Management of Gynaecological Cancer Risk in Lynch Syndrome

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Terminology

HNPCC - hereditary nonpolyposis colorectal cancer >> misleading …

- Various other cancers are “forgotten”

Implication:

“I go and have my colonoscopies and I’ll be OK.”

Lynch Syndrome (LS) is…

- Autosomal dominant germline mutation in one of several DNA mismatch repair (MMR) genes
  - Inherited
    - Irrespective of gender
- Increases the risk of several cancers
  - Risk of **endometrial** cancer: 27% to 71% (exceeds the risk of bowel cancer)
  - Risk of **ovarian** cancer: 3% to 14%
- Genetic defect in 1 of 3100 people [1]

[1]. Dunlop et al., Br J Cancer 2000

Lifetime cancer risk (females)

Cancer site	**MLH1**	**MSH2**	**MSH6**	**PMS2**
Any Lynch cancer	50%-76%	38%-78%	65%	21%-53%
Colorectal	50-53%	39-68%	18-30%	15%
Endometrial	60%	21%	30%	15%
Ovarian	20%	24%	1%	
Upper urologic tract	0.4%	9%	0.7%	
Gastric	6%	2%	4%	
Small bowel	6%	6%		
Biliary/Pancreatic	4%			
Brain tumors (gliomas)	1.7%	2.50%		

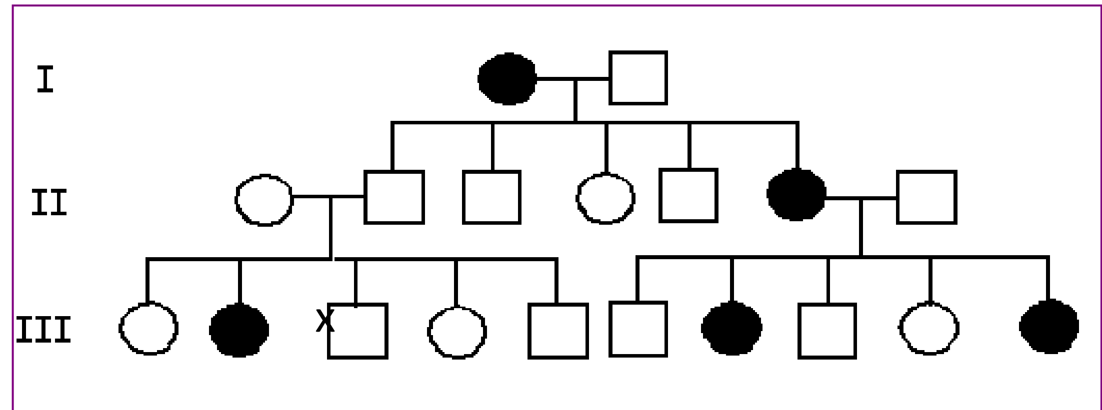
UpToDate.com

Identification of LS carriers

- **Family history**
  - Revised Amsterdam Criteria by the International Collaborative Group on HNPCC
  - Revised Bethesda Criteria for testing colorectal tumours for MSI
  - 50% of LS patients have a negative family history
- **Sentinel cancer diagnosis – Tumour based**
  - E.g. dad had bowel cancer – was Lynch tested
  - Auntie had endometrial cancer – was Lynch tested

Risk Assessment
Family History & Pedigree

Easy to do



False negative

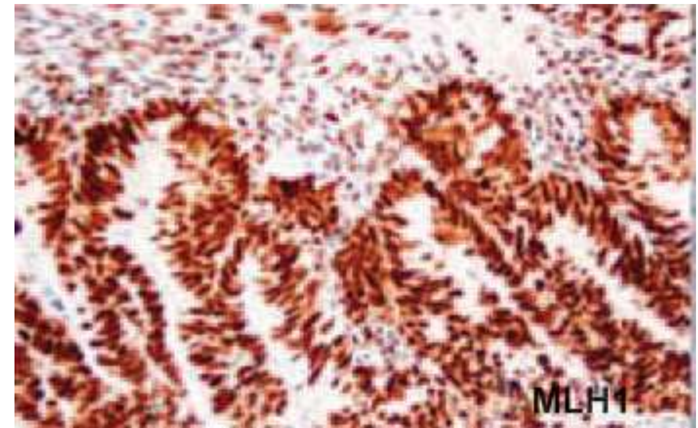
- Small families
- Adoption
- Paucity of female relatives
- Non-Paternity

Inheritance: Autosomal dominant - 50% chance of inheritance;
Penetrance: 80% breast ca, 40% ovarian ca), etc.

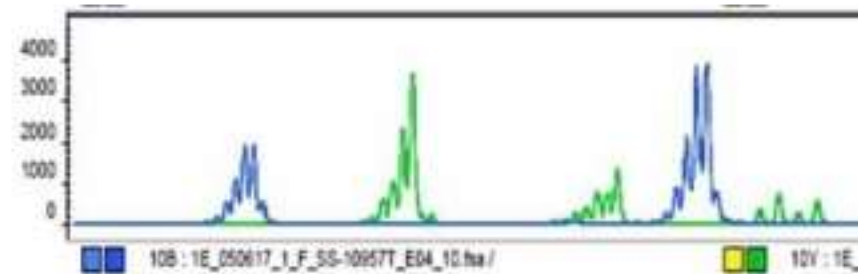
Prediction Models: use family/personal history

Tumour based Tests

- Immunohistochemistry
  - On cancer tissue
  - Is not a genetic test
  - Requires confirming genetic tests



- Microsatellite instability testing
  - Uses PCR to amplify a standard panel of DNA sequences containing nucleotide repeats



Benefits & Limitations of Genetic Testing

1. Information > Angst/Anxiety;
2. Identifies the individuals concerned;
3. If a mutation has been demonstrated on a relative, a negative result is most definite and is very reassuring;
4. If result is negative for a known mutation: Does it exclude a mutation?

Endometrial Cancer

- Majority of EC are non-Lynch related
- Lynch in only 2% to 5%
- A Lynch carrier very high risk of EC
- Mean age ~ 50 years (62 years in Non-Lynch)
  - 18% were diagnosed under the age of 50 years
- Cell types: majority are endometrioid cancers
- Location of tumour: Lower uterine segment
  - 10 of 35 patients

Risk factors for Endometrial cancer

Lynch

- Young age at menarche
- Nulliparity
- No contraceptive pill

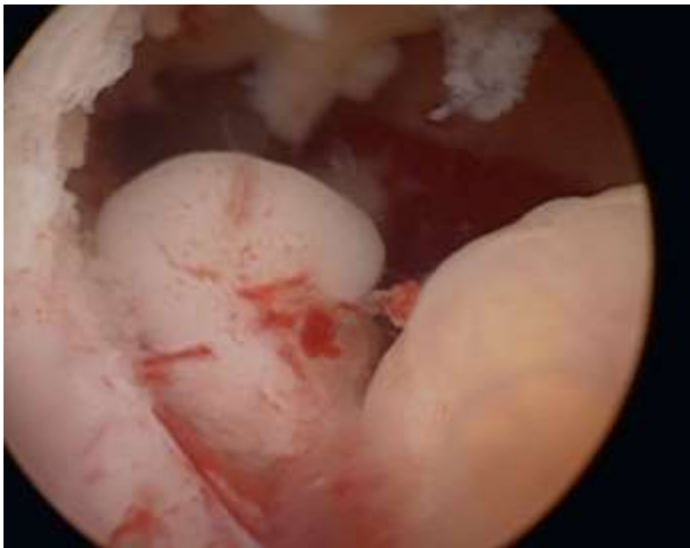
Non-Lynch

- Young age at menarche
- Nulliparity
- No contraceptive pill
- Obesity

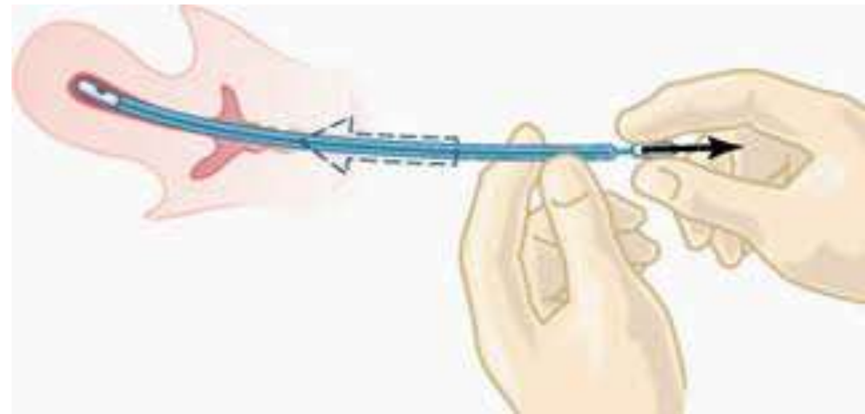
Diagnosis of Endometrial Cancer

- Abnormal bleeding = WARNING SIGN!
- Requires investigation:

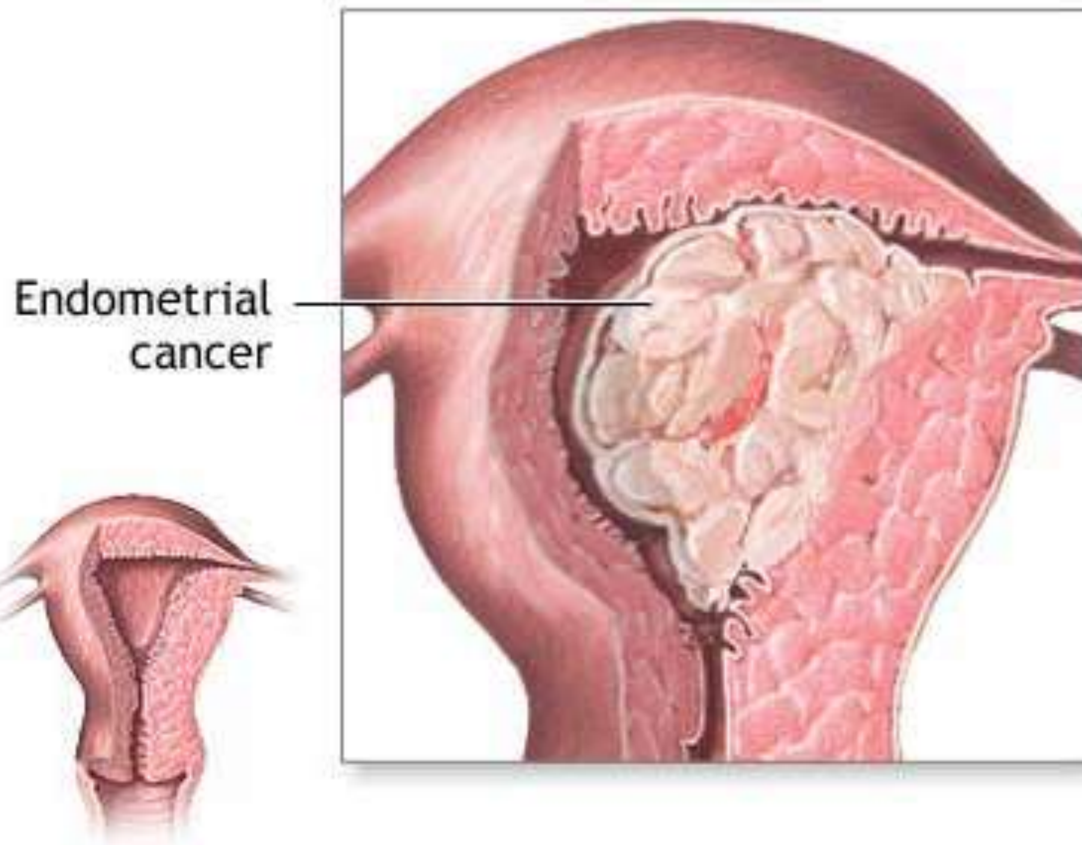
Hysteroscopy D&C



Pipelle endometrial sampling



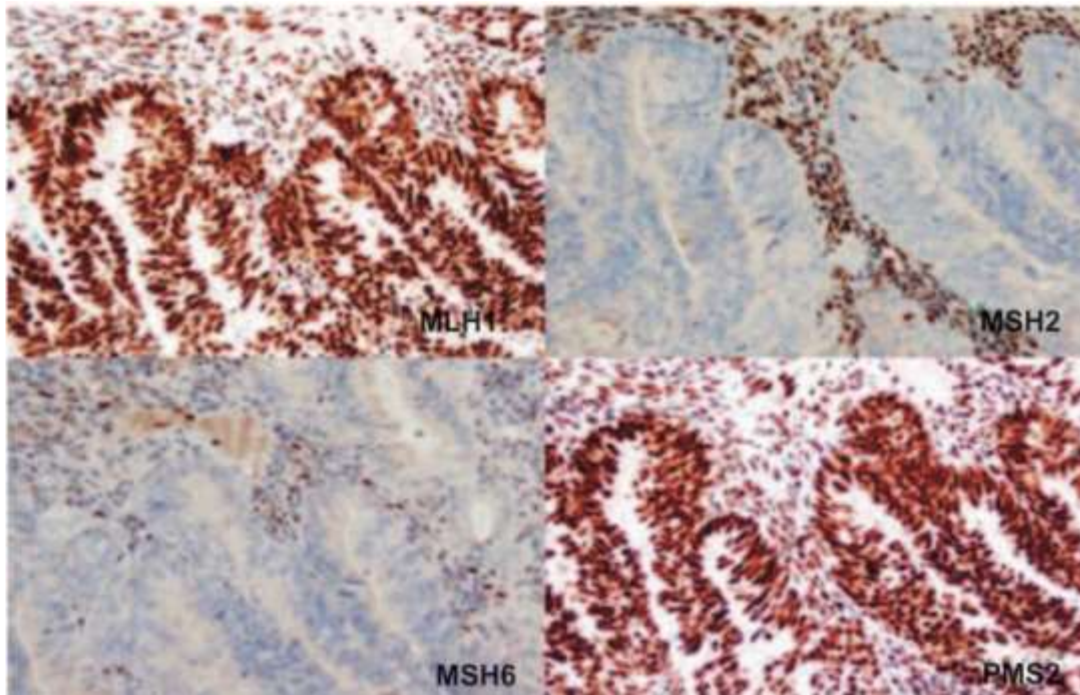
Endometrial Cancer



Treatment

- Hysterectomy
- Removal of ovaries
- ± Lymph nodes
- ± Radiation
- ± Chemotherapy

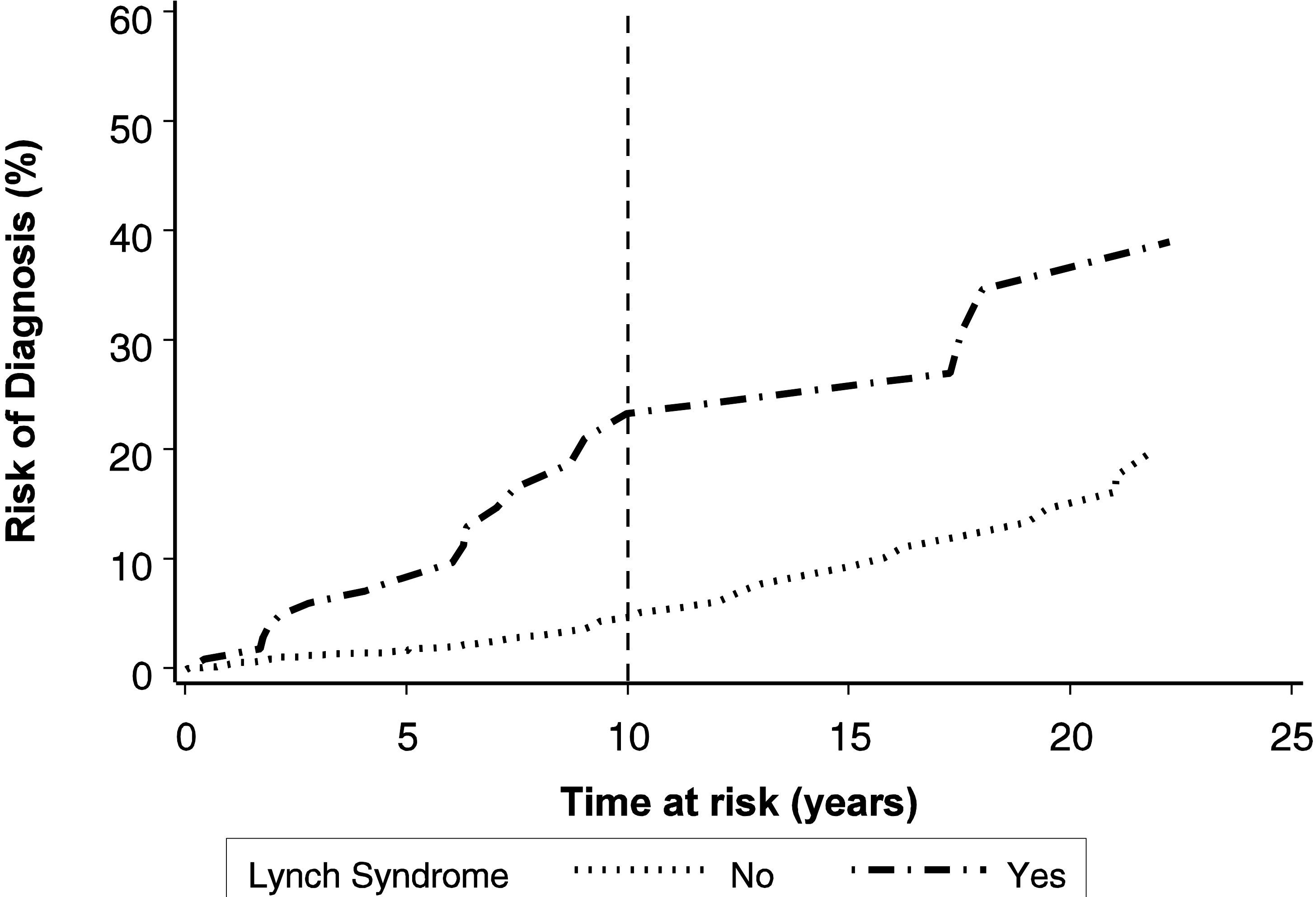
Risk of endometrial cancer finding Lynch



18% of patients who were 50 years of age or younger and were diagnosed with endometrial cancer had presumptive Lynch.

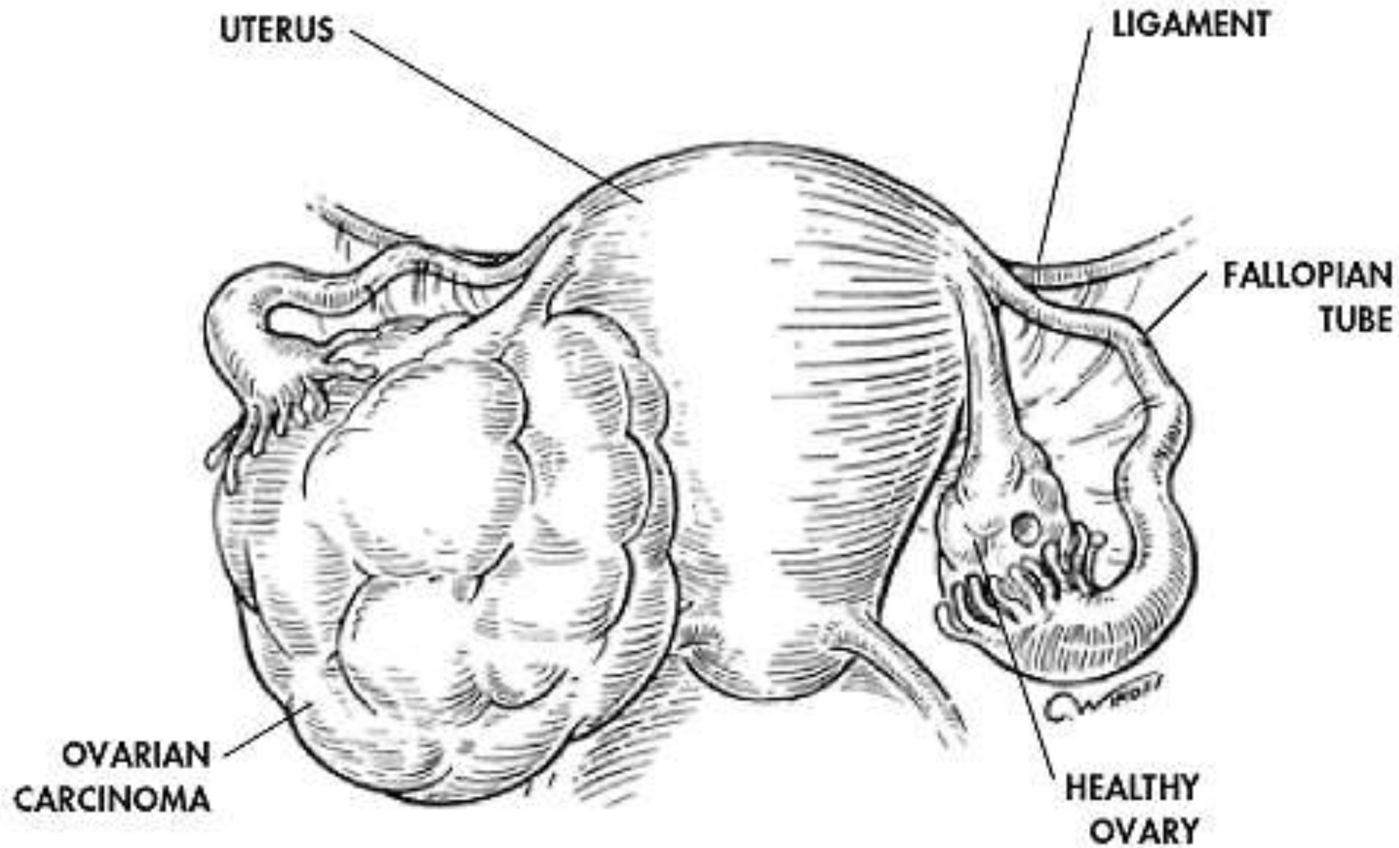
M Walsh et al: Clin Cancer Res 2008

Uterine cancer after bowel cancer



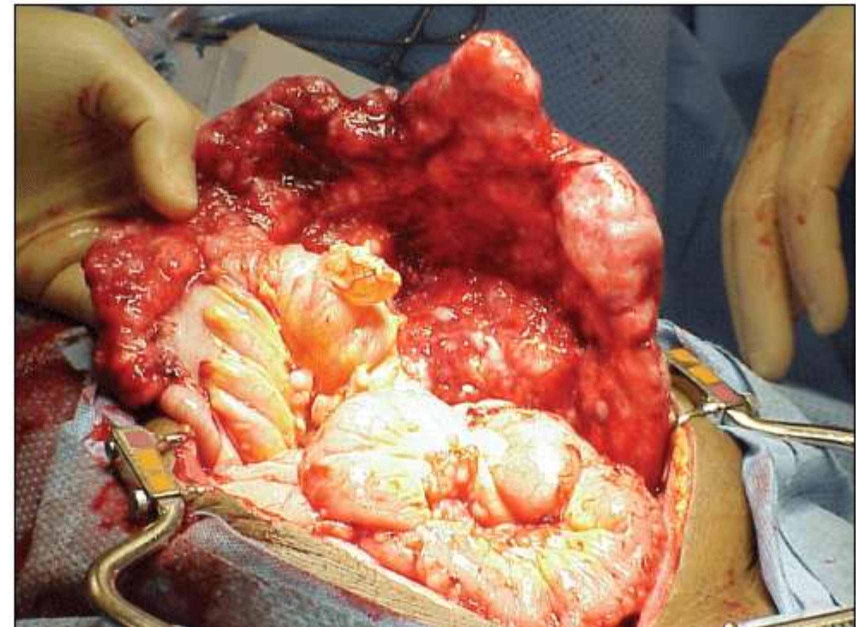
Obermair et al, Int J Cancer 2010

Ovarian Cancer



Ovarian Cancer

- Life time risk is 3% to 14% in Lynch carriers
  :: 1.3% in general population
- Patients are younger: 45 years
  :: 62 years in general population
- Histological cell types: no difference between Lynch and Non-Lynch patients
  - Stage 3 & 4
  - Poor prognosis
- Risk groups: not identifiable
- Warning signs are unspecific



Treatment of Ovarian Cancer

- Epithelial Ovarian Cancers
  - Surgery + Chemotherapy
- Non-Epithelial Ovarian Cancer
  - Limited surgery + chemotherapy
- Borderline tumours
  - Surgery only

www.battleagainstovariancancer.com

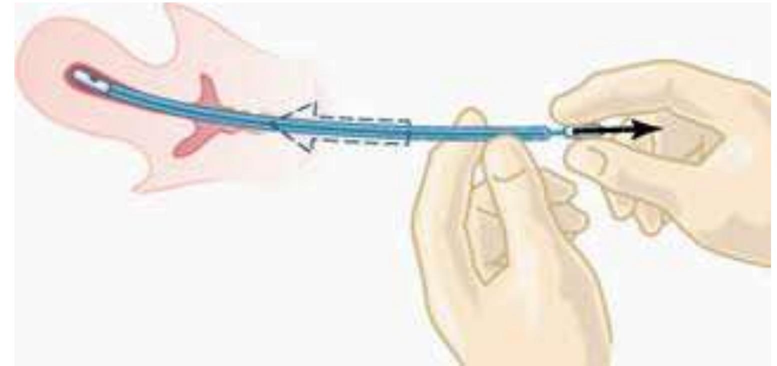
Screening & Prevention

	Uterine Ca	Ovarian Ca
Screening*	unreliable	unreliable
Chemoprevention Risk reduction	Unknown ? Mirena	50% through OCP
Prophylactic surgery (Risk reduction in %)	100%	95%

* Screening still recommended by some because of lack of effective alternatives

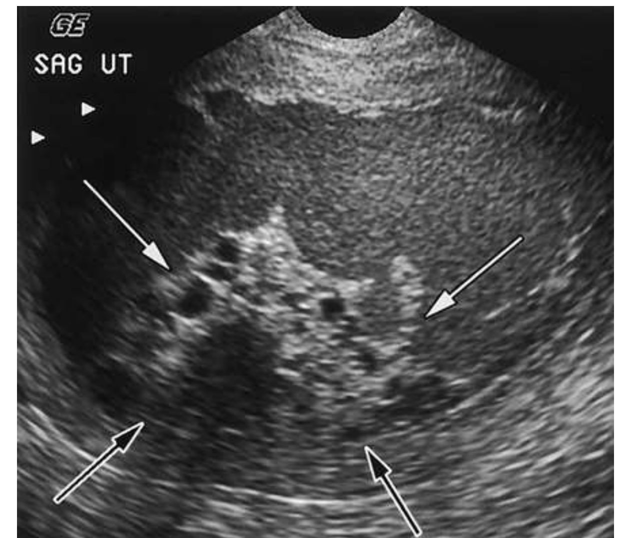
Surveillance – Endometrial Cancer

- Premenopausal women:
  - Endometrial sampling



??? RELIABLE ???

- Postmenopausal women:
  - Transvaginal ultrasound



Uterine Surveillance in Lynch/HNPCC

- 269 women with HNPCC
- Follow-up totalled 826 years of risk
- Pelvic US for a period of 13 years (annual or biennial)
- Two new cases of endometrial carcinoma –
- Neither case was detected by US
  - Both cases were early stage and presented with bleeding.

Dove-Edwin et al.: Cancer 2002

Uterine Surveillance in Lynch/HNPCC

- 41 women, median follow-up 5 years
  - 197 patients years at risk
- 179 patients had ultrasound examinations
  - 17 patients needed endometrial sampling
    - 3 patients endometrial hyperplasia with atypia
  - 1 interval cancer [not detected by US]
  - No ovarian cancers detected.

V.d. Zee et al.: Gynecol Oncol 2003

Surveillance vs. Prophylactic surgery for Lynch/HNPCC

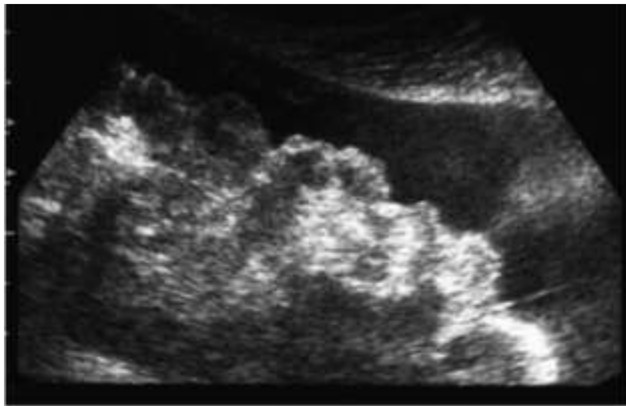
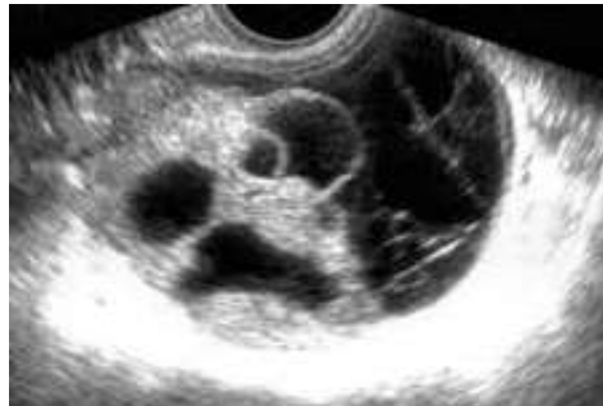
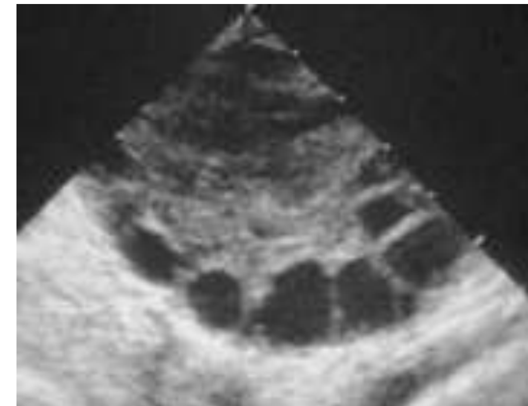
	Prophylactic Surgery	Surveillance
Endometrial Cancer	0	69 (33%)
Ovarian Cancer	0	12 (5%)

315 women with Lynch/HNPCC;
Cases: 61 prophylactic hysterectomy, 47 BSO;
200+ patients for matched controls;

Boyd-Rogers et al.: NEJM 2006

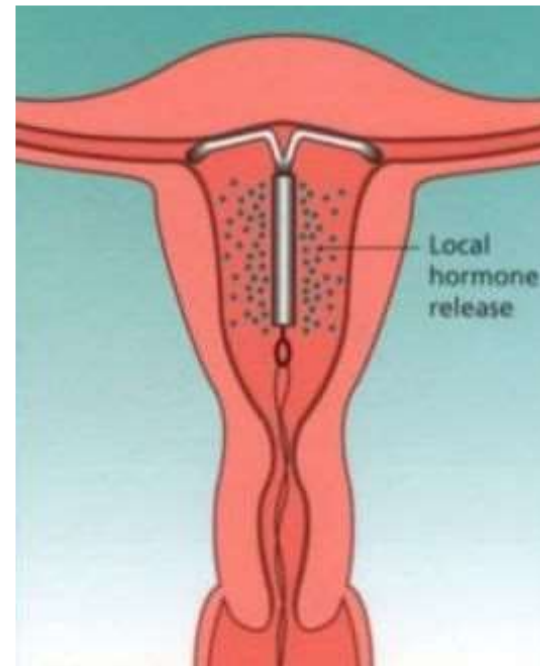
Surveillance - Ovarian Cancer

- UNRELIABLE – UNPROVEN
- Nevertheless sometimes recommended by professional societies
- Transvaginal Ultrasound & CA125

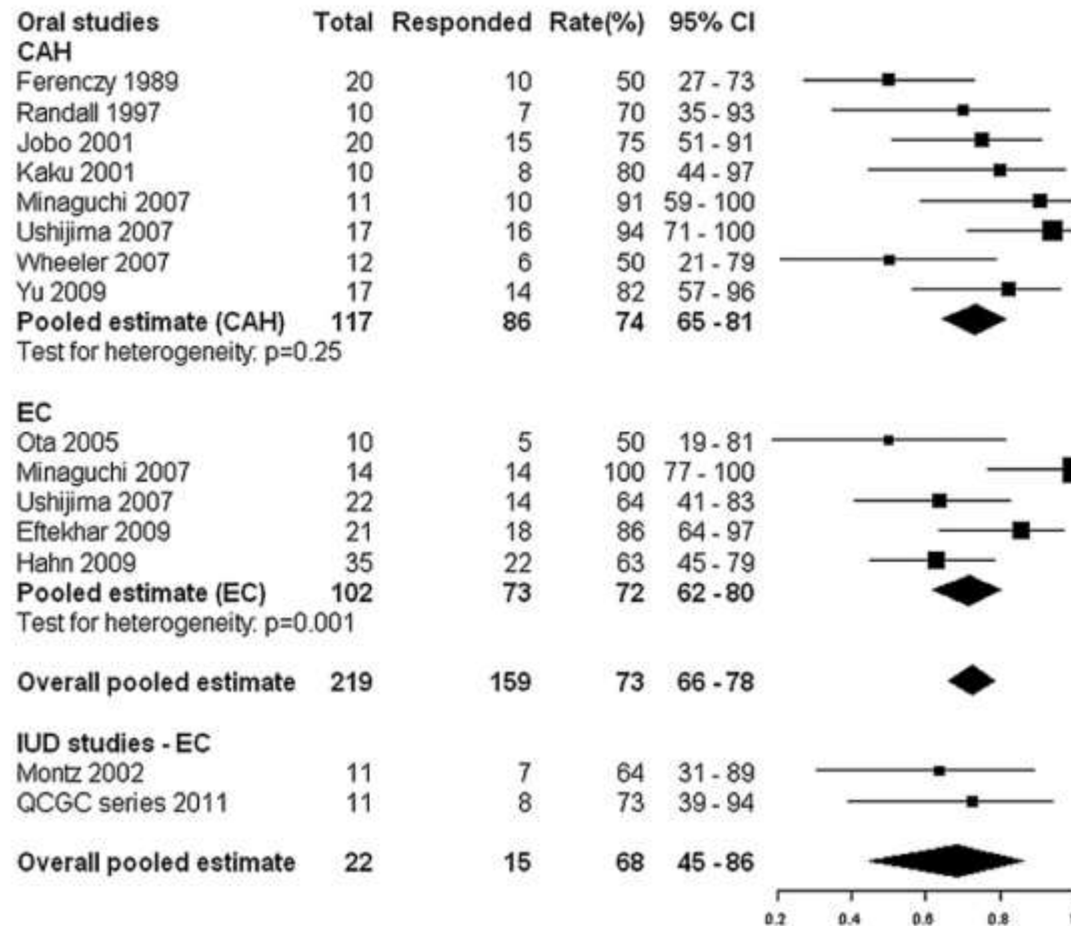
Chemoprevention

- Ovarian Cancer:
  - Oral contraceptive pill – Risk reduction by 50%
- Endometrial Cancer:
  - Mirena
    - Endometrial polyps -90%*
    - Endometrial cancer -50%**



*Wong et al: Obstet Gynecol 2013; **Soini et al Obstet Gynecol 2014

Mirena to treat endometrial carcinoma



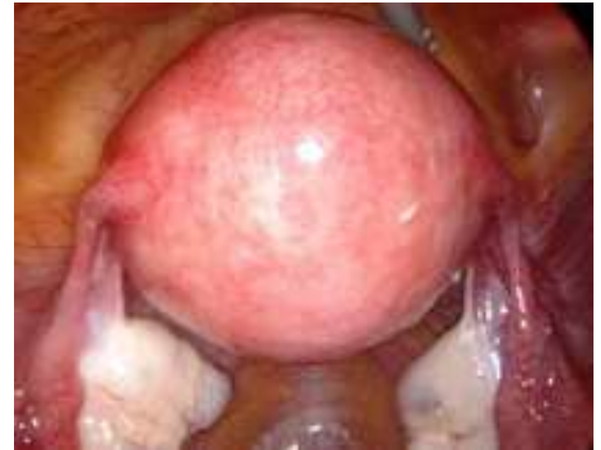
Oral studies	Total	Responded	Rate(%)	95% CI
CAH				
Ferenczy 1989	20	10	50	27 - 73
Randall 1997	10	7	70	35 - 93
Jobo 2001	20	15	75	51 - 91
Kaku 2001	10	8	80	44 - 97
Minaguchi 2007	11	10	91	59 - 100
Ushijima 2007	17	16	94	71 - 100
Wheeler 2007	12	6	50	21 - 79
Yu 2009	17	14	82	57 - 96
Pooled estimate (CAH)	**117**	**86**	**74**	**65 - 81**
Test for heterogeneity: p=0.25				
EC				
Ota 2005	10	5	50	19 - 81
Minaguchi 2007	14	14	100	77 - 100
Ushijima 2007	22	14	64	41 - 83
Eftekhar 2009	21	18	86	64 - 97
Hahn 2009	35	22	63	45 - 79
Pooled estimate (EC)	**102**	**73**	**72**	**62 - 80**
Test for heterogeneity: p=0.001				
Overall pooled estimate	**219**	**159**	**73**	**66 - 78**
IUD studies - EC				
Montz 2002	11	7	64	31 - 89
QCGC series 2011	11	8	73	39 - 94
Overall pooled estimate	**22**	**15**	**68**	**45 - 86**

Baker J et al: Gynecol Oncol 2012

Surgical Prevention

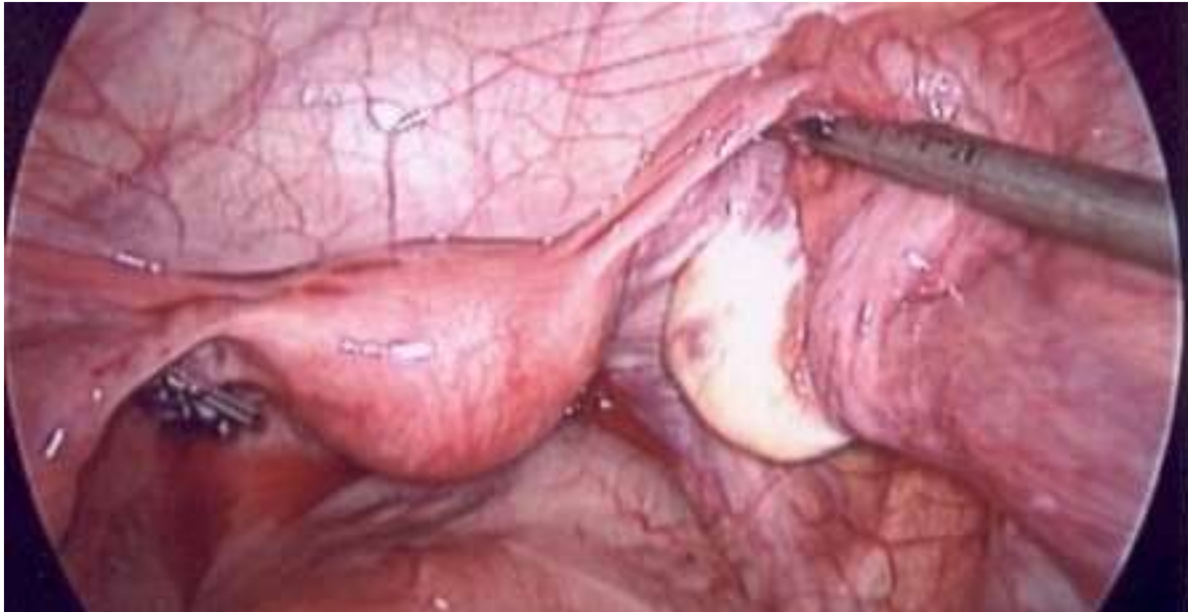
Prophylactic Surgery for Lynch

- Remove uterus = hysterectomy
- Hysterectomy is the most common gynaecological surgical procedure (~30,000 women in AUS every year)
  - 2,000 for cancer
  - 28,000 for abnormal bleeding, pain
- Ovaries should be removed.

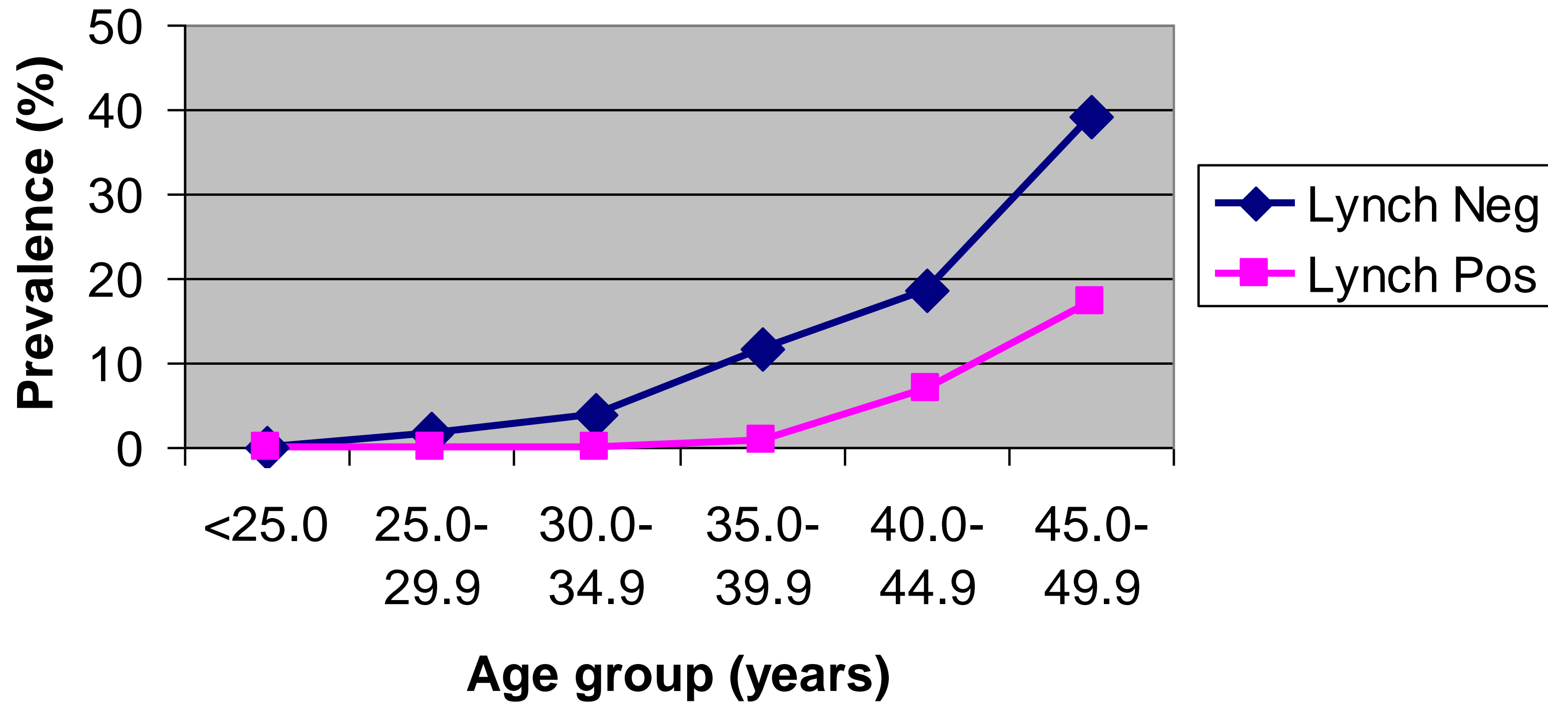


Prophylactic Surgery for Ovarian Cancer

- Label them correctly – collaborate with pathology provider
- Collect samples from peritoneal lining
- Performed by someone with an interest in Oncology / Lynch



Timing of surgery



Pre-surgical assessment

- Medical check up
- Stop blood thinners + herbs/supplements (10 d)
- Gynaecological examination
- PAP smear
- Ultrasound
- Blood tests
- Bowel Prep is not required

Surgical Approach*

- Avoid laparotomy
  - Surgical complication rate is too high
- Avoid vaginal surgery
  - Ovaries cannot be removed
  - Unsafe in women who had previous surgery (cesarean section)
- Avoid morcellation of uterus
- Laparoscopic approach is recommended
  - Hospital stay 1 or 2 days

*Obermair.info

Risks of surgery

- Conversion from laparoscopic to open (2%)
- Medical and anesthetic risks
- Risk of organ injury (bowel, bladder, ureter, bleeding, nerves) (1%)
- Deep vein thrombosis, Pulmonary embolus
- Infection (<1%)
- Menopause
- Constipation (pain killers)
- Postoperative pain
- Vaginal discharge for 6 weeks, vault haematoma
- Shoulder pain
- Fatigue
- Failure – Development of cancer
- Sexual dysfunction (?)

LS Summary & Recommendations

- Lynch is autosomal dominant inherited
  - Inherited irrespective of gender
- Challenge is to identify LS carriers
  - Indicator patients >> identify LS carriers
  - Family history unreliable
  - Immuno-stain for **<u>all</u>** patients diagnosed with endometrial cancer
    - Cost effective
    - Not miss any LS carriers

Clinical Management (1)

Young women who have not completed family

- Plan your family & consider surgery as soon as the family is completed.
- Healthy lifestyle
- Chemoprevention
  - Oral Contraceptive Pill / Mirena
- Screening
  - No major organisation in AUS/US recommends screening for uterine or ovarian cancer.
  - Endometrial sampling (yearly) from age 30 years (or 5 years prior to earliest age of cancer)
- RR-Prophylactic Salpingectomy

Clinical Management (2)

Women who completed their family

Healthy lifestyle

Prophylactic surgery

- Total Laparoscopic Hysterectomy, BSO, washings
- Very effective to prevent cancer
- Screening is very unreliable
- Surgical risks are low

FUTURE: Genomic Treatment

Pembrolizumab is a Programmed Death -1 (PD-1) inhibitor.

41 patients with mismatch-repair deficiency (various cancers).

Mismatch-repair status predicted clinical benefit of immune checkpoint blockade with pembrolizumab.

NEJM, June 2015

Prof Andreas Obermair

Obermair.info

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REFERRAL GUIDE FOR Health Professionals

MAKE AN Enquiry

Prof. Obermair specializes in surgery for gynaecological cancer and complex pelvic surgery for benign conditions.

http://obermair.info/information/gynaecological-cancer/