

בהשתתפות:

החוג למחלות ממאירות, איגוד גסטרו
האיגוד הישראלי לגנטיקה רפואית
החברה הישראלית לכירורגיה קולרקטלי
החברה הישראלית לגניקולוגיה אונקולוגית (ISGO)
החוג לאונקולוגיה של מערכת העיכול
האיגוד לפתולוגיה בישראל

המעקב הגינקולוגי בנשائיות תסמונת לינץ: אחיד או מותאם אישית?

עדכונים בהמלצות החדשות בתסמונת לינץ

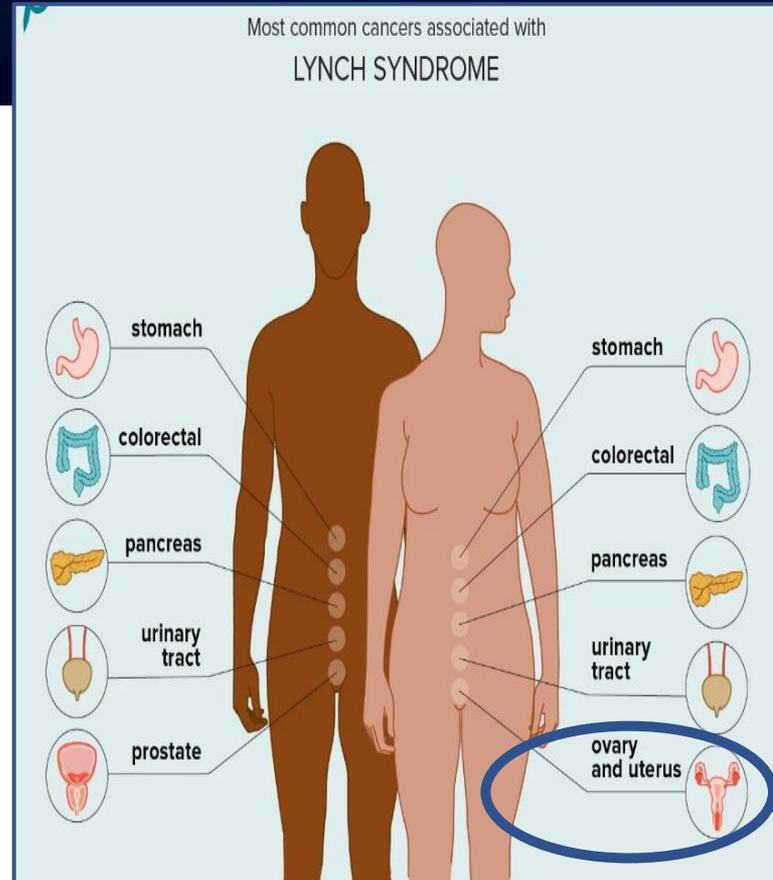
פרופ' צבי ואקנין

מנהל היחידה לגינקולוגיה-אונקולוגית, מרכז רפואי ע"ש יצחק שמיר ("אסף הרופא"), צריפין
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הפקולטה למדעי הרפואה והבריאות ע"ש גריי, אוניברסיטת ת"א

Lynch Syndrome Epidemiology In women

- ✓ One of the most common hereditary cancer syndrome **~1:250**
- ✓ Approximately 3% of newly diagnosed colorectal cancers, **~3% of endometrial cancers (EC)**.
- ✓ Characterized by **DNA mismatch repair deficiency (dMMR)**.

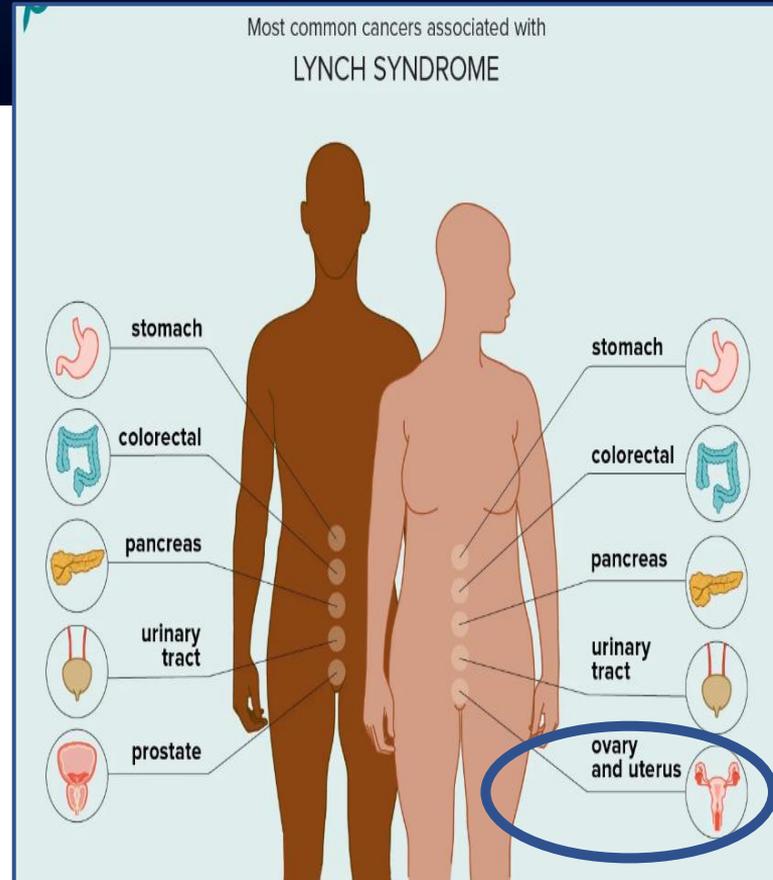
Moreira L, et al. EPICOLON Consortium. Identification of Lynch syndrome among patients with colorectal cancer. JAMA. 2012 Oct 17;308(15):1555-65.



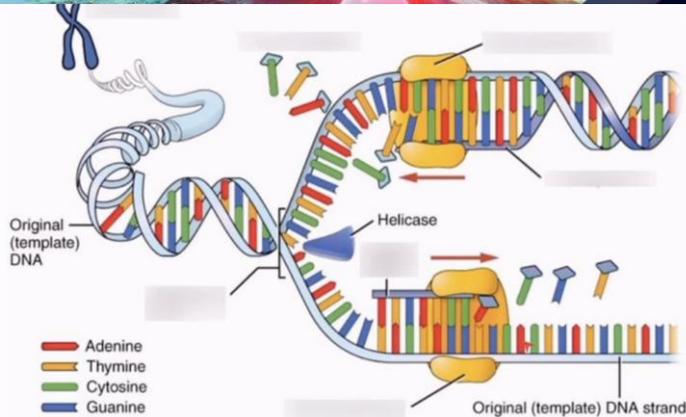
Lynch Syndrome Epidemiology In women

- ✓ About **10–30% of ECs** exhibit **dMMR** of these **3% is associated with LS.**
- ✓ MMR status is assessed by 4 MMR proteins that function as dimers:
 - **MLH1 pairing PMS2.**
 - **MSH2 pairing MSH6.**
- ✓ **MLH1 & MSH6** – High penetrance.
- ✓ **PMS2 & MSH2** – Attenuated phenotype

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What are the MMR Genes ? MLH1, MSH2, MSH6, and PMS2.



An incorrect base insertion constitutes a *mismatch*

Mismatch Base Pair (Wrong Nucleotide Match)

Or

Number of bases added to a repetitive sequence

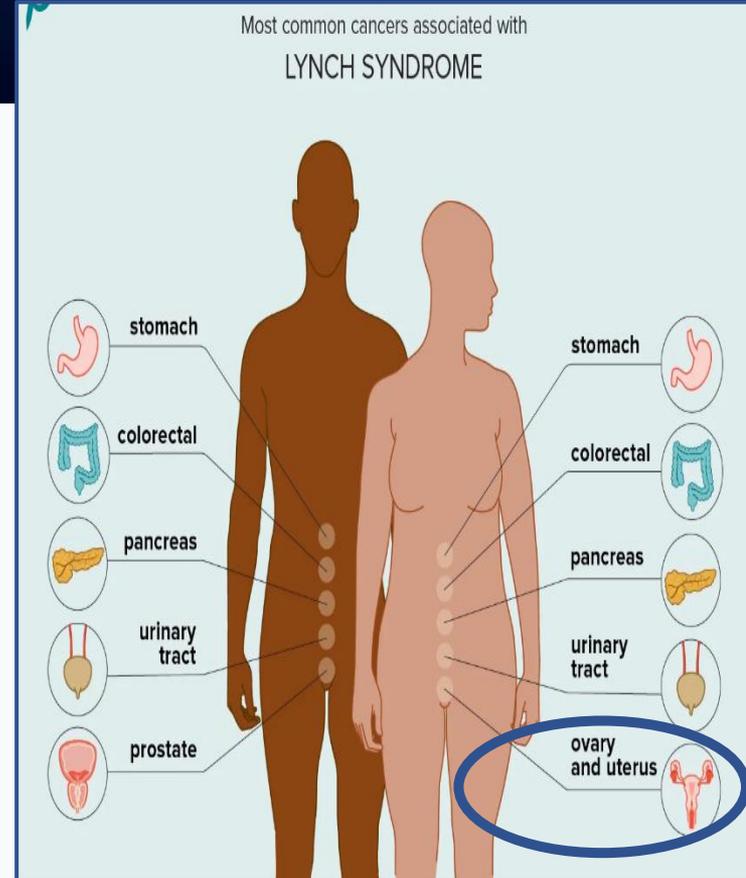


Mismatch Repair Protein Complex
Detects and Corrects Mismatches During DNA Replication

Adapted from Naveena Singh, ESGO E-Academy

Lynch Syn. in Women: Why Gynecology Matters?

- ✓ Endometrial cancer (EC) = most common LS cancer in women; **often 1st malignancy.**
- ✓ Ovarian cancer (OC) = **2nd gynecologic threat** - earlier than sporadic.
- ✓ EC typically **presents 10–20 years earlier** than general population.



Lynch Syndrome Epidemiology In women

Lifetime cancer risk related to Lynch genotypes

Cancer site	MLH1 24%		MSH2* 57%		MSH6 17%		PMS2 2%	
	Female	Male	Female	Male	Female	Male	Female	Male
Any Lynch cancer	80.2%	68.5%	83.4%	80.5%	55.2%	28.5%	40.1%	57.3%
Colorectal	48.3%	56.0%	42.6%	55.8%	17.3%	16.4%	8.5%	32.8%
Endometrial	37.2%	–	44.1%	–	45.7%	–	21.2%	–
Gastric	4.3%	8.9%	4.0%	8.3%	0.7%	0.7%	¶	2.7%
Ovarian	8.0%	–	13.4%	–	6.3%	–	2.5%	–
Ureter/kidney	2.9%	4.5%	19.5%	15.8%	3.9%	3.3%	¶	¶
Bladder	4.8%	5.6%	9.4%	13.1%	2.6%	9.0%	¶	¶
Prostate	–	15.6%	–	24.0%	–	7.0%	–	3.3%
Breast ^Δ	12.4%	–	15.5%	–	15.1%	–	12.4%	–
Brain	1.4%	0.6%	2.2%	6.6%	1.2%	0.8%	¶	¶
Small bowel	4.5%	8.3%	3.7%	7.0%	0.6%	2.8%	2.1%	3.3%
Pancreas	3.7%	3.1%	3.5%	3.3%	2.2%	1.2%	¶	¶
Bile duct/gallbladder	1.5%	4.0%	2.4%	4.6%	¶	¶	¶	¶

~3%
 ~1.3%

This table includes cumulative incidences of cancer in respective organs for males and females at 75 years of age.

* Cancer risks in individuals with a pathogenic *EPCAM* variant are similar to those with a pathogenic *MSH2* variant.

¶ Data are insufficient to make a determination.

Δ There is ongoing debate as to whether breast cancer is a Lynch syndrome-associated cancer.

Lynch Syndrome Epidemiology In women

Cumulative cancer incidences stratified by age and path-MMR variant

		Cumulative incidence at age (%[95% CI])			
	Age	Path-MLH1	Path-MSH2	Path-MSH6	Path-PMS2
Endometrium	30	0 [0-2.6]	0 [0-3.3]	0 [0-22.6]	0 [0-41.4]
	40	1.9 [0.8-4.8]	2.3 [0.9-6.2]	2.3 [0.4-24.6]	0 [0-41.4]
	50	14.7 [11-19.5]	17.5 [12.8-23.7]	12.6 [6.3-33.1]	0 [0-41.4]
	60				9.3 [3.3-47.3]
	70				12.8 [5.2-49.5]
Ovaries	75				12.8 [5.2-49.5]
	30				0 [0-41.4]
	40				0 [0-41.4]
	50	3.8-9.8	6.9-15.7	0.4-24.6	0 [0-41.4]
	60	10.1 [6.8-15.1]	12.6 [8.5-18.4]	2.3 [0.4-24.6]	3.0 [0.5-43.3]
	70	11.0 [7.4-17.1]	17.4 [11.8-27.3]	10.8 [3.7-32.9]	3.0 [0.5-43.3]
	75	11.0 [7.4-19.7]	17.4 [11.8-31.2]	10.8 [3.7-38.6]	3.0 [0.5-43.3]

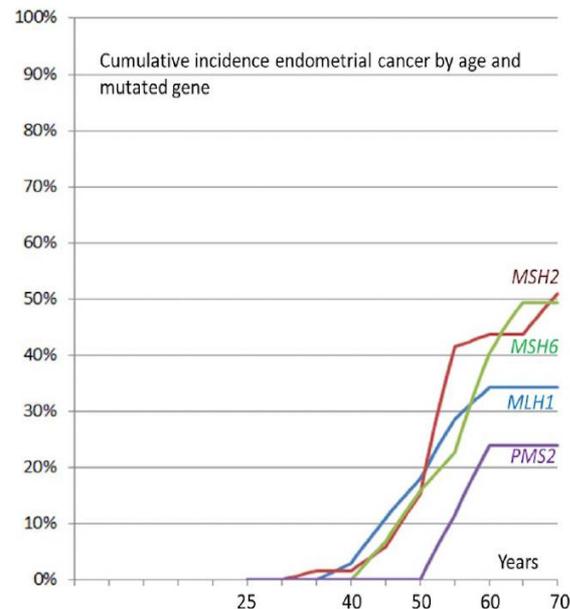
**שילוב של שכיחות גידול מסוים
 וגיל הופעה מוקדם
 דורש התאמה בהמלצות
 למעקב וניתוחים מניעתיים**

~3% age ~60

~1.3% age ~62

LS Gene Specific Gyn Cancer Risks Summary

- ✓ EC with LS - **MSH2 / MSH6** > **MLH1** > **PMS2** mutation
- ✓ OC with LS - **MSH2** > **MLH1** > **MSH6**
- ✓ **PMS2** has the **lowest risk for extra-digestive tumor**
- ✓ Estimated cumulative risks < 40 years did not exceed: 2.5% for EC nor 1% for OC irrespective of the gene.
- ✓ Median age of EC onset : **MSH2 (46 years)**, **MLH1 (51 years)**, **MSH6 (56 years)**.
- ✓ The risk of EC for **PMS2** - **not increased before 50 years**.
- ✓ A RRBSO prior to age 40 would prevent OC before age 50 in - **8% MSH2**, **4% of MLH1**, **0% of MSH6/PMS2**.
- ✓ A RRBSO **prevents death before 50 in - 1% of MLH1/MSH2**, and **0% of MSH6/PMS2** PVs.



Lynch Syn EC Surveillance - limited

TABLE 1 Recommendations for endometrial cancer surveillance in LS patients.

Committee	Recommendation
ACOG (16)	Annual endometrial biopsy or TVUS, starting at age 30–35.
NICE (20)	Focus on awareness of early gynecological cancer symptoms.
Mallorca Group (17)	Annual endometrial biopsy or TVUS starting at age 30–35.
NCCN (5)	Every 1-2 years endometrial biopsy, starting at age 30–35
MICG (22)	Emphasize symptom awareness Annual reviews from age 25.
ESGO/ESTRO/ESP (21)	Annual TVUS and endometrial biopsy MSH2 carriers: from age 30 MLH1 carriers: from age 35 MSH6 carriers: from age 40

Lynch Syn Gyn - RR surgeries

Guideline	Type of Risk-Reducing Surgery	Advised Age
ACOG 2005	Bilateral salpingo-oophorectomy (BSO)	After childbearing, typically age 35–40
NICE 2020	Hysterectomy and oophorectomy	After childbearing is complete
MICG 2019	Hysterectomy and BSO	No earlier than age 35–40, reviewed annually
Mallorca Group 2013	Hysterectomy and BSO	After childbearing, typically age 40–45
NCCN 2024	Hysterectomy and BSO; delayed BSO possible; salpingectomy as an option for premenopausal women not ready for oophorectomy	Hysterectomy at age 40, delayed BSO at age 50
ESGO/ESTRO/ESP 2021	Hysterectomy and BSO	After childbearing, preferably before age 40 *

Risk-Reducing Surgery Gene-Tailored Approach

MLH1/MSH2: Hysterectomy + Bilateral Salpingo-Oophorectomy (BSO)

Timing: Age 35–40 (after childbearing); ESGO recommends <40 years

Benefit: >95% EC risk elimination; substantial OC risk reduction

MSH6: Hysterectomy (± Delayed/Individualized BSO)

Timing: Hysterectomy age 40; BSO timing individualized (lower OC risk)

Alternative: Salpingectomy-first strategy (preserves ovarian function)

PMS2: De-Escalation (Individualize)

Strategy: Defer/omit prophylactic surgery; focus on surveillance if low family risk

Note: Growing consensus to reduce over-treatment in attenuated carriers

Surveillance Reassessment

Endometrial surveillance (TVUS/biopsy) is **optional**, **NOT proven superior to prophylactic surgery**. Best reserved for young/fertility-preserving, high-risk women unwilling to undergo early hysterectomy



Chemoprevention, Fertility Preservation & HRT

Chemoprevention (Pre-Surgical)

- **OCPs:** ~50% EC risk ↓ (mirroring sporadic data)
- **Progestin therapy:** Evidence emerging; alternative to OCP
- **Best for:** Fertility-preserving, younger carriers delaying surgery

Lifestyle Optimization

- Weight management (BMI <25)
- Physical activity ≥150 min/week
- Avoid unopposed estrogen

Hormone Replacement Therapy (HRT) After Prophylactic BSO / ERT post Hysterectomy + BSO

Recommended for premenopausal women: Estrogen ± progestin to manage vasomotor symptoms & preserve bone health. Shared decision-making on duration; careful surveillance for other LS cancers.

Fertility Preservation Options

For younger women: Chemoprevention + delayed surgery; egg/embryo banking/PGD? ; assisted reproductive technologies after prophylactic hysterectomy if using surrogacy.

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תודה על ההקשבה

שאלות ?