperplasia without concurrent endometrial cancer and 3 patients had endometrial hyperplasia with concurrent endometrial cancer. The authors demonstrated loss of the appropriate protein by immunohistochemistry in the hyperplasias and the cancers, suggesting that the mismatch repair defect may occur early in endometrial carcinogenesis [13]. Zhou et al. examined PTEN mutations, an early and frequent event in sporadic endometrial cancer, in Lynch/HNPCC associated tumors [16]. They examined 41 endometrial cancers from mutation positive Lynch/HNPCC families and found that 68% demonstrated weak or absent staining for PTEN by immunohistochemisty. Eighteen of 20 cases had somatic PTEN mutations, involving the 6(A) tracts in exon 7 or 8. The authors conclude that PTEN mutations are critical in the pathogenesis of both sporadic and Lynch/HNPCC associated endometrial cancer. Additional studies are necessary to further define the histologic and molecular phenotype of endometrial cancer in women with Lynch/HNPCC.

Even less is known about Lynch/HNPCC associated ovarian cancer. A study by Watson and the International Collaborative Group on HNPCC examined the medical records of 80 ovarian cancer patients from Lynch/HNPCC families based on germline mutation or clinical criteria [17]. They found that the mean age at diagnosis of ovarian cancer was 42.7 years and that 94% had epithelial ovarian cancer. About 56% had papillary serous ovarian cancer and 18% had endometrioid histology. Interestingly, 84% had stage I or II disease, which contrasts with sporadic ovarian cancer, in which greater than 70% of cases present with advanced stage disease. Overall survival was approximately 69% at 5 years, attributable to the early stage at diagnosis for these patients. When survival was examined stage for stage, it was similar for the cohort of Lynch/HNPCC patients as compared to published rates for sporadic patients. Many of the cases in the Watson et al. study were several decades old, before the establishment of many of the current pathological guidelines for distinguishing borderline tumors from invasive cancers. Therefore, a study in which there is careful pathological review of the ovarian tumors slides from Lynch/HNPCC patients would be useful to confirm their findings. The possible earlier stage at diagnosis is intriguing, and future collaborative studies are necessary to further define ovarian cancer in Lynch/HNPCC.

Clinical management

Screening and prevention

Currently, there have been limited studies evaluating screening for endometrial cancer in women with Lynch/HNPCC. However, clinical guidelines have been established that recommend screening for endometrial cancer beginning at age 25–35 [18]. Modalities for endometrial cancer screening include transvaginal ultrasound and an office endometrial sampling.

The use of transvaginal ultrasound to evaluate the thickness of the endometrial stripe as a screening tool for Lynch/HNPCC is not likely to be beneficial. Screening for endometrial cancer is primarily focused in the pre-menopausal age group. In this population, the thickness of the endometrial stripe changes with the menstrual cycle and is unlikely to be a sensitive or specific test for endometrial cancer. Two studies have reported their experience with ultrasound as a screening modality for endometrial cancer. Dove-Edwin et al. examined the outcome of endometrial cancer surveillance by ultrasound in 269 women with Lynch/HNPCC [19]. Women who were screened included those who were mutation positive, who had Lynch/HNPCC based on Amsterdam criteria or who did not fulfill Amsterdam criteria but had a family history suggestive of Lynch/HNPCC. No cancers were detected in 522 ultrasounds. However, two interval cases of endometrial cancer occurred. One patient had a normal surveillance ultrasound 2 years prior to developing post-menopausal bleeding. The second patient had a normal surveillance ultrasound 6 months prior to a diagnosis of a Stage I endometrial cancer. The authors conclude that an ultrasound may not be an effective method to detect early endometrial cancer. In a study by Rijcken, 41 women with Lynch/HNPCC were enrolled in a screening program [20]. 179 transvaginal ultrasounds were performed. Of those, 17 were defined to be abnormal based on thickness or irregularity of lining. 14 of the 17 patients had a follow-up endometrial biopsy that was within normal limits. One patient had a thickened endometrium to 27 mm on ultrasound and the pathology of her biopsy revealed complex atypical hyperplasia. Two additional patients had ultrasounds with an irregular endometrium and both had focal

complex atypical hyperplasia on biopsy. However, ultrasound failed to identify one patient who developed endometrial cancer. She had a normal transvaginal ultrasound and developed vaginal bleeding eight months later. At the time of diagnosis, she had a Stage IB, Grade 2 endometroid adenocarcinoma.

The endometrial pipelle biopsy is an office procedure that provides adequate tissue for pathologic diagnosis and is a reasonable screening modality. Studies performed in women presenting with abnormal vaginal bleeding have shown that the sensitivity of an office endometrial pipelle is equivalent to a dilatation and curettage (D and C) performed in the operating room [21]. Our current recommendations for our patients who are known mutation carriers include an annual office endometrial biopsy. We also include an annual transvaginal ultrasound in order to evaluate the ovaries. Annual CA-125 can be included as part of the screening program, but false positives in the pre-menopausal age range are common.

The oral contraceptive pill (OCP) has been shown to decrease risk of endometrial cancer by 50% in women at general population risk [22]. In addition, the OCP has also been shown to substantially decrease risk of ovarian cancer. We are currently conducting a chemoprevention study in women with Lynch/HNPCC using the OCP or medroxyprogesterone acetate (Depo-Provera). While the endpoint for this study will not be reduction in incidence of disease, we will examine the effect of these agents on surrogate molecular biomarkers in the endometrium.

Prophylactic surgery

Consensus guidelines reported by Burke et al. [18] state that there is insufficient evidence to recommend prophylactic hysterectomy and bilateral salpingo-oophorectomy to women with Lynch/HNPCC. However, women with Lynch/HNPCC should be counseled that prophylactic hysterectomy and bilateral salpingo-oophorectomy is a reasonable management option to consider. When child bearing is complete, a laparoscopic assisted vaginal hysterectomy and bilateral salpingo-oophorectomy or a total abdominal hysterectomy bilateral salpingo-oophorectomy (TAH-BSO) can be performed. For women with Lynch/HNPCC undergoing colon surgery, concurrent prophylactic TAH-BSO can be considered. Prophylactic bilateral salpingo-oophorectomy has been shown to decrease the risk of ovarian cancer in BRCA1 and BRCA2 mutation carriers by greater than 90% [23, 24]. While specific evidence for women with Lynch/HNPCC is not available, women with Lynch/HNPCC can be counseled that removal of the uterus and ovaries is a reasonable prevention strategy, as the risk of endometrial cancer is high and the screening strategies for ovarian cancer have not been proven to be effective.

For those gynecologists or gynecologic oncologists performing prophylactic hysterectomy and bilateral salpingo-oophorectomy in women who are known mutation carriers, consideration of finding an occult endometrial or ovarian cancer should be given. We reported a case of an asymptomatic, 48 year old woman who was a known *MSH2* mutation carrier and who underwent a prophylactic vaginal hysterectomy and bilateral salpingo-oophorectomy. At the time of final pathologic review, she was found to have a Grade 2 endometrial cancer with involvement of the endocervical glands and 5/12 mm invasion of the uterine wall. Because the endometrial cancer was not identified at the time of surgery, no staging was performed. The patient, therefore, underwent restaging performed via laparotomy [25]. We recommend that in women who are known mutation carriers undergoing prophylactic hysterectomy, a pre-operative endometrial biopsy be performed. In addition, we recommend that the uterus be examined intra-operatively by a pathologist for occult disease.

The role of endometrial cancer in identifying individuals with Lynch/HNPCC

Gastrointestinal surgeons, medical oncologists, and gastroenterologists have traditionally identified individuals as being at risk for Lynch/HNPCC. The Bethesda criteria were developed to assist clinicians in identifying individuals who may have Lynch/HNPCC. Included in the Bethesda guidelines are criteria relating to family history, age of onset of cancer, synchronous and metachronous cancers and specific histopathologic features of colon cancer. In contrast, there have been no well-defined guidelines for identifying individuals with endometrial cancer as potentially having Lynch/HNPCC. In fact, the gynecologic community has not played a significant role in identifying individuals with Lynch/HNPCC.

We recently examined a large series of women from Lynch/HNPCC families who had both a colorectal and an endometrial or ovarian cancer in their lifetime. Of the 117 women, 16 had a colorectal cancer and an endometrial/ovarian cancer diagnosed simultaneously. Of the remaining 101 women, 52 (51%) women had an endometrial or ovarian cancer diagnosed first. Forty-nine (49%) women had a colorectal cancer diagnosed first [26]. Developing criteria to assist gynecologists and gynecologic oncologists in identifying which women with endometrial cancer may have Lynch/HNPCC is crucial. By identifying that an endometrial cancer patient has Lynch/HNPCC, clinicians may institute screening for colon cancer and prevent the development of a potentially lethal second cancer. The revised Bethesda criteria focuses specifically on individuals with colon cancer [27]. We would welcome a more multidisciplinary set of guidelines that would provide clinicians with simple criteria to screen individuals for Lynch/HNPCC.

A recent study by Berends et al. [13] examined a cohort of women under age 50 with endometrial cancer,

and determined the prevalence of germline mutations in *MLH1, MSH2* or *MSH6*. Among 63 women tested, they identified five individuals with germline mutations (8%). In those women with endometrial cancer who were less than 50 years of age and had a first degree relative with a Lynch/HNPCC associated cancer, the prevalence of a mismatch repair gene mutation was 23%. The authors recommend that women with endometrial cancer under age 50 with a 1st degree relative with colon or other Lynch/HNPCC associated cancer should be considered for Lynch/HNPCC genetic testing.

Individuals with synchronous or metachronous colon and endometrial tumors are likely to have Lynch/HNPCC. In a study by Millar et al., 18% (7 of 40) women with synchronous or metachronous colon and endometrial cancers had a germline *MLH1* or *MSH2* mutation [28]. Individuals with synchronous endometrial and ovarian cancers have been identified in Lynch/HNPCC families. However, synchronous endometrial and ovarian cancers occur in about 10% of all ovarian cancers and 5% of all endometrial cancers and are not likely to be an accurate indicator of Lynch/HNPCC [29]. Clearly, more work needs to be done to assist the gynecologist or gynecologic oncologist in identifying those individuals with Lynch/HNPCC. In addition, as more information is learned about microsatellite instability in endometrial cancers, the role of molecular studies for endometrial cancer will be clarified.

Conclusion

Given the compelling recent data that women with Lynch/HNPCC have an equal or greater risk of endometrial cancer as compared to colon cancer, we support changing the name of this syndrome from Hereditary Non-polyposis Colorectal Cancer Syndrome to Lynch Syndrome. In addition, we believe a multi-disciplinary approach to the management of these individuals is crucial. Clinicians caring for women with Lynch/HNPCC need to provide counseling for both colon and endometrial cancer risks, as well as for less common cancers in Lynch/HNPCC including ovarian, ureteral and small bowel. Gastroenterologists and gynecologists need to consider coordinated screening and preventive efforts. Surgical plans for women with Lynch/HNPCC should be coordinated, when indicated. Finally, research into the natural history of Lynch/HNPCC associated endometrial cancer is necessary to provide the groundwork to determine if similar criteria for endometrial and colon cancer should be defined to identify individuals with Lynch/HNPCC.

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