Submitted: 11 September, 2024 Accepted: 24 October, 2024 Published: 15 March, 2025 DOI:10.22514/ejgo.2025.036

ORIGINAL RESEARCH

European Journal of Gynaecological Oncology

Rates of dMMR status in endometrial hyperplasia in comparison to MMR related Lynch Syndrome of endometrial cancer: a pilot study

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Abstract

Background: Lynch syndrome is the most common cause of hereditary endometrial cancer, and is associated with defective DNA mismatch repair. The purpose of the study was to identify the rate of mismatch repair deficiency in women with endometrial hyperplasia compared with the rate in endometrial cancer. **Methods**: A retrospective cohort pilot study was conducted to identify the frequency of mismatch repair deficiency in endometrial hyperplasia specimens, and compare to the known rate in endometrial cancer. A keyword search of the medical record at a single institution was performed to identify 1300 endometrial tissue blocks either from biopsy, curettage or hysterectomy. After exclusion, cohort of 91 women with endometrial hyperplasia were included for analysis. Patient characteristics for both those with normal and abnormal mismatch repair (MMR) results were analyzed using the Mann-Whitney U test and Fisher exact test. Immunohistochemical staining was performed to test for mismatch repair deficiency. **Results**: Among the 91 women with known endometrial hyperplasia specimens who met inclusion criteria, 4 specimens exhibited mismatch repair deficiency. The observed rate of mismatch repair deficiency in hyperplasia (4.4%), was found to be significantly less than that of mismatch repair deficiency seen in endometrial cancer (25%, $p < 0.0001$). **Conclusions**: Based on the data, deficient mismatch repair (dMMR) is not identified at a similar rate in endometrial hyperplasia compared to endometrial cancer. Currently there is no rationale to recommend immunohistochemical staining for mismatch repair deficiency on hyperplasia specimens, and further investigation is recommended to advance screening guidelines for Lynch syndrome. **Clnical Trial Registration**: NCT05257057.

Keywords

Mismatch repair deficiency; dMMR; Lynch Syndrome; Hereditary endometrial cancer

1. Introduction

In 25% of endometrial tumors, one of the four proteins of the DNA mismatch repair (MMR) system is defective [1]. The implications are twofold. First, mismatch repair deficiency (dMMR) is a targetable molecular finding. MMR status renders patients eligible or ineligible for specific cancer therapies. Second, the presence of a dMMR tumor indicates the patient may carry a germline mutation in the genes encoding for one or more of these four proteins, in which case she is diagnosed with Lynch Syndrome, an autosomal dominant inherited disorder. Lynch Syndrome is the most common cause of hereditary colon and endometrial malignancies [2, 3], and portends a lifetime risk of colorectal cancer of 50%–70%, a 40%–60% risk of endometrial cancer, and elevated risk for other malignancies. For these reasons, when endometrial cancer is diagnosed on a tissue specimen, that tissue is also tested for the four MMR proteins MutL Homolog 1 (MLH1), MutS Homolog 2 (MSH2), MutS Homolog 6 (MSH6) and postmeiotic segregation increased 2 (PMS2) [4, 5].

It is well established that endometrial hyperplasia, an overgrowth of the normal endometrium, is a premalignant lesion. Complex hyperplasia with atypia is associated with a greater than a 30% risk of development of endometrial cancer and a 40% risk of already-present concurrent occult endometrial cancer [6–8]. It is unknown whether hyperplasia carries similar rates of dMMR as endometrial cancer, but if so, this would have major ramifications for the diagnosis of Lynch Syndrome and cancer prevention strategies for patients and their families. Small studies ranging between 20 and 118 patients have supported the absence of at least 1 MMR protein in hyperplasia samples between 3% and 55% of cases (Table 1, Ref. [9–12]). However, follow-up data on testing for germline mutations and Lynch Syndrome is lacking. At present there is not enough evidence to support testing for dMMR in all hyperplasia specimens.

TABLE 1. Previous studies investigating microsatellite instability in endometrial specimens to evaluate for premalignancy.

Source	Study Type	Number of Samples and Type	Number (percentage) of dMMR expression	Goal	Conclusion
Lucas *et al.* [9] (2019)	Ret.	118 EIN/AH	4 (3.0%)	To determine the incidence of abnormal protein expression in endometrioid intraepithelial neoplasia/atypical hyperplasia (EIN/AH) [9]	Prevalence of abnormal MMR expression in EIN/AH adjacent to carcinoma and in the unselected group of patients with EIN/AH is similar to the reported prevalence of LS in endometrial carcinoma [9]
Han *et al.* [10] (2015)	Ret.	20 Complex EH Only	11 (55.0%)	To investigate the association between premalignant lesions of the endometrium by evaluating MLH1, MSH2, MSH6 and PMS2 expression in patients with complex endometrial hyperplasia by IHC to find appropriate group for further genetic counseling and testing [10]	More than half of the patients showed loss of expression of at least one mismatch repair protein in our study population. Genetic risk counseling and further tests are recommended for these patients [10]
Niskakoski *et al.* [11] (2018)	Ret.	Sporadic (197 samples), Lynch positive status (66 carriers) (52 cases with MLH1, 10 with MSH2 and 4 with MSH6)	Sporadic *vs.* Lynch Simple EH (2.0% *vs.* 15.0%) Complex without atypia & atypical EH (16.0% *vs.* 86.0%)	To molecularly define the multistep gynecological tumorigenesis, DNA mismatch repair gene mutation carriers with endometrial or ovarian carcinoma or endometrial hyperplasia were identified from a nation-wide registry and endometrial biopsy [11]	Identified early tumorigenic changes, including ARID1A loss, appears in EH Lynch syndrome and sporadic, whereas defective mismatch repair (Lynch syndrome) and tumor suppressor gene promoter hypermethylation (Lynch syndrome and sporadic) are detectable even in histologically normal endometrium [11]
Vierkoetter *et al.* [12] (2016)	Ret.	112 EIN Only	5 (4.5%)	To establish the incidence and type of loss of MMR protein expression in unselected premalignant lesions of endometrial adenocarcinoma, as well as the agreement of IHC staining in pretreatment EMB specimens with subsequent uterine resections [12]	Age not associated with dMMR status. Found the efficacy of evaluating EIN with MMR protein IHC as a screen for Lynch syndrome is limited [12]

Ret.: Retrospective; EIN: Endometrial Intraepithelial Neoplasia; AH: Atypical Hyperplasia; EH: Endometrial Hyperplasia; LS: Lynch Syndrome; IHC: Immunohistochemical; EMB: Endometrial Biopsy; dMMR: deficient mismatch repair; MMR: mismatch repair; PMS: postmeiotic segregation protein increased 2; MLH: MutL Homolog; MSH: MutS Homolog; ARID1A: AT-Rich Interaction Domain 1A.

The aim of this study was to compare the rate of dMMR in endometrial hyperplasia with the known rate of dMMR in endometrial cancer. If the rates were the same, it would provide a basis for expanding universal MMR testing of endometrial tumors to include testing of endometrial hyperplasia specimens. This study was performed by identifying dMMR in endometrial hyperplasia specimens, calculating the rate of dMMR in endometrial hyperplasia, then comparing it with the known rate of dMMR in endometrial cancers in the literature. It was hypothesized that the rate of dMMR in hyperplasia would be the same as the rate of dMMR in endometrial cancer.

2. Methods

A retrospective cohort pilot study was performed. The protocol was reviewed by the WellSpan Health Institutional Review Board and approved on 08 May 2019 (IRB Number 1403922-1), and study registered under ClinicalTrials.gov, NCT05257057.

Appropriate specimens were identified by performing a keyword search of the electronic medical record for "hyperplasia" on final diagnosis of pathology specimens from 01 May 2014–30 June 2022. Pathology endometrial tissue blocks labeled with the diagnosis of hyperplasia were identified. For each specimen, pathology review by a single pathologist was performed to confirm the hyperplasia diagnosis. Any specimens with unclear diagnosis were verified by a second pathologist.

Females aged 18 and older with a specimen of endometrial tissue from biopsy, curettage or hysterectomy with hyperplasia of any type were included. Women less than 18 years of age or with a known diagnosis of endometrial cancer on previous or subsequent pathology were excluded. Those patients with a final diagnosis of cancer were excluded because of the risk that cancer was already present contemporaneously at the time of the hyperplasia diagnosis and would confound the results.

Sample size determination was made based on a desired power of 80% and alpha = 0.05. A calculated 1782 cases were required to exclude a difference between the groups, *i.e.*, present of dMMR in hyperplasia specimens was equivalent to that of endometrial cancer cases (25%). Given the resources available, a pilot study of approximately 5% of this population, around 89 samples, was sought.

Informed consent was obtained via telephone. Participants who met criteria were given the option of a follow up phone call with their results. A copy of the consent form was sent to all participants. No compensation was provided.

Chart review was performed for demographic data including age, body mass index, race, ethnicity and personal or family history of endometrial or colon cancer. Cases were selected for review from chronological order from most recent. Immunohistochemistry testing for MLH1, PMS2, MSH2 or MSH6 was performed and analyzed by a single pathologist. Equivocal results were reviewed with a second pathologist. Women who desired their results were notified of them via phone call. If testing revealed dMMR, those women were counseled by a Gynecologic Oncology fellow and recommended for genetic counseling and testing. Referrals to a licensed genetic counselor for Oncology at the WellSpan institution were placed if the patients were amenable.

Patient characteristics for both normal and abnormal MMR results were analyzed using the Mann-Whitney U test (for continuous variables) and Fisher exact test (for categorical variables). The rate of dMMR was computed in this patient population. A z-test of proportion with a significance of $p < 0.0001$ compared it to the known incidence of dMMR in endometrial cancer from the literature.

3. Results

We identified 1300 endometrial pathology specimens collected during the study period, and after exclusion, 91 were available for analysis. Patient demographics are shown in Table 2. Average patient age was 54.2 ± 12.8 years and BMI 40.8 ± 10.3 kg/m^2. By type of hyperplasia, the most common was complex hyperplasia without atypia at 37 cases (40.7%), followed by complex hyperplasia with atypia at 31 cases (34.1%) and simple hyperplasia without atypia with 23 cases (25.3%). There were no cases of simple hyperplasia with atypia (0%).

Overall, 87 patients demonstrated MMR proficiency on immunohistochemical staining of their endometrial tissue, while 4 patients showed MMR deficiency. Per Table 2, there were no significant differences in the demographics, family histories or breakdown by type of hyperplasia in the MMR proficient and deficient patients.

With 4 out of 91 specimens demonstrating dMMR, the rate of dMMR for endometrial hyperplasia in this group of subjects was 4.4%. This was significant different ($p < 0.0001$) when comparing the rate of dMMR for endometrial adenocarcinoma of 25% (22%–28%) in the literature based on a meta-analysis of over 5000 women [9]. The 4 specimens with dMMR varied in the specific proteins absent on immunohistochemical staining. Table 3 details the breakdown of proteins absent. As shown, no two endometrial hyperplasia specimens with dMMR showed the same pattern of protein absence.

Only 1 of the 4 patients with dMMR found on their endometrial hyperplasia specimen underwent germline testing; this was specimen #3. This patient had formal genetic counseling followed by germline testing using a commercial test for 47 gene mutations, and none were identified. The other three patients were offered genetic testing, however either geographic location was unfavorable for future testing or patient opted for no follow-up.

4. Discussion

Analysis of this cohort revealed a significant difference in the rate of dMMR between endometrial hyperplasia (4.4%) and endometrial cancer (25%, $p < 0.0001$). The exact sample size required was not reached in this pilot study to determine whether we failed to support our hypothesis, that the rates of dMMR in endometrial hyperplasia and carcinoma are equivalent. However, to the best of our knowledge and from the procured data, there is no definitive evidence that exists to support the rates are similar.

Earlier studies examined the possibility of detecting dMMR in endometrial hyperplasia specimens. Currently there is not sufficient evidence for routine testing in precancerous lesions. A handful of small studies have supported the absence of at

TABLE 2. Patient demographics and mismatch repair protein expression from endometrial hyperplasia specimens collected 01 May 2014 until 30 June 2022.

Patient Characteristic	All Patients (N = 91)	MMR Proficient (N = 87)	MMR Deficient (N = 4)	*p*-Value
Age in years, mean (SD)	54.2 (12.8)	53.9 (12.9)	59.3 (11.3)	0.531
BMI in kg/m^2, mean (SD)	40.8 (10.3)	40.6 (10.2)	44.2 (15.0)	0.787
Race-Caucasian, N (%)	89 (97.8%)	85 (97.7%)	4 (100.0%)	1.000
Race-Black, N (%)	2 (2.2%)	2 (2.3%)	0 (0.0%)	1.000
Ethnicity-Hispanic, N (%)	3 (3.3%)	3 (3.4%)	0 (0.0%)	1.000
Ethnicity-Non Hispanic, N (%)	88 (96.7%)	84 (96.6%)	4 (100.0%)	1.000
Family History of Colon or Endometrial Cancer, N (%)	10 (11.0%)	9 (10.3%)	1 (25.0%)	0.377
Complex Hyperplasia with Atypia, N (%)	31 (34.1%)	31 (35.6%)	0 (0.0%)	0.295
Simple with Atypia, N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	N/A
Complex Hyperplasia without Atypia, N (%)	37 (40.7%)	35 (40.2%)	2 (50.0%)	1.000
Simple without Atypia, N (%)	23 (25.3%)	21 (24.1%)	2 (50.0%)	0.264

MMR: Mismatch Repair Protein; SD: standard deviation; BMI: Body mass index. MMR Deficiency is equivalent to lack of expression of the mismatch repair protein. MMR Proficient indicates expression of the mismatch repair protein. p-value significant < 0.05.

TABLE 3. Breakdown of mismatch repair proteins absent in the four deficient endometrial hyperplasia specimens.

	IHC result	Endometrial Hyperplasia Diagnosis
Specimen 1	MSH6 loss	Simple without atypia
Specimen 2	PMS2 loss	Complex without atypia
Specimen 3	PMS2, MLH1 loss	Complex without atypia
Specimen 4	MSH2, MSH6 loss	Simple without atypia

IHC: immunohistochemistry; MSH6: MutS Homolog 6; PMS2: postmeiotic segregation increased 2; MLH1: MutL Homolog 1; MSH2: MutS Homolog 2.

least 1 MMR protein occurring in hyperplasia samples; these studies have sample sizes ranging from 20 to 118 patients, and demonstrate MMR deficiency in endometrial hyperplasia between 3% and 55% (Table 1, Ref. [9–12]). These previous studies compared rates of dMMR in EIN or Atypical hyperplasia specimens, known Lynch carriers *vs.* sporadic mutations or complex hyperplasia only. This retrospective study compared the rate of dMMR in endometrial hyperplasia in both complex hyperplasia with atypia (31 cases), simple hyperplasia without atypia (23 cases). There were no cases of simple hyperplasia with atypia included in this study. However, our sample size of 91 specimens, and findings of 4% dMMR expression in endometrial hyperplasia specimens. was similar to that found in Lucas *et al.* [9]. (3% found in 118 EIN/AH specimens) and Vierkoetter *et al*. [12] (4.5% found in 112 EIN specimens). Of the four specimens with dMMR, it is notable that two were from simple hyperplasia without atypia specimens and two from complex hyperplasia without atypia specimens. None of the previous studies included simple hyperplasia specimens in their evaluation for dMMR (Table 1).

There is biologic plausibility for dMMR rates to be similar between hyperplasia and endometrial cancer—though this may only apply to a subset of patients who have a germline mutation leading to dMMR. A previous case study of serial tissue samples obtained over time from a Japanese woman with a family history of Lynch Syndrome revealed the loss of MSH2 when she had only a diagnosis of hyperplasia, 7 months prior to her endometrial cancer diagnosis [13]. It is important to note, not all the above previous studies on dMMR in endometrial hyperplasia reported follow-up germline testing. The very limited data available is conflicting; some studies show a high level of concordance between somatic dMMR in hyperplasia specimens and dMMR present in germline testing, while others suggest less than 1% of patients with somatic dMMR in hyperplasia specimens harbor a germline mutation for dMMR (namely Lynch Syndrome) [12, 14]. Our study was not powered to assess germline testing, but the one hyperplasia patient whose specimen had dMMR and underwent germline testing was negative for 47 germline mutations, including Lynch Syndrome.

The study was strong in utilizing a thoroughly maintained database in the electronic medical record, allowing for comprehensive chart review. There was consistency in the pathologic review of specimens and in clinical follow up for significant results.

While the study was intended as a pilot investigation, it was limited by its single-institution design and small sample size. The resources available did not allow for review of all endometrial tissue specimens by multiple pathologists. Therefore, unless there was a question of diagnosis, a single pathologist

reviewed the slides. Of note, the original protocol allowed for use of a keyword search for "endometrial intraepithelial neoplasia" in the electronic medical record. However, this verbiage was not utilized by the pathology department within the study period, consequently this keyword was abandoned. And since the term "endometrial intraepithelial neoplasia" is now recommended terminology by the Society for Gynecologic Oncology and the American College of Obstetricians and Gynecologists, over the 1994 World Health Organization schema used in this study, this may render our report less generalizable long-term [15]. Further, the investigation was limited by not focusing on other known risk factors for hyperplasia including BMI, age and ovulatory status; future examination of known risks factors in the setting of endometrial hyperplasia may set a threshold for additional screening.

Although the outcomes of this study do not suggest practice changes based on the diagnosis of hyperplasia, it does create opportunity for further study. The absence of MMR proteins results in genomic instability, with the insertion or deletion of noncoding single nucleotide and dinucleotide repeats called microsatellites. The finding of these altered microsatellites is termed microsatellite instability which is a marker of Lynch Syndrome associated tumors [16, 17]. While immunohistochemical staining for MMR proteins and polymerase chain reaction testing for microsatellite instability are typically correlated, the findings of this study could be either verified or expanded upon through testing for microsatellite instability.

Based on The Cancer Genome Atlas study on endometrial cancer, the outlook on the pathophysiology of this disease is changing. The new genomic categories of polymerase epsilon gene (POLE) ultra-mutated, microsatellite instability hypermutated, copy number low, and copy number high for endometrial cancer prompt follow up questions related to this current study [18]. While dMMR is typically associated with microsatellite instability, what does this mean for those cancers with precursor lesions of endometrial hyperplasia? Is the loss of expression of one of the four MMR proteins a step along the pathway to the microsatellite instability hypermutated subtype of endometrial cancer—and if so, is that only not reflected here because of the exclusion of patients with a final diagnosis of endometrial cancer? Further investigation into the genomic mutations of endometrial cancer precursor lesions is warranted to better understand the treatment and prevention of this disease.

5. Conclusions

In summary, because the rate of dMMR between endometrial hyperplasia was significantly less than that of dMMR known in endometrial carcinoma, the findings of this study do not support universal screening for dMMR on endometrial hyperplasia specimens, compared to Lynch Syndrome screening in the setting of known endometrial cancer for the purpose of targeted therapy. However, this study does highlight the need for further exploration of the genomics of endometrial cancer precursor lesions to effectively prevent and treat endometrial cancer in the future.

AVAILABILITY OF DATA AND MATERIALS

Data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

KK—conceived and designed the analysis, data collection and result interpretation, manuscript preparation. EL—principal investigator, conceived and designed the analysis, result interpretation, manuscript preparation and revision. JG—analysis, manuscript preparation and revision.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Given this was a retrospective cohort pilot study, all patient information remained de-identified and confidential with appropriate security measures placed by the WellSpan Health Institutional Review Board. Patients were consented to utilize their de-identified information within the study (IRB Number 1403922-1). This study is registered under NCT05257057. Informed consent was obtained via telephone. Participants who met criteria were given the option of a follow up phone call with their results. A copy of the consent form was sent to all participants.

ACKNOWLEDGMENT

Special thanks to the funding by the George L Laverty Foundation Trustee U/W, Verbie C Emig Trust, and the Lake Erie College of Osteopathic Medicine.

FUNDING

Grant funding for this research was provided by: The George L Laverty Foundation Trustee U/W Grant, The incidence of Lynch Syndrome in endometrial hyperplasia (Wilmington Trust #229100252). Verbie C Emig Trust Grant, Frequency of endometrial cancer precursor associated with Lynch Syndrome, March 2019 (WYH#2020.113). The Lake Erie College of Osteopathic Medicine, March 2019 (#J2019.24).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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How to cite this article: Kathryn Kennedy, Jennifer Gaertner-Otto, Eav Lim. Rates of dMMR status in endometrial hyperplasia in comparison to MMR related Lynch Syndrome of endometrial cancer: a pilot study. European Journal of Gynaecological Oncology. 2025; 46(3): 56-61. doi: 10.22514/ejgo.2025.036.