Lynch Syndrome: The GYN Oncologist's Perspective

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THE UNIVERSITY OF TEXAS
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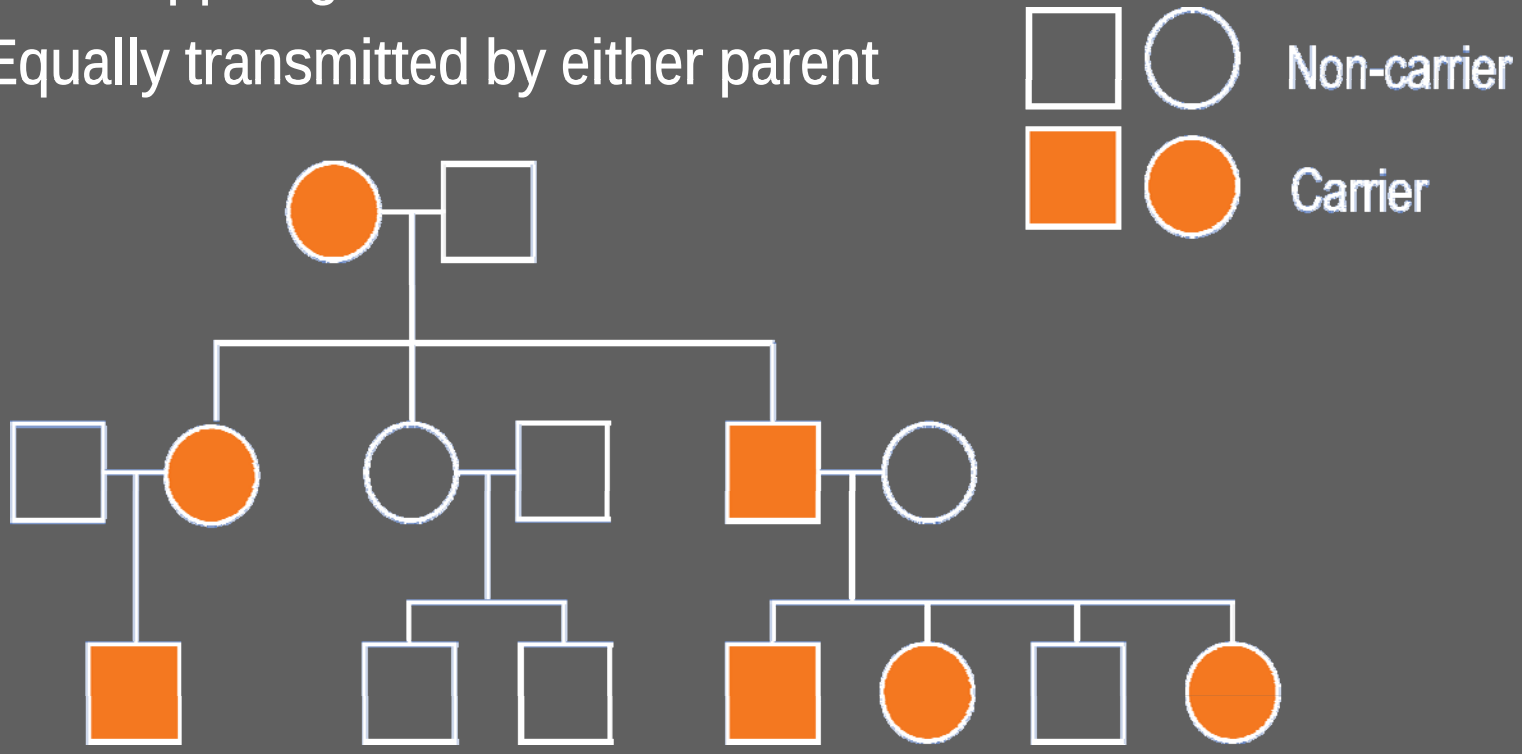
Making Cancer History®

Autosomal Dominant Inheritance

- Each child has 50% chance of inheriting the mutation
- No “skipped generations”
- Equally transmitted by either parent



Hereditary Cancer Syndromes

- Characterized by
  - Generally younger age of onset
  - More than one cancer in one patient
  - Multiple individuals in a family with cancer

Hereditary Cancer Syndromes with Endometrial Cancer

- Hereditary Non-polyposis Colorectal Cancer Syndrome (HNPCC), or Lynch Syndrome
  - Characterized by increased numbers of colon and endometrial cancers in a family

  Germline mutation in mismatch repair gene (MLH1/MSH2/MSH6/PMS2)
- Cowden's Syndrome
  - Characterized by intestinal hamartomas, breast cancer and endometrial cancers

  Germline mutation in PTEN

Overview

- What is Lynch syndrome?
- What can we learn from Lynch syndrome about prevention
- Remaining challenges to consider

Historical Perspective

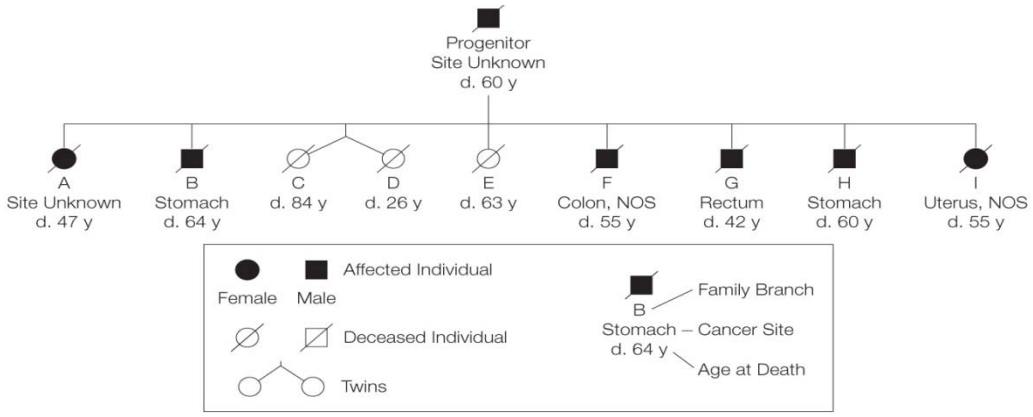
Aldred S. Warthin, MD, PhD

Henry T. Lynch, MD

Lynch I: Autosomal dominant colon cancer only families

• Lynch II: Autosomal dominant colon cancer with endometrial, ovary, small bowel, stomach cancers

Figure 2. Pedigree of Family G Generations I and II



NOS indicates not otherwise specified.

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The Human Mutator Gene Homolog *MSH2* and Its Association with Hereditary Nonpolyposis Colon Cancer

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Summary

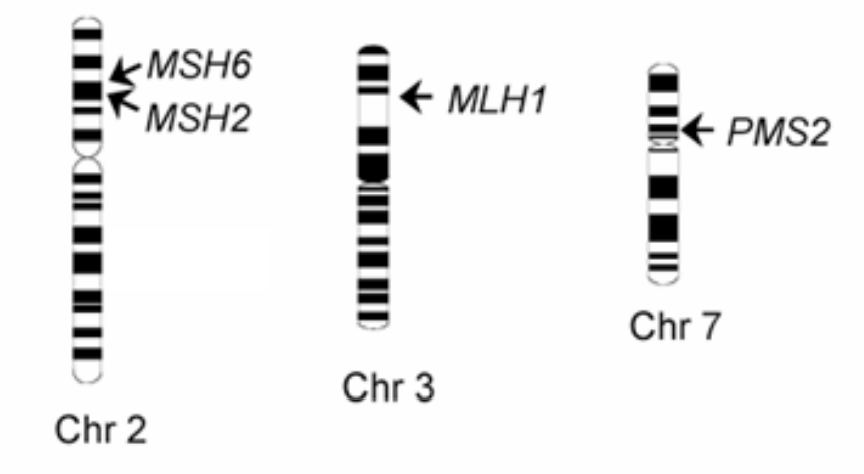
We have identified a human homolog of the bacterial MutS and S. cerevisiae MSH proteins, called hMSH2. Expression of *hMSH2* in E. coli causes a dominant mutator phenotype, suggesting that hMSH2, like other divergent MutS homologs, interferes with the normal bacterial mismatch repair pathway. *hMSH2* maps to human chromosome 2p22-21 near a locus implicated in hereditary nonpolyposis colon cancer (HNPCC). A T to C transition mutation has been detected in the −6 position of a splice acceptor site in sporadic colon tumors and in affected individuals of two small HNPCC kindreds. These data and reports indicating that S. cerevisiae *msh2* mutations cause an instability of dinucleotide repeats like those associated with HNPCC suggest that *hMSH2* is the HNPCC gene.

can give rise to mismatched bases (Friedberg, 1985). For example, the deamination of 5-methylcytosine creates a thymine and, therefore, a G·T mispair (Duncan and Miller, 1980). Second, misincorporation of nucleotides during DNA replication can yield mismatched base pairs and nucleotide insertions and deletions (Modrich, 1991). Finally, genetic recombination produces regions of heteroduplex DNA that may contain mismatched nucleotides when such heteroduplexes result from the pairing of two different parental DNA sequences (Holliday, 1964). Mismatched nucleotides produced by each of these mechanisms are known to be repaired by specific enzyme systems (Friedberg, 1990; Modrich, 1991).

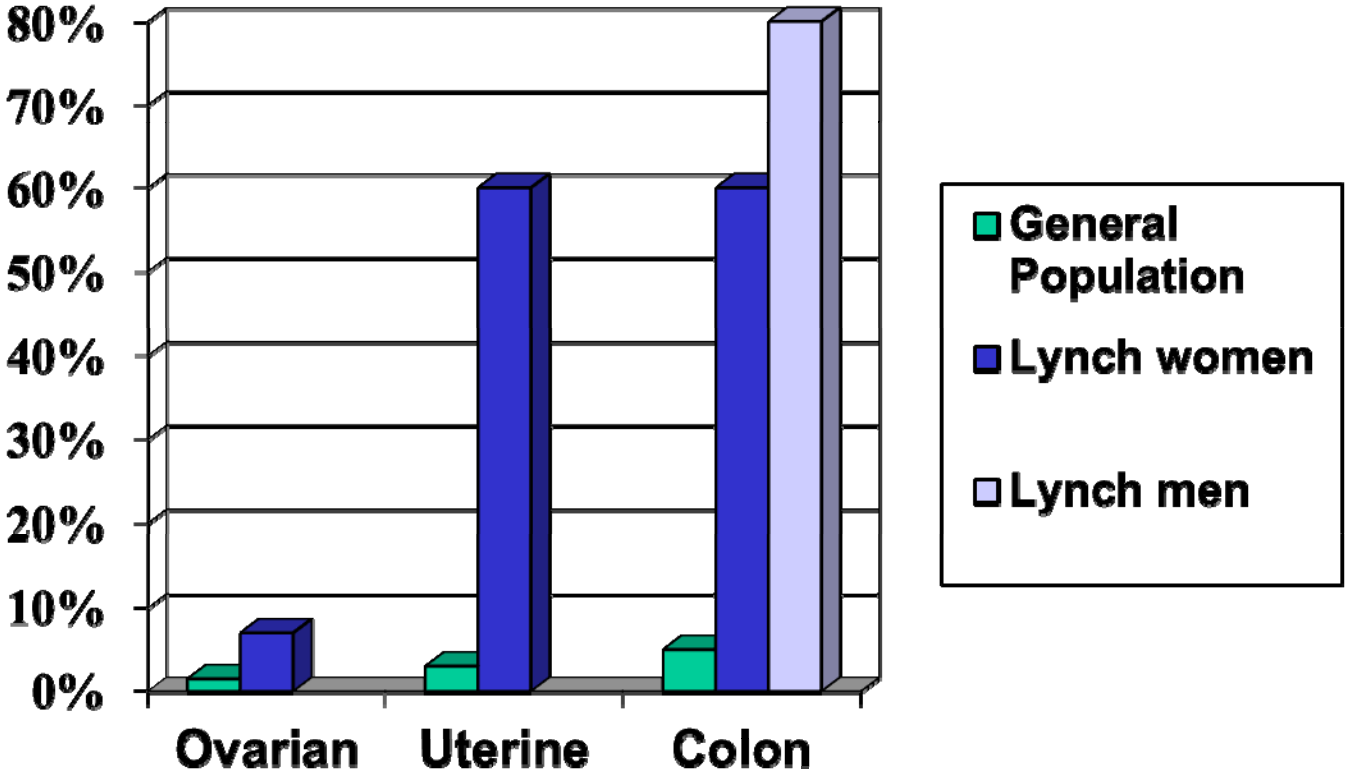
The best-defined mismatch repair pathway is the Escherichia coli MutHLS pathway that promotes a long patch (approximately 2 kb) excision repair reaction that is dependent on the *mutH*, *mutL*, *mutS*, and *mutU* (*uvrD*) gene products (Modrich, 1989, 1991). The MutHLS pathway appears to be the most active mismatch repair pathway in E. coli and is known both to increase the fidelity of DNA replication (Rydberg, 1978) and to act on recombination intermediates containing mispaired bases (Wagner and Meselson, 1976; Fishel et al., 1986). This system has been reconstituted in vitro and requires the MutH, MutL, MutS, and UvrD (helicase II) proteins along with DNA polymerase III holoenzyme, DNA ligase, single-stranded DNA-binding protein, and one of the single-stranded DNA exonucleases (ExoI, ExoVII, or RecJ) (Modrich, 1989, 1991; Lahue et al., 1989; Cooper et al., 1993). MutS protein binds to the mismatched nucleotides in DNA (Su and Modrich, 1986). MutH protein interacts with GATC sites in DNA that are hemimethylated on the adenine and is responsible for incision on the unmethylated strand (Welsh et al., 1987). Specific incision of the unmethylated strand results in increased fidelity of replication because excision repair is targeted to the newly replicated unmethylated DNA strand. MutL facilitates the interaction between MutS bound to the mismatch and MutH bound to the hemimethylated Dam site, resulting in the activation of MutH (Grilley et al., 1989). UvrD is the helicase that appears to act in conjunction with one of the single-stranded DNA-specific exonucleases to excise the unmethylated strand, leaving a gap that is repaired by the action of DNA polymerase

Genetics of Lynch Syndrome

- Genes associated with Lynch syndrome belong to the DNA mismatch repair family
  - MLH1, MSH2, MSH6, PMS2



Lifetime risk of cancer in Lynch syndrome



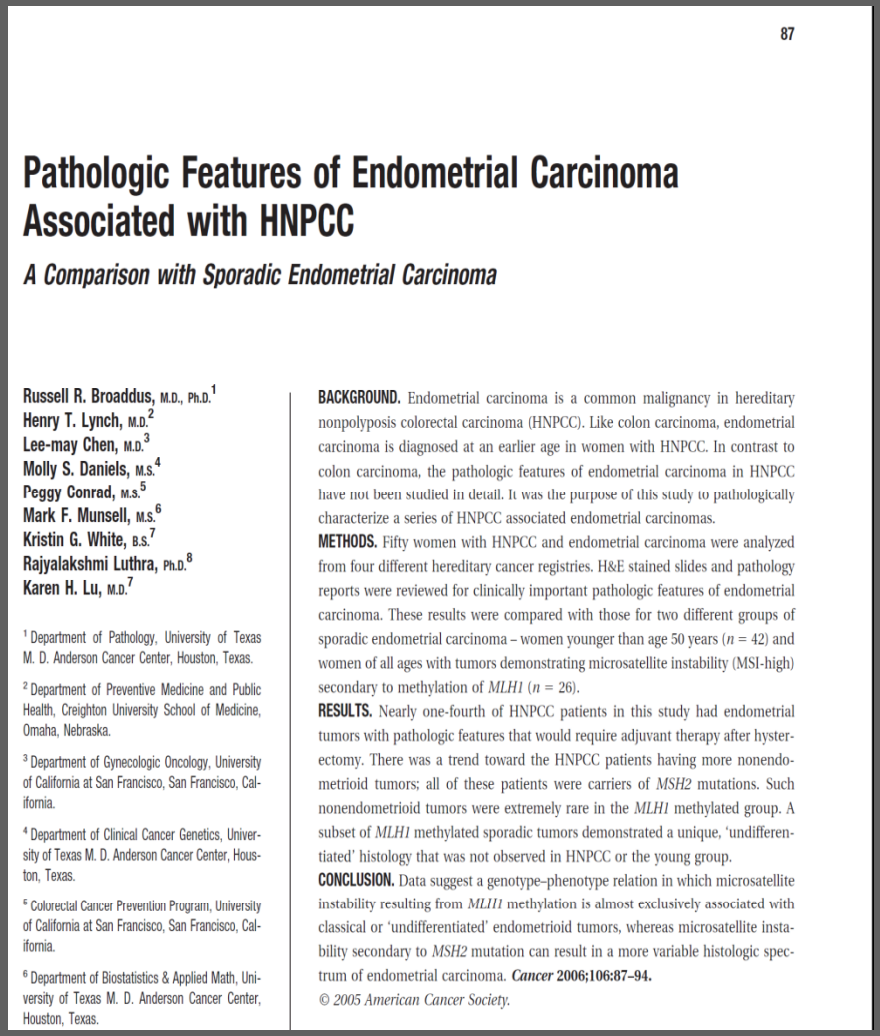
Risk of Endometrial and Colorectal Cancer in Women with Lynch syndrome

Author	Study Population	Mutation	Lifetime Risk Endometrial Cancer	Mean Age @ Dx of Endo Ca (Range)	Lifetime Risk Colorectal Cancer
Aarnio (1999)	Finland	MLH1, MSH2	60%		54%
Barrow (2009)	UK	MLH1, MSH2,MSH 6	47%		46%
Stoffel (2009)	US	MLH1, MSH2 MSH6	39%	47	43%
Baglietto (2010)	Multiple countries	MSH6 only	26% to age 70 44% to age 80	53	10% to age 70 20% to age 80

How common is Lynch syndrome

- **General population: 1/500- 1/1000**
- **Endometrial cancer: 2-3%**

Pathology of Lynch syndrome associated endometrial cancer *(Broaddus et al, Cancer 2006)*



Pathologic Features of Endometrial Carcinoma Associated with HNPCC

A Comparison with Sporadic Endometrial Carcinoma

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BACKGROUND. Endometrial carcinoma is a common malignancy in hereditary nonpolyposis colorectal carcinoma (HNPCC). Like colon carcinoma, endometrial carcinoma is diagnosed at an earlier age in women with HNPCC. In contrast to colon carcinoma, the pathologic features of endometrial carcinoma in HNPCC have not been studied in detail. It was the purpose of this study to pathologically characterize a series of HNPCC associated endometrial carcinomas.

METHODS. Fifty women with HNPCC and endometrial carcinoma were analyzed from four different hereditary cancer registries. H&E stained slides and pathology reports were reviewed for clinically important pathologic features of endometrial carcinoma. These results were compared with those for two different groups of sporadic endometrial carcinoma – women younger than age 50 years ($n = 42$) and women of all ages with tumors demonstrating microsatellite instability (MSI-high) secondary to methylation of *MLH1* ($n = 26$).

RESULTS. Nearly one-fourth of HNPCC patients in this study had endometrial tumors with pathologic features that would require adjuvant therapy after hysterectomy. There was a trend toward the HNPCC patients having more nonendometrioid tumors; all of these patients were carriers of *MSH2* mutations. Such nonendometrioid tumors were extremely rare in the *MLH1* methylated group. A subset of *MLH1* methylated sporadic tumors demonstrated a unique, 'undifferentiated' histology that was not observed in HNPCC or the young group.

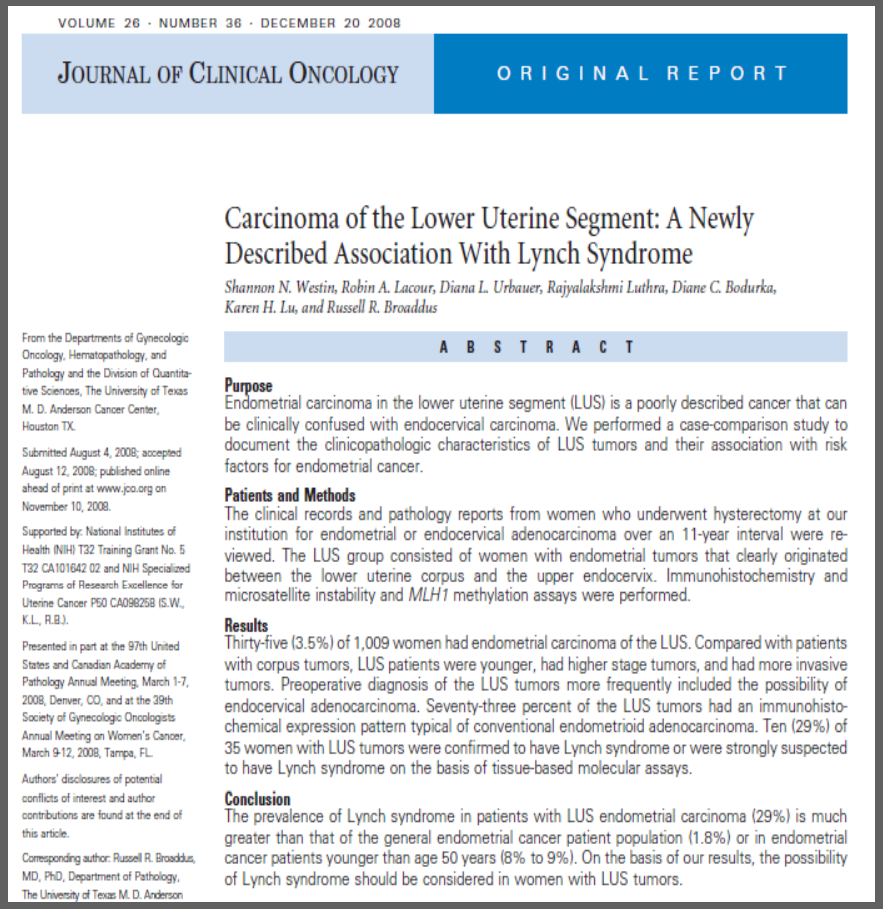
CONCLUSION. Data suggest a genotype–phenotype relation in which microsatellite instability resulting from *MLH1* methylation is almost exclusively associated with classical or 'undifferentiated' endometrioid tumors, whereas microsatellite instability secondary to *MSH2* mutation can result in a more variable histologic spectrum of endometrial carcinoma. ***Cancer* 2006;106:87–94.**

- Compared Lynch endometrial cancers with sporadic endometrial cancers.
- Includes full spectrum of histologies, mostly endometrioid, but also papillary serous and clear cell (MSH2)

- *In contrast to BRCA-associated ovarian cancers, which are almost uniformly high grade serous*

Pathology of Lynch syndrome associated endometrial cancer

(Westin et al, J Clin Onc, 2008)



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ORIGINAL REPORT

Carcinoma of the Lower Uterine Segment: A Newly Described Association With Lynch Syndrome

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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A B S T R A C T

Purpose
Endometrial carcinoma in the lower uterine segment (LUS) is a poorly described cancer that can be clinically confused with endocervical carcinoma. We performed a case-comparison study to document the clinicopathologic characteristics of LUS tumors and their association with risk factors for endometrial cancer.

Patients and Methods
The clinical records and pathology reports from women who underwent hysterectomy at our institution for endometrial or endocervical adenocarcinoma over an 11-year interval were reviewed. The LUS group consisted of women with endometrial tumors that clearly originated between the lower uterine corpus and the upper endocervix. Immunohistochemistry and microsatellite instability and *MLH1* methylation assays were performed.

Results
Thirty-five (3.5%) of 1,009 women had endometrial carcinoma of the LUS. Compared with patients with corpus tumors, LUS patients were younger, had higher stage tumors, and had more invasive tumors. Preoperative diagnosis of the LUS tumors more frequently included the possibility of endocervical adenocarcinoma. Seventy-three percent of the LUS tumors had an immunohistochemical expression pattern typical of conventional endometrioid adenocarcinoma. Ten (29%) of 35 women with LUS tumors were confirmed to have Lynch syndrome or were strongly suspected to have Lynch syndrome on the basis of tissue-based molecular assays.

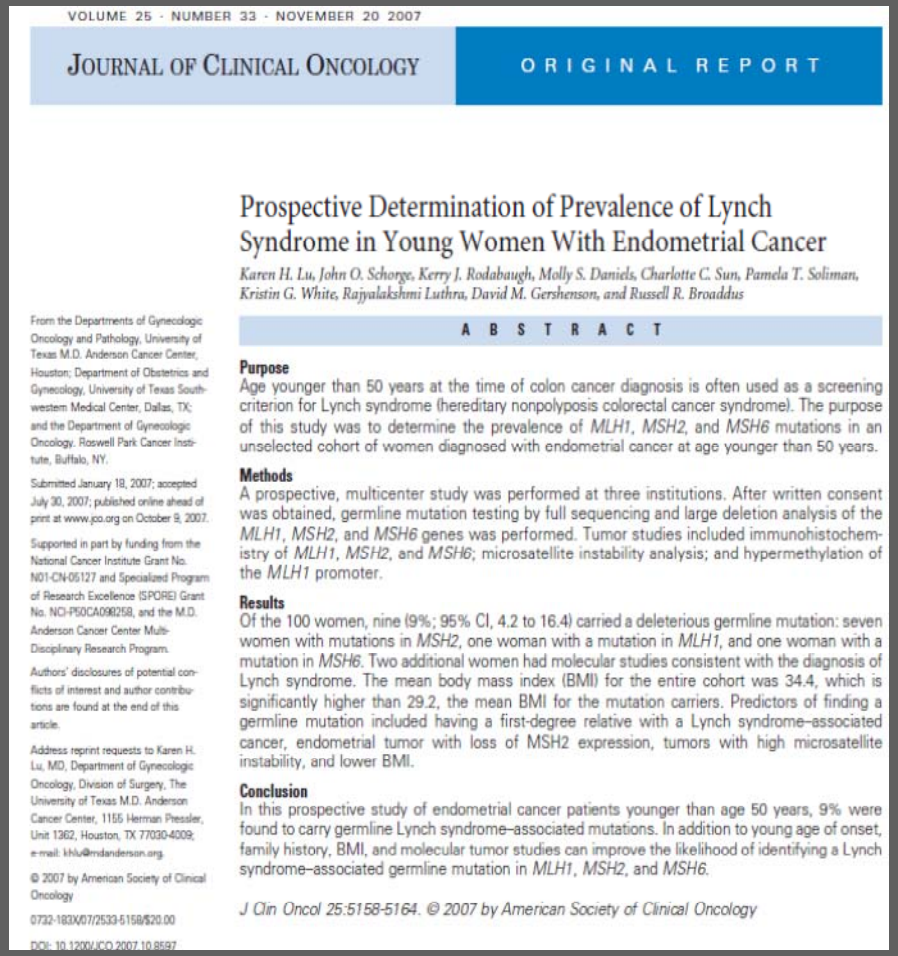
Conclusion
The prevalence of Lynch syndrome in patients with LUS endometrial carcinoma (29%) is much greater than that of the general endometrial cancer patient population (1.8%) or in endometrial cancer patients younger than age 50 years (8% to 9%). On the basis of our results, the possibility of Lynch syndrome should be considered in women with LUS tumors.

- Lower uterine segment endometrial cancers, which can often be mistaken for cervix adenocarcinomas, occur more often in Lynch syndrome
- 10 of 35 (29%) had Lynch

- *Similar to increased incidence of "right-sided colon cancer" in Lynch pts*

Prevalence of Lynch in endometrial cancer patients under age 50

(Lu et al, J Clin Onc, 2007)



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ORIGINAL REPORT

Prospective Determination of Prevalence of Lynch Syndrome in Young Women With Endometrial Cancer

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ABSTRACT

Purpose
Age younger than 50 years at the time of colon cancer diagnosis is often used as a screening criterion for Lynch syndrome (hereditary nonpolyposis colorectal cancer syndrome). The purpose of this study was to determine the prevalence of *MLH1*, *MSH2*, and *MSH6* mutations in an unselected cohort of women diagnosed with endometrial cancer at age younger than 50 years.

Methods
A prospective, multicenter study was performed at three institutions. After written consent was obtained, germline mutation testing by full sequencing and large deletion analysis of the *MLH1*, *MSH2*, and *MSH6* genes was performed. Tumor studies included immunohistochemistry of *MLH1*, *MSH2*, and *MSH6*; microsatellite instability analysis; and hypermethylation of the *MLH1* promoter.

Results
Of the 100 women, nine (9%; 95% CI, 4.2 to 16.4) carried a deleterious germline mutation: seven women with mutations in *MSH2*, one woman with a mutation in *MLH1*, and one woman with a mutation in *MSH6*. Two additional women had molecular studies consistent with the diagnosis of Lynch syndrome. The mean body mass index (BMI) for the entire cohort was 34.4, which is significantly higher than 29.2, the mean BMI for the mutation carriers. Predictors of finding a germline mutation included having a first-degree relative with a Lynch syndrome–associated cancer, endometrial tumor with loss of MSH2 expression, tumors with high microsatellite instability, and lower BMI.

Conclusion
In this prospective study of endometrial cancer patients younger than age 50 years, 9% were found to carry germline Lynch syndrome–associated mutations. In addition to young age of onset, family history, BMI, and molecular tumor studies can improve the likelihood of identifying a Lynch syndrome–associated germline mutation in *MLH1*, *MSH2*, and *MSH6*.

J Clin Oncol 25:5158-5164. © 2007 by American Society of Clinical Oncology

- 9/100 (9%) had Lynch syndrome mutations
  (7 MSH2, 1 MLH1, 1 MSH6)
- 7/9 had 1st degree relative with Lynch syndrome
- BMI for patients with Lynch: 29.2
  BMI for whole cohort: 34.4
  (p=0.01)
- Similar to 9% rate (5/58) in study by Berends et al

Overview

- What is Lynch syndrome?
- What can we learn from Lynch syndrome about prevention
- Remaining challenges to consider

Chemoprevention: Possible agents

Oral Contraceptive:

- The Cancer and Steroid Hormone Study (CASH) demonstrated that use of oral contraceptives can reduce the risk of endometrial cancer by 50%.
- Endometrial proliferation is inhibited after the first few cycles of OCP use.

Progesterone:

- Progesterone is used clinically as a treatment for endometrial hyperplasia.
- Hyperplasia with and without atypia can be converted to normal endometrium by treatment with progesterone.
- Mirena IUD

Study Design (N01-CN-05127)

Women, age 25-50, with documented Lynch gene mutation (n=50)

↓

Baseline: transvaginal ultrasound and endometrial biopsy

↓

Randomize to OCP or DepoMPA

↓

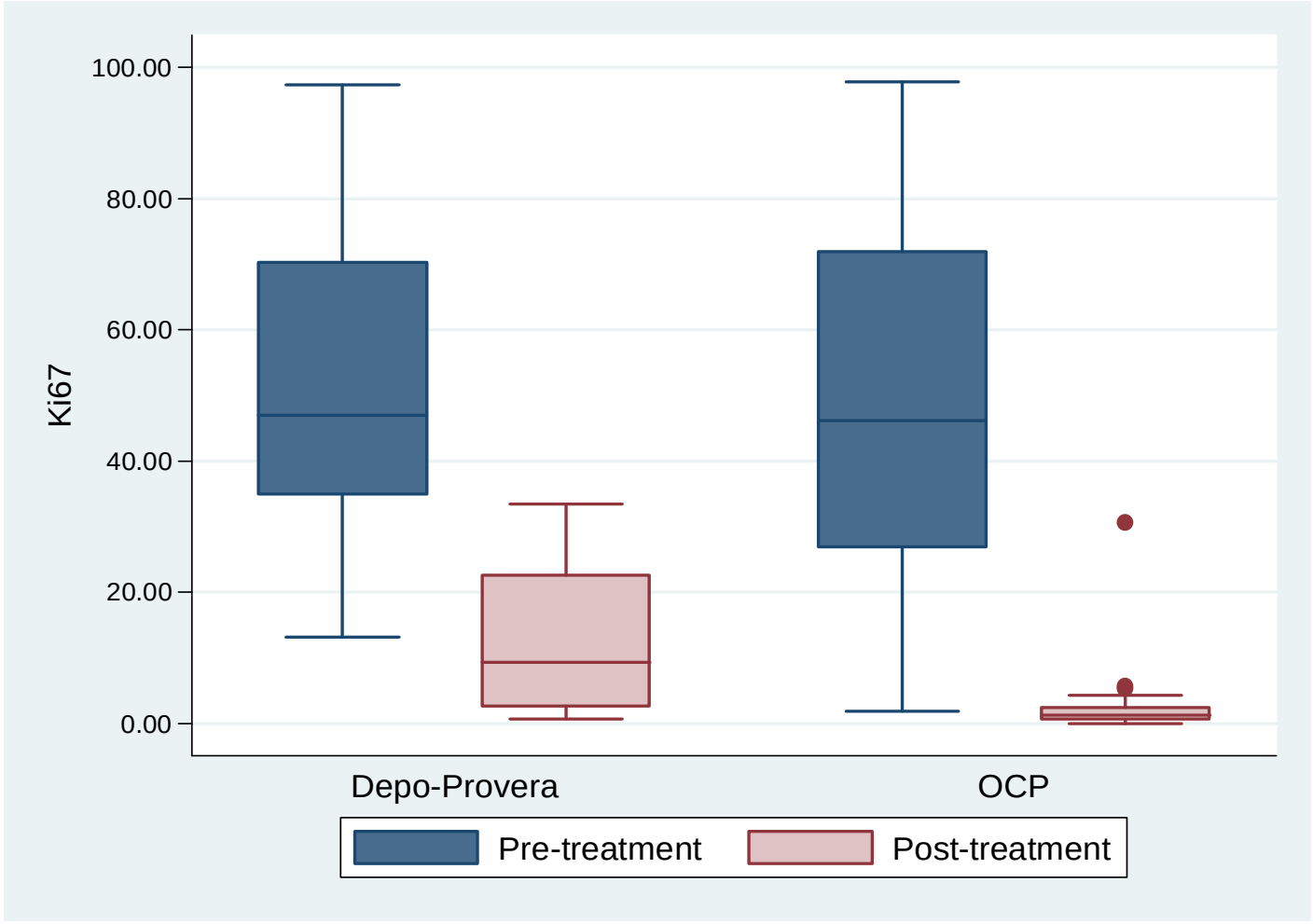
3 months: transvaginal ultrasound and endometrial biopsy

Number of women screened for eligibility:

Cumulative numbers

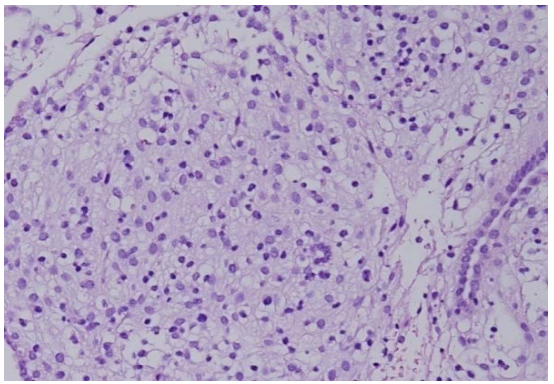
Site	2002	2003	2004	2005	2006	2007
MDACC	**50**	**100**	**150**	**238**	**313**	**333**
Creighton	**47**	**98**	**173**	**182**	**212**	**220**
UCSF	**37**	**50**	**80**	**125**	**145**	**155**
Cumulative Total	**134**	**248**	**403**	**545**	**670**	**708**

Results: Primary Endpoint Ki-67

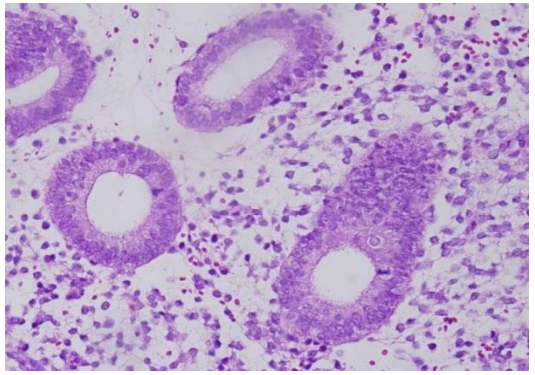


Results: Histology

- Good responses
  - 22/23 in OCP arm *
  - 20/23 in depoMPA arm



- Poor responses
  - 0/23 in OCP arm
  - 3/23 in depo MPA arm



* Pathologic finding in 1/23 in OCP arm: small foci of complex hyperplasia without atypia in background of atrophy

Results: Pre- and post-tx TVS

Endometrial thickness (mm)	depoMPA	OCP	p-value
Baseline			
Mean	5.5	6.5	0.19
Range	2.6-10.1	2.0-19	
Follow-up			
Mean	4.5	4.5	0.93
Range	1.0-9.3	2.0-10.0	
Overall change			
Mean	0.9	1.7	0.22
Range	-5.0 to 6.0	-1.0 to 5.0	

Results: Point estimate of baseline endometrial abnormalities in asymptomatic Lynch+ women

- **2/51 women: 3.9% (95% CI: 0.5% to 13.5%) of *asymptomatic* pre-menopausal women with Lynch syndrome had complex atypical hyperplasia (CAH)**

- **While 2 cases were both CAH on EMB, subsequent hysterectomy showed endometrioid adenoCA grade 1, Stage Ia for both**

Conclusions: Clinical findings

- **Confirmation of short-term ability of OCP and DepoProvera in women with Lynch syndrome**
  - **decrease proliferation (Ki-67)**
  - **induce atrophy of glands**

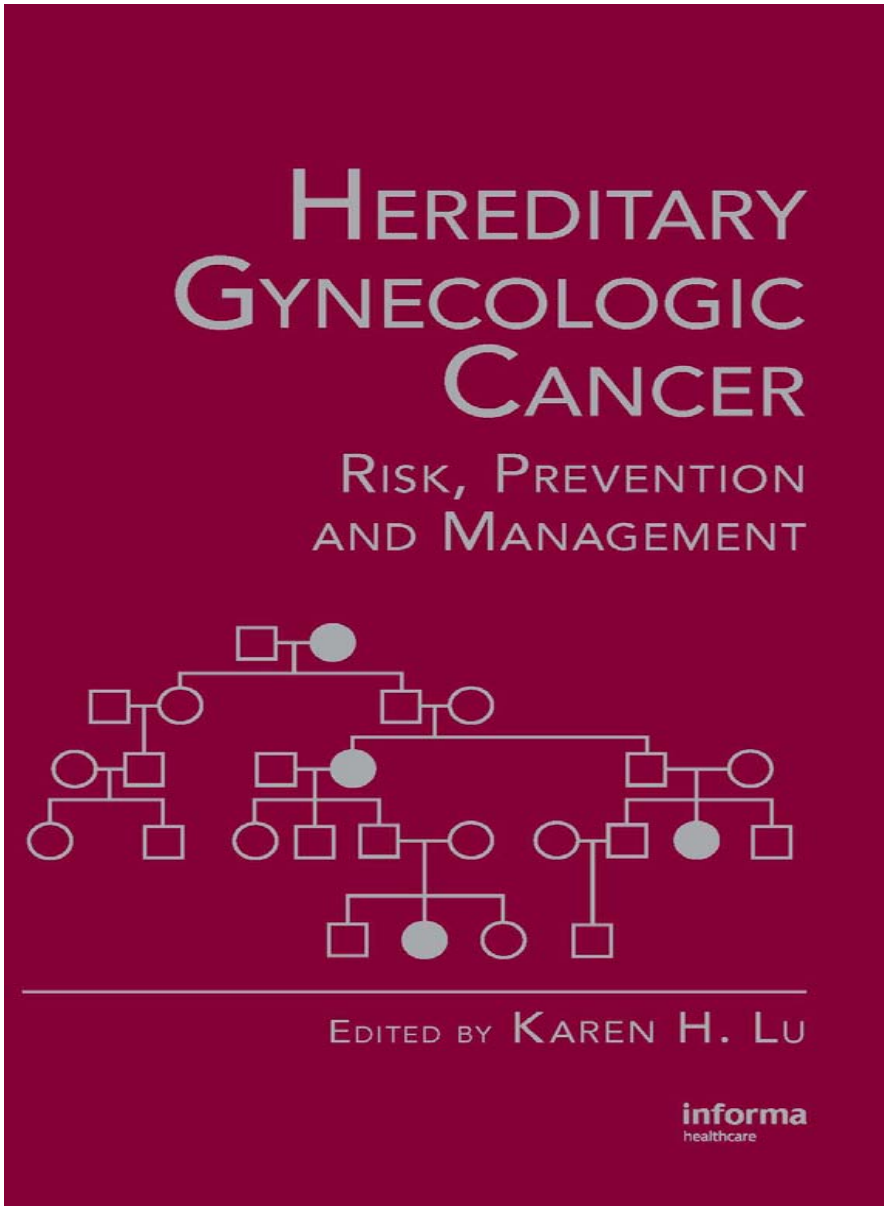
- **There is preliminary evidence to support efficacy of OCP or progestin as a chemoprevention strategy for women with Lynch syndrome**

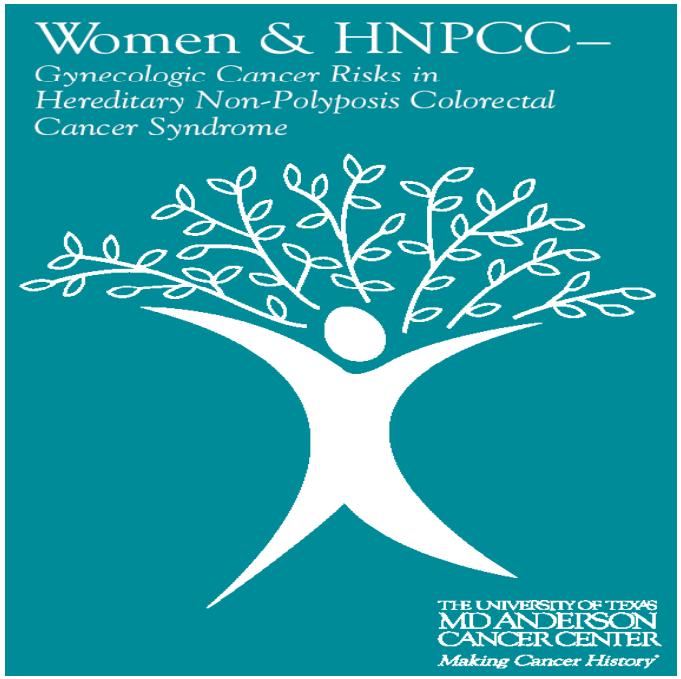
Conclusions: Clinical findings

- **TVS not sensitive at detecting complex hyperplasia or early endometrial cancer in asymptomatic women with Lynch syndrome**
- **Point estimate of having endometrial hyperplasia or cancer in *asymptomatic* women with Lynch syndrome is 4%**
- **Follow-up: European study of Mirena IUD did not complete accrual**

Where do we go from here?

- **Prevention: Do OCPs prevent Type 1 and Type 2 endometrial cancers**
  - **In Lynch syndrome?**
  - **In sporadic endometrial cancer?**
- **Prevention: Opportunity for "local" prevention**
- **Prevention: If OCPs are such a good preventive agent for endometrial cancer (and ovarian cancer), why don't women know about it?**





Uterine Cancer
research program

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