

# Prospective Study of Combined Colon and Endometrial Cancer Screening in Women With Lynch Syndrome: A Patient-Centered Approach

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## Abstract

**Background:** Endometrial and colorectal cancers are the most common cancers in Lynch syndrome. Consensus guidelines recommend annual endometrial biopsy (EMB) and regular colonoscopies. We assessed the feasibility of concurrently performing EMB and colonoscopy and evaluated women's perception of pain, satisfaction, and acceptability.

**Methods:** From July 2002 to December 2009, women who had a gene mutation for Lynch syndrome, met the Amsterdam II criteria, or had a high-risk situation that required screening were prospectively enrolled. After conscious sedation, the procedures were sequentially performed. Patients completed pre- and post-procedure questionnaires assessing pain, level of satisfaction, and acceptability. The Wilcoxon rank test and Mann-Whitney test were used to compare pain scores.

**Results:** Forty-two women completed the study. Median age was 37 years (range, 25 to 73). Nineteen had previously had an EMB in the office setting. Women reported significantly lower median levels of pain in the combined procedure compared with previous office setting biopsies ( $P < .001$ ). Regardless of parity, women reported significantly less pain for an EMB as part of the combined screen compared with an office EMB (parous,  $P = .003$ ; nulliparous,  $P = .026$ ). Women also reported a high level of satisfaction and more convenience in the combined procedure. All participants preferred combined to separately scheduled procedures and would recommend the combined procedure to their relatives.

**Conclusion:** Combined colon and endometrial cancer screening is a patient-centered approach that is feasible, acceptable, and may improve adherence to Lynch syndrome screening recommendations.

## Introduction

Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC), is an autosomal dominant syndrome caused by mutations in mismatch repair genes.<sup>1</sup> Female carriers are predisposed to developing a variety of malignancies, most commonly endometrial and colorectal cancers. Although colorectal cancers have traditionally been a primary focus in clinical care for Lynch syndrome, it is important to note that the incidence of endometrial cancer in women actually equals or exceeds that of colorectal cancer.<sup>1,2</sup> Furthermore, carriers who develop cancer are also at an increased risk of developing second subsequent metachronous malignancies.<sup>1,3,4</sup> In approximately 50% of patients with both colon and endometrial cases, endometrial cancer is frequently the sentinel event.<sup>3,5</sup>

Previously published prospective data suggest the benefit of colorectal cancer screening in Lynch syndrome carriers. Thus, consensus guidelines endorse screening every 1 to 2 years, beginning at age 20 to 25 years until age 40 years, then annually thereafter.<sup>6-8</sup> Although data on the efficacy of endometrial cancer screening in this subset of patients are limited, current recommendations advise women to undergo annual endometrial biopsy (EMB) beginning between the ages of 30 to 35 years, or 10 years before the age at which a family member first received an endometrial cancer diagnosis.<sup>9</sup> EMB has traditionally been performed as an office procedure without analgesia, and pain can be a limiting factor in successful completion.<sup>10,11</sup> Colonos-

copy is routinely performed under sedation.<sup>12</sup> Given the similarity in the recommended intervals for colorectal and endometrial cancer screening in Lynch syndrome, it is reasonable to consider offering both tests concurrently under sedation for affected women. To the best of our knowledge, colonoscopy performed in conjunction with EMB both with anesthesia has not yet been evaluated, and we were interested in pilot testing a combined screening program. The objective of this study was to assess the feasibility of performing an EMB concurrently with a colonoscopy and to evaluate women's perceptions of pain, satisfaction, and overall acceptability.

## Methods

From July 2002 to December 2009, women were prospectively enrolled if they had a genetic mutation for Lynch syndrome, fulfilled the Amsterdam II criteria, or possessed characteristics that required colon and endometrial cancer screening (Table 1 for specific categorization). The study was approved by the M.D. Anderson Cancer Center Institutional Review Board, and all participants provided written informed consent. Clinical information abstracted from medical records included demographic characteristics, parity, mode of delivery (cesarean section *v* vaginal delivery), and genetic test results.

One day before their combined procedure, patients were contacted by a research coordinator, who was not involved with any clinical aspects of the study. The coordinator used an open-

**Table 1.** Demographic and Clinical Characteristics

Characteristic	No.	%
Total No.	42	100
Age, years		
Median		37
Range		25-73
Race/ethnicity		
White	37	88
Hispanic	2	5
Black	2	5
Asian	1	2
Prior colonoscopy	34	80.1
Prior EMB	19	45.2
Risk status		
Mutation		
<i>MSH2</i>	15	36
<i>MLH1</i>	11	26
<i>MSH6</i>	1	2
Presumptive Lynch*	4	9.5
50% risk for Lynch	4	9.5
Amsterdam II positive†	3	7
Other‡	4	9.5
Parity		
Nulliparous	11	26
Parous	31	74
Delivery method		
Vaginal	23	74.2
Cesarean section	8	25.8

Abbreviation: EMB, endometrial biopsy.

\* Presumptive Lynch: personal history of colon cancer with immunohistochemical loss of MMR expression but no identifiable gene mutation.

† Amsterdam II criteria: each of the following criteria must be fulfilled: three or more relatives with an associated cancer (colorectal, endometrial, small intestine, ureter, or renal); two or more successive generations affected; one or more relatives diagnosed before the age of 50 years, one of whom should be a first-degree relative; familial adenomatous polyposis should be excluded in cases of colon cancer; tumors should be verified by pathologic examination.

‡ Family history of colon and endometrial cancer not fulfilling Amsterdam criteria with inconclusive genetic testing or no testing available, Cowden's syndrome with need for routine colon cancer screening.

**Table 2.** Median Pain Scores Reported by Women Who Underwent EMB With and Without Sedation, by Parity Status

Parity	No.	Median Pain Score* Prior EMB (without sedation)	Median Pain Score Combined EMB (with sedation)	P
Nulliparous	6	8.0	1.0	.026
Parous	13	5.0	1.0	.003
Vaginal delivery	10	4.0	1.0	.012
Cesarean section	3	7.0	2.0	.100

Abbreviation: EMB, endometrial biopsy.

\* No pain = 1 to most pain = 10.

format guide to conduct a telephone interview regarding the patient's prior experience with EMB and colonoscopy, their perception of associated pain, and their expectations regarding benefits and barriers to a combined screening procedure. Women who had previous procedures were asked to retrospectively assess pain levels associated with each procedure. Furthermore, pain scores for colonoscopies were collected as an internal control measure. Perceptions of pain were measured on a scale of 1 to 10, where 1 indicated no perceptible pain and 10 represented extreme pain.

On the day of the scheduled procedure, conscious sedation was initiated and the two procedures were sequentially performed by the clinical coordinator and endoscopy staff in an endoscopy suite containing a prearranged stretcher with lithotomy stirrups. Gynecologic supplies for the EMB were brought to the endoscopy suite by the clinical coordinator (Appendix 1, online only). A urine pregnancy test was obtained before the EMB. In the initial series of patients, EMB and colonoscopy were performed in alternating order to evaluate any difference in time and efficiency. After approximately 15 patients, colonoscopy followed by EMB was determined to be the most efficient strategy because after completion of the colonoscopy, no further anesthesia was required for the EMB portion. Thus, this sequence was used for the successive patients. The colonoscopy was performed in the standard method by a gastroenterologist and the EMB was performed by a gynecologist.

A follow-up telephone interview was conducted by a research coordinator within 24 hours to evaluate each woman's experience including acceptability, pain perception for each procedure, satisfaction, convenience, and scheduling, as well as whether the procedure met their expectations. Women were also given the opportunity to provide comments and feedback about their experiences. In addition, patients were contacted by the clinical coordinator within 1 week after the procedure to address any postprocedure complications or questions.

Descriptive statistics were used to summarize demographic and clinical variables. The Wilcoxon signed rank test was used to analyze pre- and postprocedure paired pain scores. Differences in pain scores between nulliparous and parous women were evaluated by the Mann-Whitney test. A *P* value of less than .05 was considered statistically significant for all tests.

## Results

Forty-three patients were enrolled in the study; however, one patient was unable to undergo the study procedures as a result of lacking health insurance coverage at our institution. Thus, 42 patients underwent combined screening and completed both pre- and postprocedure assessments. Median age was 37 years, with a range of 25 to 73. Patients were predominantly white (37, 88%) and married (33, 79%). The majority of women were parous (31, 74%), and of the parous patients, 23 (74.2%) had previous vaginal deliveries. In 64% of patients, a gene mutation in *MLH1*, *MSH2*, or *MSH6* was identified (Table 1).

Of the 42 patients, 19 women had previously undergone an EMB in the office setting without sedation. Date of prior EMB was available for 17 of these women, and the median interval

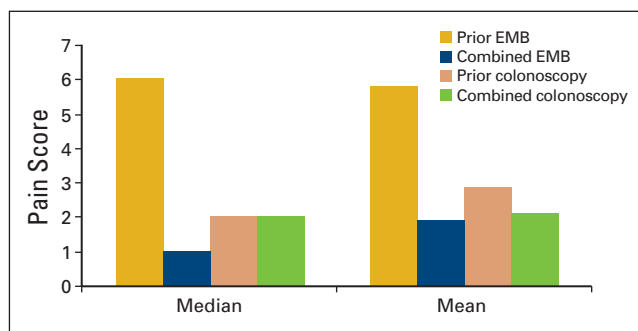
between the two procedures was 3 months. Women reported significantly lower median levels of pain in the combined procedure compared with previous office setting biopsies (1.0, mean 1.8, range 1 to 7 *v* 6.0, mean 5.8, range 1 to 10;  $P < .001$ ). Regardless of parity, women reported significantly less pain awareness for an EMB as part of the combined screen compared with an office EMB (parous: median 1.0, mean 1.4, range 1 to 2 *v* median 5.0, mean 5.2, range 1 to 9;  $P = .003$  and nulliparous: median 1.0, mean 2.7, range 1 to 7 *v* median 8.0, mean 7.3, range 4 to 10;  $P = .026$ ; Table 2). As expected, when asked about pain associated with prior colonoscopies, there was no statistically significant difference in pain perception ( $P = .13$ ; Figure 1). The median time added to the colonoscopy procedure when combined with an EMB was 5 minutes (range, 1 to 12 minutes).

The majority (38, 90%) of patients reported no difficulty with insurance coverage. The 12 patients who encountered difficulty with insurance companies did so primarily with the colonoscopy portion of the procedure, which was more challenging because these patients were from out of state and used out-of-network insurance providers. However, all insurance difficulties were eventually resolved. Approximately half (52.4%) of the study participants traveled a distance greater than 75 miles in order to receive an examination. Patients uniformly expressed an overall high level of satisfaction with the combined procedure, and 95% reported that they were either extremely or moderately satisfied. Most women (78.6%) reported that they would definitely undergo annual screening if it were offered as a combined procedure. The most frequently endorsed benefits of combined screening included greater convenience of scheduling two procedures concurrently, less overall time commitment, less pain, and less anxiety (Tables A1 and A2, online only). All participants indicated that they preferred combined screening to individually scheduled procedures. Furthermore, patients stated that they would recommend the combined procedure to their relatives. Participants indicated that they would be more likely to follow endometrial and colorectal screening recommendations if these tests were offered as a combined procedure.

**Discussion**

Women with Lynch syndrome have a cumulative lifetime risk of up to 60% for both colorectal and endometrial cancer.<sup>1,4,12</sup> In Lynch syndrome–associated colorectal cancers, regular colonoscopies have resulted in significantly decreased incidence (approximately 60%) and improved overall and colorectal cancer–related survival.<sup>7,13,14</sup> Although similar data are lacking for Lynch syndrome–associated endometrial cancers, consensus groups and expert opinions recommend routine annual surveillance. A key aspect of screening is the enhanced ability to identify premalignant lesions for early detection or cancer prevention.

In studies by Dove-Edwin et al and Rijcken et al,<sup>15,16</sup> transvaginal ultrasounds alone were shown to be an ineffective method for detecting early endometrial cancers. A large meta-analysis of sporadic endometrial cancers by Dijkhuizen et al<sup>17</sup>



**Figure 1.** Differences in pain perception for combined versus separate endometrial biopsy (EMB) and colonoscopy procedures.

advocated Pipelle EMB as an equally effective, if not superior, method compared with transvaginal ultrasound for detecting endometrial cancer in both pre- and postmenopausal women. Furthermore, in a study by Renkonen-Sinisalo et al,<sup>18</sup> results of surveillance ultrasound and intrauterine sampling either biannually or with a 3-year interval after age 30 to 35 were analyzed. There were a total of 14 endometrial cancers detected, of which 11 were asymptomatic endometrial cancers identified solely on screening. Of these 11 cases, nine were diagnosed by EMB. For the two remaining cases, there was no data from one and in the other, EMB demonstrated atrophy but was inconsistent with ultrasound findings. There were an additional 14 premalignant cases ascertained on EMB screening. Overall, 28 patients with either a preinvasive lesion or endometrial cancer were detected primarily by EMB with only 2 cases detected by ultrasound alone. Thus, the authors suggested that for Lynch mutation carriers, EMB is an essential component of endometrial surveillance and is more effective than transvaginal ultrasound alone.

Women who underwent the combined procedure strongly endorsed the benefits of sedation, primarily for the EMB portion, for which sedation resulted in less pain. They also cited greater convenience and having expert physicians in attendance as rationale for having the combined procedure. In our study, women received standard anesthesia for their colonoscopy and did not require any additional medication for the subsequent EMB segment. Most important, patients reported that they would be more likely to adhere to current recommendations of annual screening if presented with a combined screening option.

The feasibility of the proposed combined screening requires motivated providers to synchronize busy schedules and staff to assist with the provision of resources. We found that scheduling the EMB as the second procedure in the screening sequence was preferable because adequate anesthesia had already been achieved and no further medication was needed for the additional procedure. The clinical coordinator was responsible for ensuring the availability of all necessary equipment to perform the EMB in the colonoscopy suite (Appendix 1, online only). The staff at the colonoscopy facility assisted with scheduling and ensured that a stretcher with lithotomy stirrups was available for the combined screening patients. The addition of an EMB to the colonoscopy added only a median of 5 extra min-

utes to the total procedure time. In the real-world situation in which a clinical coordinator is not available, a collaborative effort by both physicians and their staff is necessary for the combined procedure to function. More specifically, commitment on the part of the endoscopy service staff leadership is necessary to implementing a standard process. Gynecologic staff is needed to provide detailed instructions about equipment (Appendix 1). Further, the arrangement for a stretcher with lithotomy stirrups in the endoscopy suite should be coordinated among the endoscopy suite staff and the gastroenterologist. When possible, the endoscopy suite staff should be aware of the appropriate billing codes for the EMB procedures and have the paperwork ready for the gynecologist. We found that scheduling the EMB procedure as the second procedure facilitated scheduling coordination of the two physicians.

One limitation of this study is that the pain perception measures from previous EMB and colonoscopy experiences were based on retrospective recall. However, the time interval between the previous EMB and the current procedure was relatively short. In addition, the study population was composed of highly motivated, self-selected individuals who frequently sought out new treatment opportunities and thus may not be representative of patients with Lynch syndrome. Approximately half of the women (21 of 42) traveled more than 75 miles. Only one patient was unable to complete the study because her insurance did not cover the colonoscopy at an out-of-network institution. For patients who were able to have a colonoscopy at our institution, there was no difficulty in reimbursement for the EMB. However, because many of our patients were from another state, several experienced some difficulty obtaining coverage for their colonoscopy at our institution. We have not had an issue with insurance reimbursements for two providers from different specialties using the same ICD 9 codes.

In conclusion, combined colorectal and endometrial cancer screening is a (to our knowledge) novel, patient-centered approach for delivering critical risk management services to a population that has a high probability for developing cancer. In this study, we demonstrate that combined screening for women with Lynch syndrome is feasible, acceptable, and provides women with a significant decrease in pain during the EMB. In addition, patients cited more convenience, less time commitment, and decreased anxiety when the procedures were combined. These findings underscore the importance of evaluating

patient-centered approaches for cancer screening and surveillance, not only in Lynch syndrome carriers, but also in persons with other hereditary cancer syndromes. These patients require more frequent testing compared with the general population, and methods to encourage greater compliance may ultimately translate to reduced morbidity and mortality from syndrome-related cancers. The ability of other institutions to implement this combined screening modality will be important in determining its more widespread utility.

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The authors indicated no potential conflicts of interest.

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