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Endometrial and Ovarian Cancer in Women with Lynch syndrome: Update in Screening and Prevention

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Abstract

Women with Lynch syndrome have an additional need to address the substantial increased lifetime risk of endometrial and ovarian cancer. Endometrial or ovarian cancer can be the presenting cancer in individuals with Lynch syndrome, or can be a second cancer. Lifetime risk of endometrial cancer in women with MLH1 or MSH2 mutations is approximately 40%, with a median age of 49. Women with MSH6 mutations have a similar risk of endometrial cancer but a later age of diagnosis. Lynch syndrome associated endometrial cancers are primarily endometrioid, although non-endometrioid subtypes including clear cell, papillary serous and MMMT have been reported. In addition, endometrial cancers arising in the lower uterine segment, while rare in the general population, are enriched in women with Lynch syndrome. Ovarian cancer risk in women with Lynch syndrome is 6–8%, and Lynch-syndrome associated ovarian cancers exhibit a variety of histopathological subtypes. Studies of endometrial cancer screening in Lynch syndrome have been small, and more recently have focused on the use of office endometrial biopsy to identify pre-malignant and early stage cancers. Prevention options include the use of oral contraceptives, which are known to be highly effective for decreasing risk of both endometrial and ovarian cancer in the general population, and prophylactic surgery to remove the uterus and ovaries.

Introduction

For women with Lynch syndrome, risk of gynecologic cancers is substantial, often equaling or exceeding their risk of colon cancer. Endometrial or ovarian cancer can be the presenting cancer in women with Lynch syndrome, or can be a second cancer. In a study of women with Lynch syndrome who developed both a colon and a gynecologic cancer, Lu et al found that 50% of cases presented with a gynecologic cancer as their “sentinel cancer”.[1] Efforts over the last 15 years have focused on describing the pathology of Lynch-associated endometrial and ovarian cancers, as well as defining prevention and screening strategies. This chapter will provide an update on these topics.

Lifetime endometrial cancer risks associated with Lynch syndrome have been reported by many groups. The more recent studies are able to report more precise estimates, given larger sample sizes, focus on proven germline mutation carriers, and adjustment for ascertainment bias. Bonadona et al.[2] studied 537 French families with Lynch syndrome mutations (mostly MLH1 and MSH2), and found lifetime endometrial cancer risk of 35% (95% CI 17% to 60%), with risk highest for women with MLH1 mutations. Similarly, Stoffel et al.[3] found a 39% (95% CI 31% to 47%) lifetime risk of endometrial cancer for women with MLH1 or MSH2 mutations in a study of Lynch syndrome families identified through two USA cancer genetics clinics. Given the relative rarity of MSH6, PMS2, and EPCAM mutations, data regarding cancer risk are more limited for these Lynch syndrome subtypes. For women with

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MSH6 mutations, Bonadona et al.[2] report a lifetime endometrial cancer risk by age 80 of 17% (95% CI 8% to 47%), while Baglietto et al.[4] found a lifetime endometrial cancer risk by age 80 of 44% (95% CI 30% to 58%) in a multinational study population. Senter et al.[5] found a lifetime (to age 70) endometrial cancer risk of 15% for women with PMS2 mutations. Women with EPCAM mutations have been reported to have up to a 12% lifetime risk of endometrial cancer[6,7].

Lynch syndrome associated endometrial cancers can occur at a range of ages, but average age at diagnosis is younger than in the general population. Average age at endometrial cancer diagnosis in women with Lynch syndrome was reported in one recent study[2] to be 49 (range 26 – 87), and in another recent study[3] was 47.5 (range 29 – 73). The histopathology of Lynch syndrome-associated endometrial cancers has been reported to be primarily endometrioid, but non-endometrioid subtypes (including clear cell, papillary serous, and MMMT) were also seen[8]. While endometrial carcinoma of the lower uterine segment (LUS) comprises less than 5% of all endometrial cancers, women with LUS tumors are at high risk for Lynch syndrome; Westin et al[9] found that 29% of women with LUS tumors were likely to have Lynch syndrome. The reason for why LUS tumors occur in higher proportion in women with Lynch syndrome is unknown, but mirrors the increased proportion of right-sided colon tumors in individuals with Lynch syndrome.

An increased risk of ovarian cancer in women with Lynch syndrome has also been reported by many groups. Bonadona et al[2] report lifetime (to age 80) ovarian cancer risk of 8% (95% CI 2% to 39%). Engel et al[10] focused on Lynch syndrome cancer risks other than colorectal and endometrial in a combined German and Dutch cohort, and also found a lifetime ovarian cancer risk of 8% (95% CI 5.8% to 10.3%), with risk highest for women with MSH2 and MSH6 mutations. These lifetime ovarian cancer risk estimates are also in general agreement with Watson et al[11], who analyzed four Lynch syndrome registries (Denmark, Holland, Finland, USA) and found lifetime ovarian cancer risk in women with Lynch syndrome to be 6.7%. Age at diagnosis of Lynch syndrome-associated ovarian cancer is also younger than in the general population; average ages at diagnosis of Lynch syndrome-associated ovarian cancer of 42 – 48 have been reported, with an overall range of 26 – 79[10,12,13]. Watson et al.[13] found Lynch syndrome-associated ovarian cancers to exhibit a variety of histopathological subtypes, mostly but not exclusively epithelial and invasive, with 22% presenting with synchronous primary endometrial cancer. Ketabi et al.[12] reviewed 63 invasive epithelial ovarian cancers in Lynch syndrome mutation positive families in Swedish and Danish registries, and found them to be predominantly endometrioid, serous, or clear cell.

Surveillance

There are no recommendations for endometrial cancer screening in the general population, as the majority of women present with symptoms (irregular vaginal bleeding) and are diagnosed at an early stage. Because of the substantial lifetime risk of endometrial cancer in women with Lynch syndrome, a number of investigators have proposed surveillance strategies. However, most of these studies are small single institution studies, and no randomized prospective data are available to inform practice.

Earlier studies examining the use of transvaginal ultrasound (TVS) as a screening modality for women with Lynch syndrome were not successful. Transvaginal ultrasound of the endometrial stripe varies throughout the menstrual cycle in pre-menopausal women, who make up a large proportion of the patient population who would undergo screening. These studies demonstrated a lack of sensitivity for TVS as a screening modality for endometrial cancer.[14,15]

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Subsequent studies have focused on the role of endometrial biopsy in screening women with Lynch syndrome. Renkonen-Sinisalo et al reported 11 cases of endometrial cancer found during annual endometrial biopsy screening in 175 women with known Lynch syndrome. Eight cases of cancer and 1 case of complex hyperplasia were detected on biopsy and an additional 14 cases of hyperplasia were also identified. There was a stage shift in the women with Lynch syndrome who underwent screening as compared to those women with endometrial cancer who presented with symptoms, but no significant difference in overall survival was noted.[16]

In addition, a study by Jarvinen et al described the long-term effectiveness of endometrial biopsy and TVUS performed every 2–3 years in a cohort of 103 women with Lynch syndrome. After a 11.5 year follow up in which women were screened with annual TVS and endometrial biopsy, 97.1% were compliant with gynecologic screening. While gynecologic surveillance with TVS and endometrial biopsy resulted in the identification of a number of endometrial and ovarian cancers, the authors state that the effect of surveillance for endometrial cancer is difficult to prove because the outcome of endometrial cancer is favorable even for those women who are not screened but present with symptoms.[17]

In a recent study of 41 women with Lynch syndrome, 69 office hysteroscopy-guided endometrial biopsies (OHES) were performed. Four women were found to have EC/atypical endometrial hyperplasia on biopsy. No interval cancers occurred over a median follow-up of 22 months.[18]

Finally, a new concept of performing MSI analysis on endometrial washings has been proposed and feasibility has been tested on two patients with Lynch syndrome who had endometrial cancer.[19]

Both office hysteroscopy and endometrial washings have potential as outpatient screening options for women with Lynch syndrome, but the persistent question of whether any screening is necessary for a cancer that generally presents with symptoms at an early stage remains.

Current guidelines are based on consensus opinion only and in general recommend annual endometrial biopsy starting at age 30–35 or 5–10 years prior to the earliest diagnosis of EC in the family.[20] The NCCN does not have specific recommendations for endometrial cancer screening.[21] Certainly women with Lynch syndrome should be counseled specifically on symptoms related to endometrial cancer, including post-menopausal bleeding, or heavy or irregular bleeding in pre-menopausal women. For those women choosing to undergo screening with endometrial biopsy, a recent prospective study showed that conducting endometrial biopsy at the time of colonoscopy is a patient-centered option that decreases pain associated with the biopsy and increases patient satisfaction.[22]

Chemoprevention

Oral contraceptives have been demonstrated to be effective endometrial cancer chemopreventive agents in women at general population risk. The Cancer and Steroid Hormone Study (CASH) was a large case-control study that reported a 50% decrease in risk of endometrial cancer risk in women taking oral contraceptives.[23] Lu et al performed a prospective endometrial cancer chemoprevention study in 51 women with Lynch syndrome that examined endometrial biomarkers before and after short term treatment with either oral contraceptives or depomedroxyprogesterone acetate.[24] After 3 months of use, decrease in proliferation markers (Ki-67) occurred with both treatments, as well as development of the classic histologic changes in the endometrium that accompany OCP and depomedroxyprogesterone use, including decidualization of the stroma and atrophic glands.

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The expected histologic and anti-proliferative response in the endometrium of these high risk individuals suggested that oral contraceptives and depomedroxyprogesterone are reasonable chemopreventive agents for women with Lynch syndrome, although additional studies are needed. Oral contraceptives may also be an effective chemopreventive agent for ovarian cancer in women with Lynch syndrome. Multiple studies have reported that oral contraceptives reduce ovarian cancer risk by 50% in women at general population risk.[25,26] While data are limited, oral contraceptives may be an important chemoprevention option for the both endometrial and ovarian cancer risk in women with Lynch syndrome.

Risk reducing surgery for Lynch syndrome-associated gynecologic cancers

Given the increased risks of both endometrial and ovarian cancer in women with Lynch syndrome, and the limitations of screening for these cancers, risk reducing total hysterectomy and bilateral salpingo-oophorectomy (THBSO) is a consideration for women with Lynch syndrome. THBSO was shown to significantly reduce the risk of endometrial cancer in women with Lynch syndrome by Schmeler et al.[27] This same study also found that no ovarian cancers occurred post-THBSO in women with Lynch syndrome, but the prevented fraction did not reach statistical significance, likely because of the relative rarity of Lynch syndrome-associated ovarian cancer. Primary peritoneal cancer after THBSO in women with Lynch syndrome has been reported[28,29]; the magnitude of the risk is unknown, but given that only three cases have been reported in the literature, the risk is likely low.

THBSO has been endorsed by NCCN and other expert panels as a risk-reducing option that should be considered by women with Lynch syndrome who have completed childbearing.[20,21,30] Premenopasual THBSO will result in premature menopause, therefore consideration should be given to how this affects timing of surgery as well as medical management after surgery. An additional consideration regarding timing of THBSO is that Bonadona et al.[2] found that cumulative risk to age 40 of endometrial cancer did not exceed 2%, and for ovarian cancer did not exceed 1%, suggesting that prevention efforts should focus on women 40 and older. In order to address the possibility of occult endometrial cancer at the time of risk reducing THBSO, preoperative endometrial biopsy is recommended[27]. If a woman is known to have Lynch syndrome and also needs colon surgery, THBSO could be performed concomitantly.[20,30]

Because endometrial cancer often (but not always) presents with symptoms such as abnormal vaginal bleeding, and because survival rates for endometrial cancer are high[31], it is not clear to what extent surgical prevention of endometrial cancer in women with Lynch syndrome would impact morbidity and mortality. While screening colonoscopy has been proven to reduce colorectal cancer morbidity and mortality in patients with Lynch syndrome[32], there are no such data regarding THBSO. However, modeling studies have shown that risk-reducing hysterectomy and bilateral salpingo-oophorectomy can be a cost-effective strategy in women with Lynch syndrome and could increase life expectancy[33–35]. Stuckless et al.[36] studied the impact of gynecologic cancer screening on a population of women with Lynch syndrome, and found that two women with Lynch syndrome were diagnosed with ovarian cancer within a year of prior screening and subsequently died, and argue that this reinforces the recommendation for women with Lynch syndrome to consider risk-reducing hysterectomy and bilateral salpingo-oophorectomy after childbearing is complete.

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Conclusion

The substantial risk of endometrial cancer in women with Lynch syndrome has been well-defined, as has the clear benefit of surgical prevention with hysterectomy and bilateral salpingo-oophorectomy. For women who are not ready for surgical prevention, screening with endometrial biopsy annually and transvaginal ultrasound to examine the ovaries is reasonable, although definitive efficacy data are not available. Discussion of the symptoms of endometrial cancer is an overlooked strategy for these high risk women and may be as effective as the proposed screening strategy of annual endometrial biopsy. Oral contraceptives are clearly an effective chemopreventive for both endometrial and ovarian cancer in the general population, and biomarker studies support its use in women with Lynch syndrome. Finally, coordination of screening and prevention strategies with GI colleagues should be a priority in managing these high risk individuals.

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