Histologic Evaluation of Prophylactic Hysterectomy and Oophorectomy in Lynch Syndrome

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Abstract: Women with Lynch syndrome (LS) are at increased risk for endometrial (EC) and ovarian carcinoma (OC). Current surveillance recommendations for detection of EC and OC in LS patients are not effective. Small studies have shown that prophylactic hysterectomy and bilateral salpingo-oophorectomy (P-TH-BSO) are the most effective and least expensive preventive measures in these patients. Data regarding histologic findings in prophylactic specimens in these patients are lacking. All LS patients who underwent P-TH-BSO at the Memorial Sloan-Kettering Cancer Center from 2000 to 2011 were identified. Slides were evaluated for the presence of endometrial hyperplasia (EH), EC, OC, or any other recurrent histologic findings. Twenty-five patients were identified, with an age range of 36 to 61 years. Fifteen patients had a synchronous or prior colorectal carcinoma, and 2 patients had a history of sebaceous carcinoma. Focal FIGO grade 1 endometrioid ECs were detected in 2 patients; 1 was 54 years of age (*MSH2* mutation; superficially invasive), and the other was 56 years of age (*MLH1* mutation; noninvasive). Focal complex atypical hyperplasia, unassociated with carcinoma, was seen in 3 patients, ages 35 and 45 (*MLH1* mutations) and 53 years (*MSH2* mutation). One patient (44 y, with *MSH2* mutation) was found to have a mixed endometrioid/clear cell OC and simple EH without atypia. The OC was adherent to the colon but did not show distant metastasis. In our study, P-TH-BSOs performed because of the presence of LS revealed incidental EC and/or EH in 24% of cases and OC in 4%. The ECs were low grade, confined to the endometrium, and seen in patients older than 50 years. Prophylactic hysterectomy allows detection of early lesions in LS; these lesions appear to be small and focal. This small series of prophylactic hysterectomies may provide some clues about LS-associated endometrial carcinogenesis.

Key Words: Lynch syndrome, hereditary nonpolyposis colorectal carcinoma syndrome, prophylactic hysterectomy, endometrial carcinoma, endometrial hyperplasia, ovarian carcinoma

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Lynch syndrome (LS) is an autosomal dominant syndrome that results from germline mutations in DNA mismatch repair (MMR) genes, including *MLH1*, *PMS2*, *MSH2*, and *MSH6*. LS predisposes carriers to malignancies involving several anatomic sites, including colon, endometrium, ovary, urothelium, and pancreas, among others.[1] Women with LS are at particularly high risk for gynecologic malignancies; this risk equals or exceeds their risk for colon cancer.[1] More than half of the women with LS present with a gynecologic malignancy as their sentinel cancer.[1,2]

The lifetime risk for endometrial (EC) and ovarian carcinoma (OC) in these patients is 40% to 60%[3–6] and 4% to 12%,[4,6] respectively, which is significantly higher than that of the general population. The frequency of germline MMR gene mutations in EC is 1.8% to 2.2%,[7] which is similar to that for colon carcinomas. In younger patients, this frequency increases to 9%.[8]

Screening and surveillance measures for colorectal cancer (CRC) patients with LS are well developed. The Amsterdam and Bethesda guidelines focus primarily on CRCs. Surveillance colonoscopy at intervals of 1 to 3 years has been shown to substantially reduce morbidity and mortality from CRC in LS patients.[9] The role of prophylactic colectomy in LS is controversial.[10–12]

Current surveillance measures for detection of EC and OC in LS patients are not as effective. These measures include annual pelvic examination with transvaginal ultrasound, pelvic ultrasound, CA-125 level, and endometrial biopsy starting at age 25 to 35 years. These surveillance techniques have not shown clinical benefits, and cases of EC and OC that were not detected by these measures have been reported.[13] The effect of chemoprevention with oral contraceptives in the setting of LS is currently not known.

Small studies have shown that prophylactic hysterectomy and bilateral salpingo-oophorectomy after the age of 35 years or once child bearing is complete can prevent development of EC and OC in women with LS.[14] In a study by Schmeler et al,[15] none of the women who underwent prophylactic surgery developed EC or OC, compared with a 33% rate of EC and a 5% rate of OC in the control group.

Prophylactic surgery has also been shown to be more cost-effective and to result in the highest number of quality-adjusted life years, compared with surveillance for gynecologic cancers in women with LS.[16] Another study compared the cost-effectiveness of no prevention,

prophylactic surgery at the age of 30, prophylactic surgery at the age of 40, annual screening from the age of 30, or annual screening until the age of 30, followed by prophylactic surgery at the age of 40 (combined strategy).[17] The combined strategy showed the highest net health benefit but was substantially more expensive compared with the next best option of prophylactic surgery at the age of 30.[17]

Incidental ECs and OCs have been reported in prophylactic specimens from LS patients[13,15,18,19]; however, there are currently only limited and small studies concerning pathologic findings in prophylactic specimens from LS patients, and the histologic findings in these specimens are not well described. The aim of this study was to describe our experience with prophylactic surgery in patients with LS. We wanted to assess the incidence of neoplastic or preneoplastic conditions in the uteri and ovaries of these patients.

MATERIALS AND METHODS

After obtaining approval from the Memorial Sloan-Kettering Cancer Center Institutional Review Board, we identified all patients who underwent prophylactic risk-reducing gynecologic surgery for LS at our institution between the years 2000 and 2012. Patients were identified by searching pathology reports for a clinical history of "Lynch syndrome or HNPCC" and/or the terms "prophylactic hysterectomy" in the diagnosis. LS was ascertained by the means of Amsterdam II criteria. The patients with a history diagnostic of or highly suggestive of LS were subsequently tested for germline DNA MMR gene(s) mutations. Detailed information regarding selection of patients is outlined in Table 1.

We included patients who underwent hysterectomy alone and those who underwent hysterectomy and salpingo-oophorectomy.

The endometria and ovaries of P-TH-BSO specimens were submitted entirely for histologic evaluation. Fallopian tubes were submitted entirely using the SEE-FIM protocol only in patients with known *BRCA1/2* mutations or with a history of breast cancer. Hematoxylin and eosin sections from the endometrium were reviewed and evaluated for the presence of any pathologic abnormality including EH and EC. Other recurrent benign histologic findings, such as endometrial metaplasia, adenomyosis, endometriosis, and the presence of leiomyomas were also recorded. The ovaries and fallopian tubes were evaluated for the presence of any pathologic abnormality, including endometriosis.

In cases in which EH or EC and OC were diagnosed, immunohistochemical (IHC) staining analyses for the DNA MMR proteins (MLH1, MSH2, PMS2, and MSH6) were performed. Clinical information was obtained from the Electronic Medical Records, including mutational analysis results when available.

TABLE 1. Identification of Patients With LS

	n (%)
CRC before age of 50 y	15 (60)
Strong family history suggestive of LS (per revised Amsterdam criteria)	17 (68)
History diagnostic of LS (per revised Amsterdam criteria)	4 (16)
Strong family history of CRC	21 (84)
Strong family history of EC	1 (4)
Strong family history of CRC and EC	12 (48)
Patient part of known LS kindred with known germline mutation	5 (20)

TABLE 2. Summary of Surgical Data

Type of surgery	
TH	2 (8%)
TH-BSO	18 (72%)
TH-BSO and colectomy	5 (20%)

TH indicates total hysterectomy; TH-BSO, total hysterectomy and bilateral salpingo-oophorectomy.

RESULTS

Twenty-five patients with a clinical diagnosis of LS who underwent a prophylactic risk-reducing gynecologic surgery were identified. Patient age ranged from 36 to 61 years, with a median age of 48 years.

The surgical data are summarized in Table 2. The vast majority of patients underwent prophylactic TH-BSO, whereas 2 patients underwent hysterectomy only. Five patients underwent prophylactic TH-BSO at the time of colectomy, which was indicated for CRC.

A substantial number of patients had a personal history of cancer, most frequently CRC, which was seen in 64% of the patients (Table 3). Two patients also had a history of sebaceous carcinoma.

A strong family history of cancer in first and second degree relatives was also noted for all patients: CRC (84%), CRC and EC (52%), OC (19%), and breast cancer (31%). Other LS malignancies—including urothelial (19%), gastric (19%), and pancreatic cancer (19%)—were also occasionally seen.

Five of 25 (20%) prophylactic hysterectomies showed atypical EH and/or EC. Three (12%) showed complex atypical hyperplasia (CAH) without EC, and 2 (8%) contained FIGO grade 1 ECs in a background of CAH. One EC focally involved the lower uterine segment and was superficially invasive into the myometrium. The tumor showed the so-called multicystic, elongated, and

TABLE 3. Personal History of Cancer

No history of malignancy	3 (12%)
Colonic polyps with no dysplasia	1 (4%)
Colonic polyp with dysplasia	1 (4%)
CRC	16 (64%)
Sebaceous carcinoma	2 (8%)
Breast cancer	1 (4%)
Thyroid cancer	1 (4%)

fragmented pattern of myometrial invasion, characterized by fragmented and eosinophilic endometrial glands surrounded by a prominent fibromyxoid stromal reaction with inflammatory cells.[20] No lymphovascular invasion was identified. The other carcinoma arose focally within a background of diffusely distributed CAH and was confined to the endometrium (Fig. 1A). The latter case was the only one in which diffuse atypical EH was noted. In all other cases, the carcinoma and/or hyperplasia were focal findings, constituting less than one half of an ×40 field (Fig. 1B). In 1 case, there were several topographically discrete foci of CAH, each measuring only a few millimeters in size (Fig. 1C). Simple hyperplasia without atypia was seen in 1 case (4%).

Four hysterectomies lacking carcinoma and atypical hyperplasia displayed mucinous metaplasia (Fig. 2A). Both ECs were also noted to display mucinous differentiation (Fig. 2B).

Eight patients had undergone either endometrial biopsy or curettage at the Memorial Sloan-Kettering Cancer Center, and 1 patient had undergone both biopsy and curettage. None of the patients was diagnosed with either hyperplasia or carcinoma before hysterectomy. One of the patients diagnosed with adenocarcinoma at hysterectomy had an endometrial biopsy that was reported to show "superficial endocervical mucosa and mucus." Given the finding of mucinous metaplasia in the non-neoplastic endometrium and mucinous differentiation in the adenocarcinoma at hysterectomy, we believe that the findings at endometrial biopsy were best interpreted as mucinous metaplasia. Two patients subsequently diagnosed with atypical hyperplasia at hysterectomy had preoperative sampling. One was noted to have an atrophic endometrium on biopsy, whereas the other had proliferative endometrium with focal gland crowding. Of the 4 patients with mucinous metaplasia at hysterectomy, unassociated with atypical hyperplasia or carcinoma, 2 had preoperative sampling. One had suboptimal tissue for diagnosis, and the other was noted to have numerous neutrophilic microabscesses within proliferative endometrial glands. None of the patients found to have hyperplasia or carcinoma at hysterectomy had histories of vaginal bleeding or abnormal cervicovaginal cytology. One patient with EC, however, was found

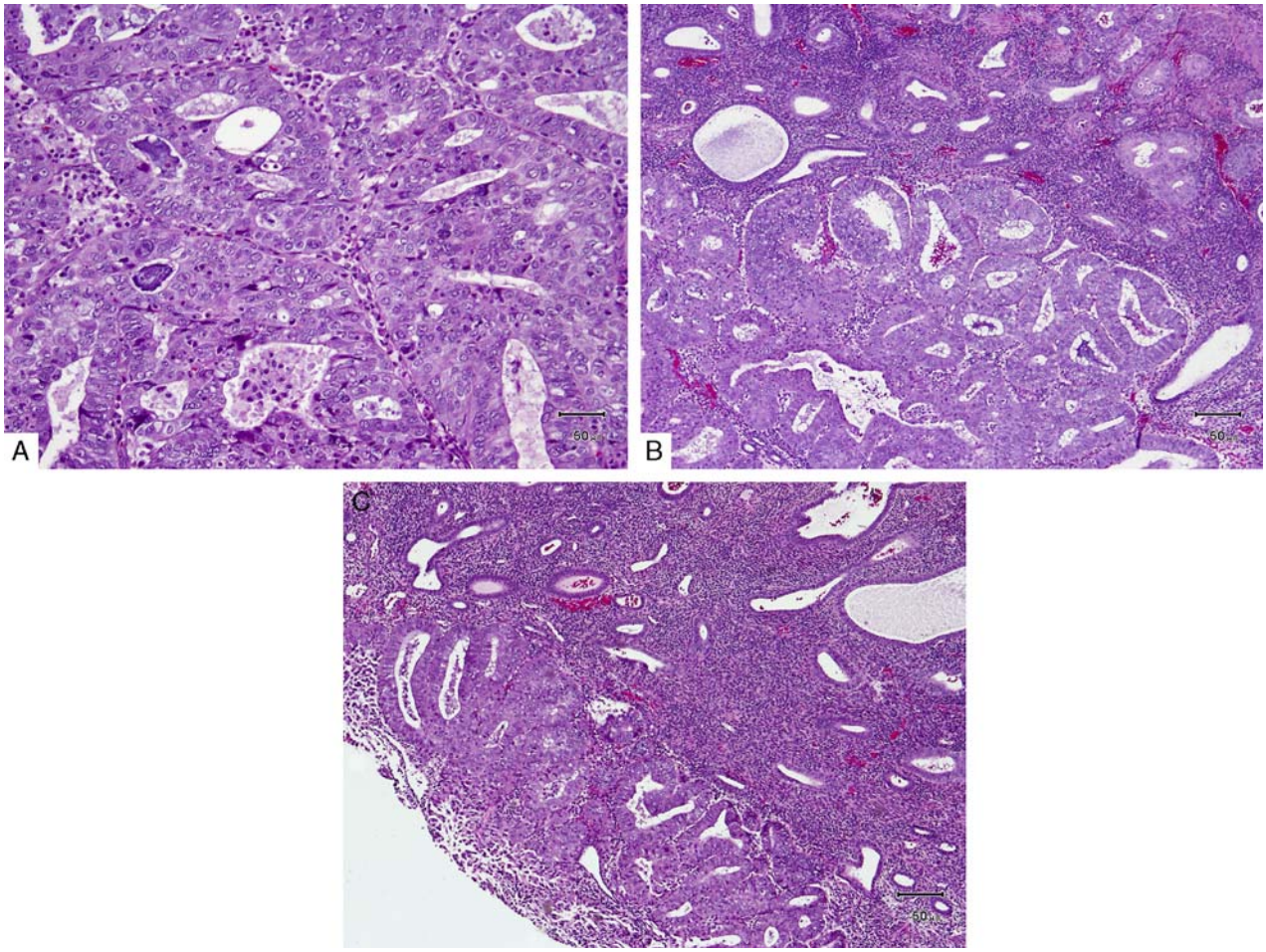

FIGURE 1. A, Focal low-grade endometrioid adenocarcinoma (shown here) in a background of atypical hyperplasia. B, Small focus of atypical hyperplasia. C, Small focus of atypical hyperplasia, topographically separate from that illustrated in (B).

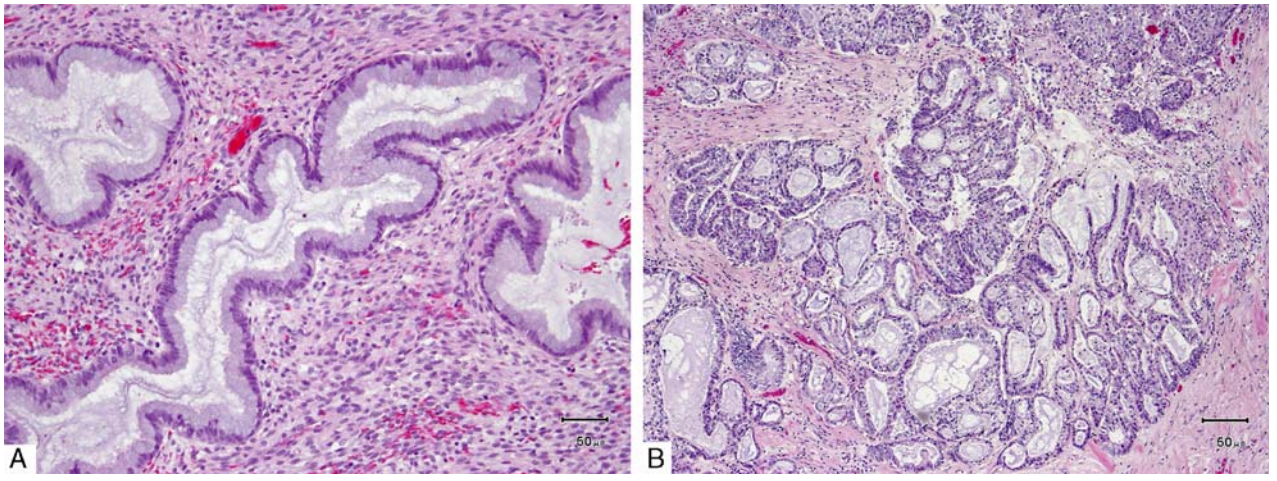

FIGURE 2. A, Focal mucinous metaplasia in non-neoplastic endometrium. Note benign-appearing mucinous epithelium with associated endometrial stroma. B, Low-grade endometrioid adenocarcinoma with mucinous differentiation.

to have multiple fibroids and a thickened endometrium (16 mm) upon preoperative ultrasound imaging.

One of 23 (4%) oophorectomy specimens showed an ovarian carcinoma in addition to simple, nonatypical hyperplasia of the endometrium. This was detected in a 44-year-old patient who underwent prophylactic hysterectomy and salpingo-oophorectomy at the time of colectomy for known CRC. The left ovary showed a mixed endometrioid and clear cell adenocarcinoma (Fig. 3), which was associated with endometriosis and invaded into the colonic wall. The colectomy showed 2 separate CRCs. The endometrium showed simple hyperplasia without atypia.

Five patients had ovarian endometriosis, but it was associated with carcinoma only in the mixed clear cell and endometrioid carcinoma, described above. This case showed foci of endometriosis, atypical endometriosis, and carcinoma. Atypical endometriosis was not seen in any of the other cases.

The fallopian tubes did not show significant pathologic findings in any of the cases.

Results for DNA MMR gene mutational analysis were available for 20 of 25 patients. Eight patients had *MSH2* mutations, 8 showed mutations in *MLH1*, 2 in *MSH6*, and in 1 case, a *PMS2* variant of unknown significance was detected. In 1 patient no mutations were found in any of the MMR genes, despite a family history diagnostic of LS, including a personal history of CRC that showed loss of MLH1 and PMS2 expression by IHC. The tumor tested microsatellite instability-high (MSI-H) by polymerase chain reaction and was found to be negative for MLH1 promoter methylation.

IHC studies conducted on cases with atypical hyperplasia and carcinoma showed loss of MMR proteins concordant with the underlying gene mutation. This abnormal staining pattern was seen in all cases of hyperplasia (Table 4). The ovarian carcinoma showed loss of MSH2 and MSH6, in keeping with patient's MSH2 mutation. The patient's endometrial simple hyperplasia and colonic tumors also showed similar loss of MSH2 and MSH6 staining.

Of the 8 patients with *MSH2* mutations, 3 (37.5%) showed significant findings. These included 1 EC, 1 CAH, and 1 OC. *MLH1* mutations were seen in 8 patients; 2 showed significant findings, including 1 EC and 1 CAH. No carcinoma or hyperplasia was detected in patients with *MSH6* mutations or *PMS2* variant.

DISCUSSION

In our study, significant pathologic abnormalities were detected in the endometrium in 6 of 25 (24%) prophylactically removed uteri, consisting of simple hyperplasia without atypia (4%) complex atypical EH (12%) or EC (8%). One of 23 (4%) oophorectomy specimens showed an incidental ovarian carcinoma.

Incidental uterine and ovarian carcinomas in prophylactic specimens from LS patients have been

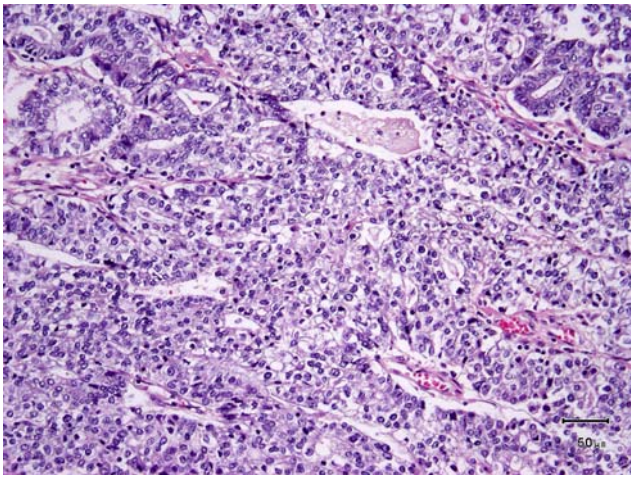

FIGURE 3. Mixed endometrioid and clear cell adenocarcinoma of ovary.

TABLE 4. Summary of Cases With Incidentally Found Neoplasms

Patient Age (y)	Procedure	Findings	Gene Mutation	IHC for DNA MMR Proteins	Personal History
56	TH-BSO	EC	*MLH1*	MLH1/PMS2 loss	CRC
54	TH-BSO	EC	*MSH2*	MSH2/MSH6 loss	Sebaceous carcinoma, colon polyps
35	TH-BSO + colectomy	CAH	Not available	MSLH1/PMS2 loss	CRC
45	TH-BSO	CAH	*MLH1*	MSLH1/PMS2 loss	None
53	TH	CAH	*MSH2*	MSH2/MSH6 loss	CRC
44	TH-BSO + colectomy	OC + SH	*MSH2*	MSH2/MSH6 loss	CRC

Of the 8 patients with *MSH2* mutations, 3 (37.5%) showed significant findings (1 EC, 1 CAH, and 1 OC), and of the 8 patients with *MLH1* mutations, 2 (25%) showed significant findings (1 EC and 1 CAH). No carcinoma or hyperplasia was detected in cases with *MSH6* mutations and the *PMS2* variant.

described. Pistorius and colleagues found stage 1 EC in 2 of 4 patients (ages 47 and 49 y) who underwent prophylactic surgery at the time of colectomy for CRC. Both patients had *MSH2* mutations, and in both cases the tumors were not detected by surveillance.[18] Schmeler et al[15] found incidental EC in 3 of 61 (5%) patients who underwent prophylactic hysterectomy (ages 38, 48, and 58 y); 2 were stage I, and 1 was stage II at diagnosis. Chung et al[19] reported a case of stage IIA mixed endometrioid and clear cell carcinoma of the endometrium at prophylactic surgery in a 48-year-old woman with an *MSH2* mutation.

The 2 ECs detected in our study were stage I, well-differentiated endometrioid adenocarcinomas with mucinous features. Both were focally present in a background of CAH. In cases with CAH, the cytologic atypia was often a focal, and not diffuse, finding.

One ovarian carcinoma was detected in our study. This tumor showed mixed endometrioid and clear cell histology and occurred in a background of endometriosis and atypical endometriosis. Clear cell and endometrioid carcinomas are the most frequent ovarian carcinoma subtypes associated with LS. There may be an association between tumors arising in endometriosis and LS, although there are currently only rare case reports on this subject.[21] There is a case report of an ovarian endometriotic cyst with loss of MLH1 staining in a woman with *MLH1* mutation, suggesting that endometriosis may be a precursor lesion.[22] We have also noted several cases of gynecologic tumors with MMR abnormalities arising in extraovarian endometriosis (Garg and Soslow unpublished data, 2012). Indirect evidence to support this hypothesis is the fact that both ovarian tumor types that are LS associated also originate in ovarian endometriosis. It is not known whether the incidence of endometriosis is higher in patients with LS, compared with the general population. Larger studies are needed to further elucidate the association between endometriosis and LS.

Both patients in our study with incidentally found endometrioid carcinoma were older than 50 years of age, whereas the patient with ovarian carcinoma was 44 years old. This is consistent with previous studies that have shown that many LS patients present with EC at an age older than 50 years. The risk for EC and OC before age 40 in LS has been found to be very low.[23] The youngest patient is our study with CAH was 35 years old.

Risk for EC and OC in LS appears to differ by the mutated gene. The risk for EC is estimated to be 54%, 21%, and 16%, and the risk for ovarian cancer is 20%, 24%, and 1% at age 70 for mutations in *MLH1*, *MSH2*, and *MSH6*, respectively.[23] In our study, 1 patient with EC had an *MLH1* mutation, whereas the second had an *MSH2* mutation. The patient with ovarian carcinoma showed an *MSH2* mutation. All cases with endometrial CAH also had either *MLH1* or *MSH2* mutations. Fifteen of 19 (79%) patients with available mutational analysis were proven carriers of germline mutations involving either *MLH1* or *MSH2*, reflecting the means by which they were identified (see the Materials and methods section). The majority of the patients (17 of 25; 68%) already had a confirmed diagnosis or a medical history of CRC, and 5 of 25 (20%) had P-TH-BSO at the time of primary surgical intervention for CRC. This explains the significant overrepresentation of *MLH1*/*MSH2* mutations within the cohort. The family history and age-dependent criteria (Amsterdam II and Revised Bethesda) show optimal results in prospective identification of LS patients with CRC[9] but fail to prospectively identify most LS-associated ECs.[7] This in part can be explained by the significantly higher frequency of *MSH6* mutations in LS patients with EC.[24–26] LS due to *MSH6* mutations is characterized by lower penetrance through generations, predisposition for EC in female patients, and a lower degree of MSI in tested tumors.[7,25,27–30] Women with *MSH6* mutations are at particular risk for developing EC, but these patients often develop EC later compared with those with *MLH1* or *MSH2* mutations, and the risk increases substantially after the age of 50.[31,32] These data suggest that prophylactic surgery in women with *MSH6* mutations can be delayed to 45 years. Neither patient with *MSH6* mutations in our study (ages 51 and 59 y) had EC or OC at the time of prophylactic surgery.

ECs associated with LS may show certain morphologic characteristics, including histologic heterogeneity, mucinous differentiation, tumor necrosis, dedifferentiation, tumor-infiltrating lymphocytes, peritumoral lymphocytic infiltration, and origin in the lower uterine segment.[33–39] Both carcinomas identified in our study showed mucinous differentiation and increased tumor-infiltrating (>40 tumor-infiltrating lymphocytes per 10 high-power fields) and peritumoral lymphocytes. Both tumors involved the anterior wall of the uterine corpus, and 1 also involved the

lower uterine segment. The incidental ovarian carcinoma was mixed endometrioid and clear cell type. The patient, an *MSH2* germline mutation carrier, was incidentally found to have multicentric CRC of the sigmoid colon at the time of prophylactic colectomy and TH-BSO. DNA MMR-deficient OC is frequently associated with loss of expression of MSH2 and MSH6 and clear cell histology.[40]

This small series of prophylactic hysterectomies may provide some clues as to how ECs develop in the setting of LS. There is evidence suggesting that these tumors arise in association with EH, like other type 1 ECs. However, unlike in typical sporadic type 1 carcinomas, the associated hyperplasia is often a focal finding. This suggests that transformation from a non-neoplastic endometrium to atypical hyperplasia and carcinoma may be accelerated in the setting of high levels of MSI. The focality of significant findings, theoretically, also has diagnostic implications. None of the biopsy or curettage specimens that preceded hysterectomy were diagnostic of either hyperplasia or carcinoma in this series. In a previous publication about ECs diagnosed in women younger than 40 years of age,[41] we reported grading discrepancies in 10% of cases when comparing preoperative and hysterectomy diagnosis. In all these cases, the tumor grade assessed at hysterectomy was higher than in the preoperative sample. Along with the data presented here, this suggests not infrequent sampling error in the setting of LS, which is theoretically attributable to the focal nature of abnormalities, tumor progression that occurs at an accelerated rate by telomere shortening and acquisition of additional mutations,[42] and intratumoral heterogeneity. Although not recognized in this series of early endometrial neoplasia, intratumoral heterogeneity has been reported to be a characteristic feature of carcinomas that arise in the setting of LS.[33,43–45] At least some of the intratumoral heterogeneity reported might be due to the presence of collision tumors that arise in spatially discrete foci, which then coalesce. The presence of several separate foci of CAH in 1 of our cases lends credence to this idea.

Finding small foci of atypical hyperplasia and/or adenocarcinoma in a background of normal cycling endometrium or atrophy suggests that the hormonal milieu or the endometrium's response to the hormonal milieu might differ in LS patients as compared with other patients. It has been hypothesized that LS-associated ECs arise through a distinctive estrogen-unrelated carcinogenic pathway.[46,47] Along these lines, numerous studies have shown correlations between low body mass index and the presence of microsatellite unstable EC[41,48–52]; these correlations do not apply to sporadic type 1 EC.

It is also interesting that all of the cases of CAH in our series showed abnormal IHC staining for the DNA MMR proteins. Loss of staining for MSH2 and MSH6 was also noted in simple hyperplasia of the endometrium in the patient with *MSH2* mutation and OC and CRC. These findings suggest that MMR abnormality is an early event in endometrial carcinogenesis. Previous studies have also found abnormal staining for MMR proteins in EH.[53–55] Mucinous metaplasia and mucinous differentiation in EC were frequent findings in a study by Cathro et al.[56] They suggested that mucinous differentiation may be more commonly encountered in MSI-H ECs than in those that were not MSI-H.[56] In an earlier study,[34] we reported 3 MSI-H ECs with extensive mucinous metaplasia as compared with only 1 in the control group, numbers that were insufficient for statistical analysis. One of the first papers that reported the presence of characteristic morphologic traits in LS-associated EC[39] sought to study this issue, but the results were inconclusive. It is possible that mucinous differentiation is a common early event in LS-associated endometrial neoplasia and that tumor progression from this substrate results in overgrowth and replacement of the low-grade mucinous metaplastic lesion. This remains an issue for further study, because it is well known that extensive mucinous differentiation in CRC is associated with MSI-H status.

SUMMARY

Incidental EC or OC was detected in 8% and 4% of our prophylactic specimens, respectively. The endometrial tumors were of low grade and low stage and seen in patients older than 50 years. Prophylactic hysterectomy allows recognition of early lesions in LS, which appear to be small and focal.

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