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Molecular Pathogenesis of Endometrial Cancers in Lynch Syndrome

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Abstract

Objective—We hypothesized that Lynch Syndrome (LS)-associated endometrial cancer (EC) develops from morphologically normal endometrium that accumulates molecular changes to progress through a continuum of hyperplasia to carcinoma, similar to sporadic EC. The primary objective of this study was to determine if LS-associated EC involves progression through a pre-invasive lesion. The secondary objective was to identify molecular changes contributing to endometrial carcinogenesis in LS.

Methods—Women with a confirmed mismatch repair gene mutation for LS undergoing a prophylactic or therapeutic hysterectomy were eligible. Case controls were matched for EC and hyperplasia based preferentially on age and histology. Mutation status of *PIK3CA*, *KRAS*, *AKT*, *LKB1*, *CTNNB1*, and *PTEN* was assessed.

Results—Concurrent complex atypical hyperplasia (CAH) was found in EC in 11 (39.3%) and 21 (46.6%) of LS and sporadic cases, respectively. Loss of PTEN expression was common in both sporadic (69%) and LS EC (86.2%). There was no significant difference in frequency of KRAS mutation in sporadic EC (10.3%) compared to LS EC (3.4%). AKT and LKB1 mutations were rarely observed. Mutations in PIK3CA and CTNNB1 occurred more frequently in sporadic EC compared to LS EC.

Conclusions—Hyperplasia, particularly CAH, is part of the pre-invasive spectrum of disease in LS-associated EC as indicated by the presence of complex hyperplasia and CAH in LS cases. While PTEN loss is common in both LS and sporadic EC cases, there was a lack of additional mutations in LS associated EC cases. This suggests that in the context of the mismatch repair defects in LS, fewer additional molecular changes are required to progress from pre-invasive lesions to carcinoma.

Introduction

Endometrial carcinoma (EC) is the most common gynecologic malignancy in the United States; approximately 5% are attributed to an inherited predisposition¹. Lynch syndrome (LS), previously known as Hereditary Nonpolyposis Colorectal Cancer (HNPCC), accounts for the majority of such cases. Women with LS have a 40–60% predicted lifetime risk of developing EC, in addition to a 40–60% lifetime risk for colorectal cancers^{2–4}. The risk for EC appears to differ slightly based on the specific germline mutation in mismatch repair genes; *MLH1*, *MSH2*, and *MSH6*. The estimated lifetime risk at age 70 years is 40% for *MSH2* carriers, 27% for *MLH1* mutation carriers, and 26% for *MSH6* carriers^{5–7}.

Similar to the well-established adenoma to carcinoma sequence of colon cancer development, sporadic endometrial cancer is thought to develop through a continuum of complex hyperplasia with atypia (CAH) to well-differentiated cancer⁸. The risk of endometrial hyperplasia progression to carcinoma has been previously characterized in a large nested case-control study by Lacey et al.⁹. This study demonstrated a cumulative progression risk of 4.6% for endometrial hyperplasia (simple or complex) without atypia to carcinoma over 20 years and a 30% cumulative risk for atypical hyperplasia progression to carcinoma⁹. Risk factors for sporadic endometrioid EC include age, obesity, nulliparity, and an excess of estrogen to progesterone¹⁰. In early carcinogenesis, the endometrium is believed to accumulate molecular changes that lead to complex atypical hyperplasia (CAH), the direct precursor lesion to endometrioid endometrial tumors¹¹. These tumors are commonly associated with abnormalities in the tumor suppressor PTEN, oncogenes KRAS and beta-catenin, and in the DNA mismatch repair genes. For LS-associated tumors, it is unknown whether the endometrium progress through a continuum of precancerous lesions to cancer similar to sporadic endometrial cancers. Furthermore, while previous studies have shown that LS-associated colorectal cancer patients progress in an accelerated fashion from pre-invasive lesions to invasive disease it is not known whether this accelerated progression is present in endometrial cancer development¹². The presence of endometrial hyperplasia in LS carriers has been reported, but few studies have attempted to identify important molecular changes associated with malignant transformation in this population^{11–13}.

We hypothesized that LS-associated EC develops from morphologically normal endometrium that accumulates molecular changes to progress through a continuum of hyperplasia to carcinoma similar to sporadic EC. The primary objective of this study was to determine if LS-associated endometrial carcinogenesis involves progression through a pre-invasive lesion. The secondary objective was to identify molecular changes contributing to endometrial carcinogenesis in women with LS. To better understand the role of pre-invasive lesions in LS-associated endometrial carcinogenesis, we examined molecular changes in pre-invasive and invasive lesions in a cohort of women with LS who underwent hysterectomy for prophylaxis or treatment of endometrial cancer.

Methods

Study participants

Institutional review board approval was obtained for this study. Women with a confirmed mismatch repair (MMR) gene mutation (*MLH1*, *MSH2*, or *MSH6*) for LS undergoing a prophylactic or therapeutic hysterectomy were eligible. Cases were selected based on availability of paraffin embedded tissue in the MD Anderson tissue bank as well as from patient's enrolled in the Lynch syndrome registry that had provided tumor blocks for analysis. Case controls were matched 2:1 for sporadic EC and CAH based preferentially on age and histology. Case controls were further chosen to approximate year of diagnosis and stage from the MD Anderson tissue archive. Clinical parameters were abstracted from patients' medical records. Patients were divided into 3 groups based on their histopathologic diagnoses: EC, hyperplasia, and benign endometrium.

Immunohistochemical analysis and pathology review

H&E slides for corresponding endometrial specimens were acquired for all patients and reviewed by a single gynecologic pathologist (BD) to confirm the diagnosis and to establish the presence or absence of concurrent endometrial hyperplasia in EC cases. Pathologic information in cases of EC, including histology, grade, stage, and co-existence of endometrial hyperplasia were ascertained. *PTEN* expression was assessed by immunohistochemistry (IHC) using antibody from Dako 6H2.1 in a 1:100 dilution (Carpinteria, CA). *PTEN* IHC for all samples was scored by one pathologist (BD) as positive, negative, or heterogeneous using an established scoring system¹⁴. In all cases, stromal cells and blood vessels had intensely positive expression for *PTEN*, thus serving as internal positive controls. Endometrial tissue considered positive showed diffuse positive cytoplasmic and nuclear staining in the majority of cells (Figure 1a). Positive staining in endometrial tissue (cancer, CAH, or benign) was comparable to that detected in normal stromal cells. Endometrial tissue with no or only rare cells staining were considered negative for *PTEN* (Figure 1b, <10%). Endometrial tissue with distinct areas of positive and negative staining was designated as having a heterogeneous staining pattern, which indicates local loss of *PTEN*. Cases with heterogeneous staining were combined with the negative *PTEN* staining cases for analysis purposes. Previous studies have shown this immunohistochemical method is superior to *PTEN* sequencing for determining *PTEN* protein loss¹⁴.

Mutational analysis

Tumor DNA was isolated according to standard procedures. Mutational analysis was performed using Sequenom MassARRAY (San Diego, CA) as described previously¹⁵. Briefly, a mass spectroscopy-based approach evaluating single nucleotide polymorphisms was used to detect hotspot mutations in our genes of interest (*PIK3CA*, *KRAS*, *AKT*, *LKB1*, and *CTNNB1*). PCR and extension primers were designed using Sequenom, Inc. Assay Design.

Statistical analysis

Statistical analysis was performed using Fisher's exact test, Chi square, and one way ANOVA. One-way ANOVA was used to compare differences in age among LS carriers. $p < 0.05$ was considered significant for all tests.

Results

There were 67 patients with *MLH1*, *MSH2*, or *MSH6* mutations in the LS cohort and 84 case matched controls (hyperplasia and EC sporadic cases were matched 2:1 for each LS case) enrolled in the study. Clinical characteristics are summarized in Table 1. Among LS patients, 30 patients had normal endometrium, 8 had hyperplasia (2 with complex hyperplasia without atypia and 6 with CAH), and 29 patients had EC. In the sporadic control group, there were 10 patients with normal endometrium, 16 with CAH, and 58 patients with EC. In the LS cohort, the median age at surgery was 43 years (range 32–57) in the normal endometrium group, 39 years (range 35–49) in the hyperplasia group, and 49 years (range 37–62) in the EC group. Women with LS-associated EC were significantly older than both LS carriers with normal endometrium ($p = 0.0025$) and women with hyperplasia ($p = 0.0019$). Mutations in *MSH2* were the most common MMR mutation in LS carriers. Women with sporadic EC were significantly more obese ($p = 0.008$) compared to women with LS associated EC. There was no significant difference between women in the three groups with regards to parity ($p = 0.33$).

Pathologic characteristics of LS-associated endometrial cancer cases and case-matched controls are summarized in Table 2. Only 17.9% of LS associated EC were grade 1 tumors, 32.1% grade 2, and 50% grade 3. Among the sporadic ECs, 12.1% were grade 1 tumors, 74.1% grade 2, and 13.8% grade 3. The majority of both LS and case-matched EC cases were stage I at the time of diagnosis (75.9% and 67.2%, respectively). In LS-associated EC, the majority (62.1%) of the ECs were endometrioid histology, and another 24.1% of a mixed histology.

Table 3 displays the frequency of EC with concurrent hyperplasia in LS and the case-matched cohort. Confirming the importance of complex hyperplasia in the progression to EC, concurrent hyperplasia was common in both LS and case-matched EC cases. In LS-associated EC, 11 cases (37.9%) had concurrent CAH, in addition to 1 (3.4%) with concurrent CH without atypia, and 1 (3.4%) with simple hyperplasia without atypia. In the case-matched cohort 21 (36.2%) displayed concurrent CAH. None of the women in either the LS or sporadic cohort with EC arising in a background of hyperplasia had advanced stage disease (stage III or IV).

Common gene mutations previously reported in sporadic EC (*PTEN*, *PIK3CA*, *KRAS*, and *CTNNB1*) was also present in our sporadic EC cohort and to a lesser extent in the LS associated EC cohort. As shown in Table 4, in this set of LS associated EC cases, there were 4 (13.8%) *PIK3CA* mutations, 1 (3.4%) *KRAS* mutation, and 2 (6.9%) *CTNNB1* mutations. In a similar fashion, in the sporadic EC cases, there were 23 (39.7%) *PIK3CA* mutations, 6 (10.3%) *KRAS* mutations, 22 (37.9%) *CTNNB1* mutations, 1 (1.7%) *LKB1* mutation, and 1 (1.7%) *Akt* mutation. There was similar frequency of *KRAS* mutations in both sporadic EC

and LS associated EC cases. However, *CTNNB1* and *PIK3CA* mutations both occurred significantly more frequently in the sporadic EC cohort than in the LS-associated EC cohort ($p=0.002$ and $p=0.015$ respectively).

In both LS- associated and sporadic EC, *PTEN* loss by IHC occurred commonly (86.2% and 69.0%, Table 5). Among the hyperplasia cases, only 1 of 6 (12.5%) LS-associated CAH demonstrated *PTEN* loss while 11 of 16 (68.8%) of the sporadic CAH cases showed *PTEN* loss. Furthermore, *PTEN* loss was more common in benign endometrium in LS compared to average risk women (43.3% versus 10%) ($p=0.057$). Co-aberrations in *PTEN/PIK3CA* or *PTEN/PIK3CA/KRAS* were less common in LS-associated endometrioid EC compared to case-matched endometrioid EC (Table 6). In sporadic EC cases with concurrent CAH, both *PIK3CA* mutations and *PTEN* loss were common. However, in LS-associated EC cases with concurrent CAH, only *PTEN* loss was regularly observed.

Discussion

Sporadic endometrioid endometrial cancer is thought to develop through a continuum of CAH to well-differentiated cancer⁸. Bokhman et al previously reported an estimated 30–40% of sporadic endometrioid EC cases coexist with CAH¹⁶. Furthermore, as demonstrated by Lacey et al. patients with hyperplasia without atypia and CAH had a progressive increase in lifetime risk of progression to EC. In a screening study of LS patients by Renkonen-Sinisalo et al, the authors demonstrated the presence of endometrial hyperplasia among asymptomatic women during surveillance endometrial biopsy in 8% of Lynch mutation carriers (both complex hyperplasia and CAH were observed)¹⁷. In our cohort of LS-associated EC patients, we found that complex hyperplasia and CAH existed in 12% of our LS carriers. CAH also occurred concurrently with EC in 37.9% of our LS cases, supporting the likelihood that CAH is part of the pre-invasive disease spectrum. LS EC with concurrent CAH occurred primarily in the endometrioid histotype (9 of 11). These findings of endometrial hyperplasia in Lynch mutation carriers lend further support to the pre-invasive disease continuum that may include complex hyperplasia with or without atypia.

There have been very few studies reporting on molecular alterations in hyperplasia and EC from LS carriers. Zhou et al, in a study with 41 cases, aimed to determine whether *PTEN* is involved in the pathogenesis of EC in Lynch carriers and whether *PTEN* inactivation preceded MMR deficiency. The authors demonstrated a 68% *PTEN* loss by IHC in their LS-associated EC cases. They then performed mutation analysis on 20 of the 28 *PTEN* null cases and found that 17 of the 20 cases (85%) had a somatic *PTEN* mutation¹⁸. *PTEN* loss occurred in approximately 86% of LS- associated EC cases and was observed in 43% of LS benign endometrium samples. Future studies with larger numbers of LS associated CAH will help determine if *PTEN* is an early event in the development of LS associated EC. In our study population, *PIK3CA* mutations were more common in sporadic EC cases, and *KRAS* and *CTNNB1* mutations were infrequent in LS carriers. However, *KRAS* and *CTNNB1* occurred in our sporadic EC cases at a frequency similar to previously reported data. The lack of other mutations in our LS-associated EC cases may suggest that in the presence of an existing MMR deficiency, loss of *PTEN* function may be sufficient to drive tumorigenesis. Future studies in which CAH can be microdissected from concomitant EC may be helpful to

delineate the order of mutations in LS associated EC pathogenesis. Cohn et al, examined CAH concomitant with EC, but physically remote from, the cancer for MSI and KRAS mutations with unknown germline MMR status. They observed some cases of MSI positive CAH specimens lacked the KRAS mutation seen in the coexisting cancer supporting their proposed model in which loss of DNA MMR precedes KRAS mutation¹⁹. This suggests that although LS-associated EC appears to progress along the continuum of CAH to carcinoma in a manner similar to sporadic EC, the molecular changes that are accumulated during this progression may be different in LS²⁰. It is suspected that women with LS develop DNA mismatch repair abnormalities resulting in decreased DNA repair and increased loss of *PTEN*. In our LS cohort, the absence of additional mutations suggests that fewer molecular changes are necessary to drive tumorigenesis. Future studies with more comprehensive mutational analysis will be essential to determine whether LS-associated EC involves overall fewer genetic mutations, which specific gene mutations are involved, and which gene mutations occur in CAH versus EC.

Other known risk factors in sporadic EC have not been well documented in LS mutation carriers. Chronic unopposed estrogen exposure is thought to trigger the transformation to hyperplasia then EC. In our study, parity did not significantly differ across groups. However, obesity was significantly more frequent in sporadic EC indicating perhaps a less important role of obesity in LS mutation carriers. It is unclear in women with LS whether obesity and superfluous estrogen have an additive effect; future investigation is warranted to elucidate.

One limitation of our study is that it is a retrospective review with an inherent ascertainment bias. All patients were self-selected or approached because they were LS mutation carriers. Interestingly, our study population is different from other large studies of Lynch syndrome mutation carriers in that more than half of our women were *MSH2* carriers. This differs from the majority of European study populations from Scandinavian registries where mutations are predominantly in *MLH1*^{17, 21}. This may have broader implications for the type of mutations that are found in the US population, as *MSH2* mutations carry an overall increased lifetime risk of developing EC.

In conclusion, our results indicate that hyperplasia, particularly CAH, is part of the pre-invasive spectrum of disease in LS-associated EC as indicated by the presence of complex hyperplasia and CAH in LS cases. While *PTEN* loss is common in both LS and sporadic EC cases, there was a lack of *PIK3CA* and *CTNNB1* mutations in LS-associated EC cases. Additional studies with more cases are needed to identify molecular mutations in the LS-associated CAH to help elucidate the sequence of molecular alterations leading to tumorigenesis and whether this progression is accelerated in EC. Furthermore, knowledge of the molecular alterations can facilitate potential targeted therapeutic interventions in the treatment of LS-associated EC.

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Figure 1.

A) Endometrial tissue considered to be positive demonstrated diffuse positive cytoplasmic and nuclear staining in the majority of cells. B) Endometrial tissue with no or only rare cells staining was considered negative for phosphatase and tensin homolog (PTEN).

Table 1

Clinical Characteristics

	Lynch Syndrome			Case-Matched Cohort		
	EC (n=29)	Hyperplasia (n=8) ⁺	Benign (n=30)	EC (n=58)	CAH (n=16)	Benign (n=10)
Age (years)						
Median	49 [*]	39	43	52	52	51
Range	37–62	35–49	32–57	31–61	40–61	25–54
Mutation						
MLH1	8 (27.6%)	3 (37.5%)	11 (36.7%)	NA	NA	NA
MSH2	16 (55.2%)	5 (62.5%)	17 (56.7%)			
MSH6	5 (17.2%)	0	2 (6.6%)			
BMI						
24.9	12 (49.2%)	6 (75%)	13 (48.2%)	5 (8.6%)	6 (37.5%)	4 (40%)
25–29.9	7 (25%)	0	6 (22.2%)	11 (19%)	2 (12.5%)	1 (10%)
30	9 (32.1%)	2 (25%)	8 (29.6%)	42 (72.4%) ^a	8 (50%)	5 (50%)
Parity						
0	9 (31%)	0	6 (20%)	22 (38%)	6 (40%)	4 (40%)
1	20 (69%)	8 (100%)	24 (80%)	36 (62%)	9 (60%)	6 (60%)

^{*} p<0.05

⁺ Includes complex hyperplasia without atypia (n=2) and complex hyperplasia with atypia (n=6)

^a p=0.008

Table 2

Pathologic Characteristics of Endometrial Cancers

	Lynch Syndrome EC	Case Matched Cohort EC
	n= 29	n= 58
Grade		
1	5 (17.9%)	7 (12.1%)
2	9 (32.1%)	43 (74.1%)
3	14 (50%)	8 (13.8%)
Stage		
1	22 (75.9%)	39 (67.2%)
2	3 (10.3%)	7 (12.1%)
3/4	4 (13.8%)	12 (20.7%)
Histology		
Endometrioid	18 (62.1%)	54 (93.1%)
Mixed	7 (24.1%)	3 (5.2%)
Undifferentiated	2 (6.9%)	0
UPSC ^I	2 (6.9%)	1 (1.7%)

^I Uterine papillary serous carcinoma

Table 3

Endometrial Cancers with Concurrent Hyperplasia

	Lynch Syndrome	Case Matched Cohort
Total EC cases	n= 29	n= 58
EC with hyperplasia	13 (44.8%)	21 (36.2%)
Concurrent SH ¹ w/o atypia	1 (3.4%)	0
Concurrent CH ² w/o atypia	1 (3.4%)	0
Concurrent CAH ³	11 (37.9%)	21 (36.2%)

¹ Simple hyperplasia

² Complex hyperplasia

³ Complex atypical hyperplasia

Table 4

Mutational Analysis

	Lynch Syndrome			Sporadic		
	EC	Hyperplasia	Benign	EC	CAH	Benign
	(n=29)	(n=8)	(n=30)	(n=58)	(n=16)	(n=10)
PIK3CA	4 (13.8%)	0	1 (3.3%)	23 (39.7%)*	1 (6.3%)	0
KRAS	1 (3.4%)	0	0	5 (8.6%)	0	0
CTNNB1	2 (6.9%)	0	1 (3.3%)	18 (31.0%)*	0	1 (10%)
LKB1	0	0	0	1 (1.7%)	0	0
AKT	0	0	0	1 (1.7%)	0	1 (10%)

* p<0.05 compared to Lynch Syndrome EC

Table 5

PTEN Status Determined by Immunohistochemistry

		Lynch Syndrome		Case-Matched Cohort			
		Hyperplasia		Benign		EC	
EC		CAH ¹	CH ²	CAH ¹	EC	CAH ¹	Benign
		n=6	n=2	n=30	n=58	n=16	n=10
PTEN loss		1 (12.5%)	0	13 (43.3%)	40 (69.0%)	11 (69.0%)	1 (10%)
	PTEN present	5 (83.3%)	2 (100%)	17 (56.7%)	18 (31.1%)	5 (31.3%)	9 (90%)

¹Complex Atypical Hyperplasia

²Complex Hyperplasia

Table 6

Co-aberrations

Abnormal pathway	LS EC (n=29)		Case-Matched EC (n=58)	
	Endometrioid	Non-Endometrioid	Endometrioid	Non-Endometrioid
PTEN loss + PIK3CA mutation only	2	2	11	1
KRAS mutation (activation) only	0	1	4	1
PTEN loss + PIK3CA mutation + KRAS mutation (activation)	0	1	5	1