Endometrial and Ovarian Cancer in Lynch Syndrome

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Abstract

Lynch syndrome (LS) is an autosomal dominant familial cancer risk syndrome that occurs due to a germline mutation in one of several mismatch repair genes and is associated with an increased risk of colorectal, endometrial, and ovarian cancer. The risk of endometrial cancer equals or exceeds that of colorectal cancer in women with LS. The diagnosis of gynecologic cancer precedes that of colorectal cancer in over half of women with metachronous gynecologic and colon cancers, making gynecologic cancer a "sentinel cancer" for LS. There are no studies addressing the effectiveness or safety of chemoprevention for women with LS. Surveillance with gynecologic examination including assessment of symptoms, transvaginal pelvic ultrasonography, endometrial biopsy, and CA125 tumor marker assessment can be offered, but has not been shown to improve outcomes for these patients. Prophylactic hysterectomy with bilateral salpingo-oophorectomy performed after the completion of childbearing may be offered for gynecologic cancer prevention.

Keywords

- Lynch syndrome
- endometrial cancer
- ovarian cancer
- surveillance
- prophylactic surgery

Objectives: On completion of this article, the reader should be able to summarize the management of gynecologic cancer risk in women with Lynch syndrome.

Henry Lynch and colleagues first described Lynch syndrome (LS) in 1966. They published the pedigrees of two families with a high frequency of multiple cancers, particularly colon cancer. They noted the high incidence of endometrial cancer (EC) and relatively low incidence of cervical cancer as compared with the general population. There was one patient in each kindred with ovarian cancer (OC).[1]

LS is an autosomal dominant familial cancer risk syndrome that occurs due to a germline mutation in one of several mismatch repair genes (MLH1, MSH2, MSH6, PMS1, or PMS2). The risk of colorectal carcinoma in patients with LS is lower in females (30–54%) than in males (74–~100%).[2,3] There is an increased incidence of malignancy at certain extracolonic sites, including EC and OC. In a study by Lu and colleagues, the gynecologic cancer was diagnosed first in over half of patients with LS who had metachronous colorectal and gynecologic malignancies. Thus, gynecologic cancer has been called a "sentinel cancer" in women with LS.[4] It is important for physicians caring for patients with colorectal cancer to understand the principles of gynecologic cancer surveillance and prevention in women with LS.

Endometrial Cancer

The lifetime risk of EC in the general population is estimated at 2.62%.[5] Among women with LS, the lifetime risk of EC has been estimated to be 42 to 54%, and may equal or exceed the risk of colorectal cancer.[2,3] The incidence of sporadic EC rises with age until about age 70, when the rate begins to decline.[6] In a study by Vasen et al of 125 cases of EC in LS families from seven countries, the mean age at diagnosis of EC in women with LS was 48 years (range, 27–72 years). Fifty-seven percent of patients were diagnosed under age 50 years.[7]

EC is an infrequent cause of death in women with LS. In the same study by Vasen and colleagues, only 12% of patients died of EC.[7] Boks et al used Netherlands cancer registry data to evaluate the EC outcomes of 50 patients with LS-associated EC who were age and stage matched with 100 patients with sporadic EC. The overall 5-year survival rate was 88% for patients with LS-associated EC as compared with 82% for

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patients with sporadic EC ($P = 0.59$). Stage, tumor histology, and survival by stage were similar between the two groups.[8]

Broaddus et al evaluated 50 women with EC from four U.S. hereditary cancer registries. They observed that 86% were of endometrioid histology with 14% being of the more aggressive nonendometrioid subtypes (papillary serous, clear cell, or malignant mixed müllerian tumors). This is similar to the reported distribution of EC histology in the general population, where ~80% are of endometrioid type and 20% are of nonendometrioid type.[9]

In contrast, Carcangiu et al identified a higher percentage of nonendometrioid histology in women with LS-associated ECs, with 56.5% being of endometrioid and 43.5% being of nonendometrioid histology. In this study, LS-associated ECs were of higher grade and more commonly demonstrated vascular invasion than sporadic ECs. There was no difference in survival between the two groups. The difference in grade and stage of presentation among LS-associated tumors in this study may be due to a greater percentage of nonendometrioid tumors in LS patients, whereas the different distribution of tumor histology compared with previous studies may be related to differences in the distribution of MMR mutation.[10]

Tumors of the lower uterine segment are a rare form of EC that can clinically be confused with endocervical adenocarcinoma. Westin et al evaluated 35 patients with ECs of the lower uterine segment. Ten (29%) of these tumors occurred in a woman with confirmed or strongly suspected LS.[11] Some studies have suggested that tumors of the lower uterine segment are associated with adverse prognostic features.[12,13] This has yet to be confirmed specifically for patients with LS-associated tumors of the lower uterine segment.

The National Comprehensive Cancer Network (NCCN) recommends consideration of genetic counseling/testing for EC patients younger than 55 years with a significant family history. They further suggest that screening for LS with immunohistochemistry should be considered in all EC patients, particularly those younger than 55.[14] Some centers have implemented immunohistochemistry and/or microsatellite instability screening of all colorectal and ECs, regardless of age at diagnosis or family history, to identify individuals with LS.[15] This approach has been endorsed for colorectal cancer, but not routinely for EC, by the Evaluation of Genomic Applications in Prevention and Practice Group of the Centers for Disease Control.[16]

Ovarian Cancer

According to the Surveillance, Epidemiology, and End Results (SEER) Program, the lifetime risk of OC in the United States is 1.39%.[6] The lifetime risk of OC in women with LS has been estimated at 6.7 to 12%.[2,17] The mean age at diagnosis of LS-associated OC is 42.7 to 49.5 years, which is ~16 to 20 years earlier than the mean age of diagnosis of sporadic OC.[18–21] These tumors are predominantly invasive epithelial cancers. In one study, nonepithelial tumors comprised only 6.4% of LS-associated OCs, whereas borderline tumors of the ovary accounted for 4.1% of LS-associated epithelial ovarian tumors.[20]

LS-associated OCs are typically of an earlier stage than sporadic OCs. Two-thirds of sporadic OCs are diagnosed in stage III or IV. Among patients with LS-associated OC, 77% to 85% were diagnosed in stage I or II.[19–21] Importantly, LS-associated OCs in these studies were symptomatic and not identified as part of a screening program. The distribution of histologic types of LS-associated OC was reported to be similar to sporadic OC in some studies.[20,21] At least one author has identified an overrepresentation of endometrioid and clear cell subtypes as compared with sporadic OC.[18]

Consistent with the observation of an earlier stage at diagnosis, LS-associated OCs have a relatively good prognosis. Crinjen et al observed similar 5-year survival rates among patients with LS-associated and those with sporadic OCs who were matched for age, stage, and year of diagnosis, at 64.2% and 58.1%, respectively.[21] Grindedal et al reported that the 5-, 10-, 20-, and 30-year OC specific survival rates among women with LS-associated OCs were 82.7%, 80.6%, 78%, and 71.5%, respectively.[19]

The finding of metachronous cancers in a young patient is concerning for a familial cancer risk syndrome. Approximately 1 to 2% of women with a gynecologic malignancy have two or more synchronous primary sites.[22] Among young women, the incidence of a synchronous OC in a patient with EC may be as high as 7 to 29%.[23–26] Watson et al evaluated 80 LS-associated OCs. Among these patients, 21.5% were diagnosed with a synchronous EC.[20] Soliman and colleagues evaluated 102 patients with synchronous OCs and ECs. Tumor was available for genetic analysis in 59. The patients were divided into risk groups based on family history. There were two patients whose histories met Amsterdam criteria and were classified as high risk. Fourteen patients had a personal history of or a first-degree relative with a LS-associated malignancy and were classified as medium risk. All others were low risk. All of the patients with a suspected mismatch repair gene mutation based on tumor testing were in the high and medium risk groups. Overall, 7% patients met either clinical or molecular criteria for LS.[27]

Management of Gynecologic Cancer Risk

Chemoprevention

Several clinical trials have evaluated chemoprevention strategies for colorectal cancer in patients with LS. There are no published studies evaluating chemoprevention strategies for gynecologic malignancies in patients with LS. Oral contraceptive use has been demonstrated to decrease the risk of both EC and OC in the general population.[28,29] Most studies suggest that oral contraceptive use decreases the risk of OC in BRCA1 or BRCA2 mutation carriers.[30–35] There may be an increased risk of breast cancer associated with oral contraceptive use in BRCA1 and BRCA2 carriers.[36–38] There are no data in the literature addressing the effectiveness or safety of oral contraceptive use to prevent EC and/or OC in women with LS.

Surveillance

Routine EC screening is not performed in the general population because of the low prevalence of the disease and good

survival rates. Due to the common occurrence of postmenopausal or other abnormal vaginal bleeding, most women with EC present at an early stage. Currently available screening modalities for EC include gynecologic exam with assessment of symptoms, particularly postmenopausal or other abnormal vaginal bleeding, transvaginal pelvic ultrasound to assess the endometrial stripe thickness in postmenopausal women, and office endometrial biopsy.

In the general population, OC is uncommon, but has a high mortality. Routine screening for OC is not performed in the general population due to multiple studies demonstrating that it is ineffective in improving mortality and may result in complications related to the evaluation of false-positive screening tests.[39,40] Even in patients with BRCA1 or BRCA2 mutations, there is no evidence that screening is effective in early diagnosis or improving survival of OC.[41–43] Currently available screening modalities for OC include gynecologic exam with assessment of symptoms, transvaginal pelvic ultrasound, and CA125 tumor marker blood testing.

The American Cancer Society recommends that women known or suspected to have LS undergo annual EC screening with endometrial biopsy beginning at age 35.[44] The NCCN guideline for gynecologic cancer surveillance in patients with LS states that there is no clear evidence to support EC screening. Annual office endometrial biopsy may be used in select patients. The NCCN does not support routine OC screening in LS. Transvaginal ultrasonography for endometrial and OC surveillance may be considered at the physician's discretion.[15] Both groups recommend patient education regarding prompt reporting of abnormal bleeding as the cardinal symptom of EC.

Lindor and colleagues published a systematic review of the evidence regarding management of asymptomatic individuals with LS. They recommend offering annual endometrial biopsy beginning between the ages of 30 to 35 years to screen women for endometrial cancer. Transvaginal pelvic ultrasound can be offered to screen for ovarian cancer. Assessment of endometrial stripe thickness with transvaginal ultrasound is useful only in postmenopausal women. The authors of this review acknowledge that the there is insufficient evidence to recommend for or against these interventions and that the evidence is insufficient to assess the effects on health outcomes.[45]

De Jong et al reported a small, but not statistically significant, decrease in EC mortality in patients with LS diagnosed with EC during the period 1990 to 2004, after the introduction of a systematic screening program with annual transvaginal pelvic ultrasound and CA125 tumor marker determination beginning between the ages of 30 to 35, as compared with those diagnosed during the period 1960 to 1975. It was unclear if this was because surveillance is ineffective or due to the low mortality from this disease. There was an increased risk of death from OC after the introduction of systematic screening.[46]

Transvaginal pelvic ultrasound alone has not been shown to be effective in detecting ECs in patients with LS. In a study by Dove-Edwin and colleagues, 292 women with LS or from LS-like families were screened with annual or biennial transvaginal pelvic ultrasound with follow-up of up to 13 years. No cancers were detected by screening. Two interval cancers presented with vaginal bleeding. Both were stage I and were cured.[47]

Rijcken et al retrospectively reviewed 10 years of experience with annual transvaginal pelvic ultrasonography and CA125 tumor marker testing for screening of women with LS. Premalignant complex atypical endometrial hyperplasia was identified in three screened patients. One interval EC was detected due to the development of postmenopausal vaginal bleeding 8 months after a normal screening ultrasound. The patient had a stage I cancer, which was cured. No OCs were detected either by screening or outside of screening.[48]

The detection of endometrial hyperplasia or EC in asymptomatic women with LS may be improved by the use of endometrial sampling. Renkonen-Sinisalo et al assessed the addition of endometrial biopsy to transvaginal pelvic ultrasound biannually or at 3-year intervals beginning between the ages of 30 to 35. They evaluated 175 women who attended 503 surveillance visits. There were 14 cases of EC. Of these, 11 ECs were diagnosed by screening examination, eight were diagnosed by endometrial biopsy, and four were diagnosed by transvaginal ultrasound. Transvaginal ultrasound missed six cases of EC. Endometrial biopsy detected 14 additional cases of potentially premalignant endometrial hyperplasia. There were two interval ECs and four interval OCs diagnosed. The authors concluded that EC surveillance with endometrial biopsy and transvaginal ultrasound was more effective than transvaginal ultrasound alone. There were not enough events to determine if surveillance improved survival.[49]

Although office endometrial biopsy may improve the effectiveness of EC screening in patients with LS, it may decrease compliance with recommended screening due to the discomfort associated with the procedure. Huang and colleagues have reported on the feasibility of combining endometrial biopsy with colonoscopy for screening of women with LS. The authors reported less pain, high patient satisfaction, and greater patient convenience with the combined approach.[50]

Prophylactic Surgery

Prophylactic hysterectomy with bilateral salpingo-oophorectomy (BSO) performed after the completion of childbearing has been recommended for patients with LS as the definitive approach to gynecologic cancer prevention. Schmeler and colleagues performed a retrospective review of data from three hereditary cancer registries from 1973 to 2004.[51] They identified 380 women with confirmed germline mutations of MLH1, MSH2, or MSH6. Follow-up information was available for 315 women. Their objective was to determine the reduction in risk of gynecologic malignancy associated with prophylactic hysterectomy and BSO in women with LS.

Of the 315 women in this study, 61 (19%) had undergone gynecologic surgery (47 hysterectomy and BSO, 14 hysterectomy only), either for prophylaxis or for a benign gynecologic condition. For the evaluation of EC prevention, 61 women who had undergone hysterectomy with or without BSO were matched with 210 controls with LS who had an intact uterus

and ovaries. For the evaluation of OC prevention, 47 women who had undergone BSO were matched with 233 controls with LS and intact ovaries. The women were followed from the date of surgery until the occurrence of EC, OC, or primary peritoneal cancer, or until the observations were censored due to death or date of last contact.

No ECs were diagnosed in the hysterectomy group with 69 (33%) ECs diagnosed in the control group. The median age at diagnosis of EC in the control group was 46 (range, 30–69). Of these cancers, 48 (70%) were stage I, 4 (6%) were stage II, 6 (9%) were stage III, none were stage IV and 11 (16%) were of unknown stage. There were three deaths from EC.

Similar to the EC group, there were no OCs diagnosed among the women who underwent BSO. There were 12 (5.5%) OCs diagnosed in the control group. The median age at diagnosis of OC in the control group was 42 (range, 31–48). Of the patients with OC, five (42%) were stage I, three (25%) were stage II, two (17%) were stage III, none were stage IV, and two (17%) were of unknown stage. Synchronous EC and OC occurred in three (25%) of the OC cases.

This study demonstrated a 100% efficacy for prophylactic surgery in preventing EC and OC. This was statistically significant for EC, but not for OC due to the small numbers. This study was unable to assess the effect of prophylactic surgery on survival. Given the generally good prognosis of EC and the low incidence of OC, demonstration of a survival advantage for prophylactic surgery would require an impractically large number of patients. There was no difference in total cancer mortality between the two groups.

There are some drawbacks to prophylactic surgery. Surgical complications can occur. In one study, the complication rate (including fever; need for transfusion; and injury to bowel, bladder, or ureter) for hysterectomy performed for benign disease varied with the route of surgery. It was 12.6% for abdominal hysterectomy and 3.7% for laparoscopically assisted vaginal hysterectomy.[52] The risk of complications may be increased in colorectal cancer patients who have undergone prior surgery and pelvic radiotherapy. Prophylactic surgery results in loss of fertility, and certainly should be postponed until after completion of childbearing. BSO in young women results in premature menopause, with symptoms such as hot flashes, night sweats, vaginal dryness, and sexual dysfunction. There is also an increase in osteoporosis and cardiovascular risk with premenopausal BSO. Although hormone replacement therapy can be prescribed, compliance may be poor.

There may still be a small risk of peritoneal carcinoma in LS patients who undergo prophylactic hysterectomy with BSO. Schmeler and colleagues reported two patients with LS who had undergone previous hysterectomy with BSO who subsequently developed primary peritoneal cancer 12 and 8 years later. The magnitude of this risk is unknown, but patients undergoing prophylactic surgery should be counseled regarding this risk.[53]

Conclusions

Lifetime risk of endometrial and ovarian cancer is increased in patients with Lynch syndrome. Endometrial cancer in Lynch syndrome patients occurs at a younger age than sporadic endometrial cancers, but has similar survival rates. Ovarian cancer in Lynch syndrome patients is diagnosed at a younger age and earlier stage compared with sporadic ovarian cancers. Lynch syndrome-associated ovarian cancer has similar survival compared with sporadic ovarian cancers. Screening for endometrial and ovarian cancer in patients with Lynch syndrome should begin between the ages of 30 to 35 years and may include a full examination, education regarding abnormal symptoms, annual endometrial biopsy in premenopausal patients, transvaginal ultrasound, and CA125. Prophylactic surgery after completion of childbearing with hysterectomy and bilateral salpingo-oophorectomy has been shown to decrease endometrial and ovarian cancer incidence in Lynch syndrome patients, but does not change survival.

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