MOUNT SINAI HOSPITAL
Joseph and Wolf Lebovic Health Complex

Princess Margaret Hospital
University Health Network

UNIVERSITY OF TORONTO
FACULTY OF MEDICINE

Highlights from the latest research in Lynch syndrome

Familial Gastrointestinal Registry
Education Night

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Topics to be covered

Recent developments in Lynch syndrome:

- Colorectal cancer risk & surveillance
- Gynecologic cancer risk & surveillance

(Dr. Sarah Ferguson)

- Other Lynch syndrome cancers
- Aspirin & reducing cancer risk

Familial GI Cancer Registry, Mount Sinai Hospital

1,064 germline mismatch repair mutation carriers from 355 families

MSH2	546 (51%)
MLH1	397 (37%)
MSH6	81 (7.6%)
PMS2	34 (3.2%)
EPCAM	6 (0.6%)

Female 595 (56%) Male 469 (44%)

Cumulative lifetime colorectal cancer risk

Risk to age 70 yrs (%, omitting index case)

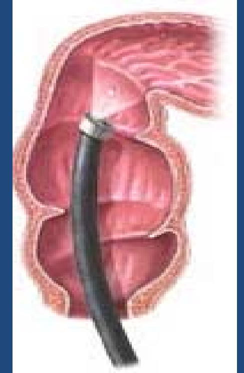
Colorectal Cancer	**MSH2** (539)	**MLH1** (384)	**MSH6** (77)	**PMS2** (29)
Male (451)	68.9 ± 6.4	84.7 ± 6.9	40.7 ± 25.2	25.0 ± 21.7
Female (584)	53.0 ± 5.9	46.0 ± 6.2	43.4 ± 18.8	28.6 ± 17.1

$p < 0.0001$

FGICR data:

- Men are at significantly higher risk compared to women (MSH2 & MLH1)
- MSH6 & PMS2 carriers are at significantly lower risk compared to MSH2 & MLH1

Colorectal cancer screening in Lynch syndrome



- Regular colonoscopy leads to reduction CRC related mortality in LS
- Finland 1995: 10 yr follow up of 251 LS
  - initial screening ± surveillance every 3 yrs
  - CRC: Screening 6/133 (4.5%) vs controls 14/118 (11.9%)
- Netherlands 2010: 7.2 yr follow up of 745 LS
  - 33/745 (4.4%) developed CRC during colonoscopy surveillance
  - 0-1 yrs: 2 (6.1%); 1-2 yrs 14 (42%); 2-3 yrs 17 (52%)

Colonoscopic surveillance in Lynch syndrome

European Expert Guidelines 2013

- A 3 year interval between colonoscopies has proven to be effective (Grade *B* recommendation)
- In view of advanced CRC detected between 2-3 years after colonoscopy, the recommended interval for LS gene carriers is 1-2 years (Grade *C* recommendation)

Cumulative Lifetime Gynecological Cancer Risk

Risk to age 70 yrs (%, omitting index case)

Cancer	**MSH2** (315)	**MLH1** (200)	**MSH6** (50)	**PMS2** (14)
Endometrial (155)	50.7 ± 6.5	53.3 ± 8.5	65.0 ± 19.7	0
Ovarian (40)	24.3 ± 7.6	5.1 ± 2.5	0	0
Colorectal (234)	53.0 ± 5.9	46.0 ± 6.2	43.4 ± 18.8	28.6 ± 17.1

FGICR data:

- Risk of endometrial cancer similar to CRC
- Similar risk of endometrial cancer for MSH2, MLH1 & MSH6 carriers
- MSH2 carriers appear to be at higher risk for ovarian cancer compared to MLH1 & MSH6

Gynecologic cancer surveillance in Lynch syndrome

European Expert Guidelines 2013

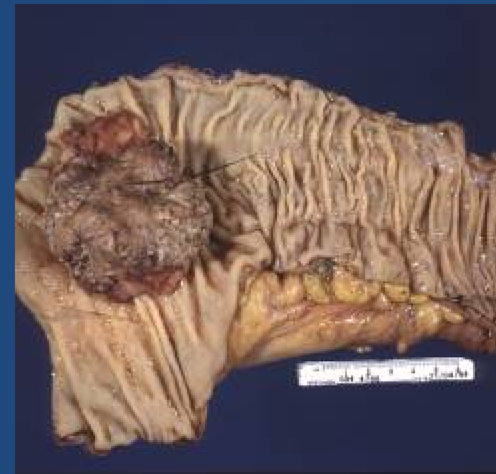
- In LS the risk of developing endometrial cancer equals risk of developing CRC
- Value of endometrial cancer surveillance is still unknown
- Gyne exam, transvaginal ultrasound & aspiration biopsy starting at 35-40 yrs may lead to detection of premalignant disease & early cancer (Grade *C* recommendation)

Lynch-Associated Cancers

why 'HNPCC' not preferred

Amsterdam II

- Colorectal
- Endometrial
- Small bowel
- Ureter & transitional cell kidney
- Sebaceous adenoma/carcinoma
- Keratoacanthoma



Ontario MOH

- Amsterdam II
- Stomach
- Hepatobiliary (pancreas, bile duct)
- Brain

Cumulative Lifetime Non-Gynecological Extracolorectal Cancer Risk

Risk to age 70 yrs (%)

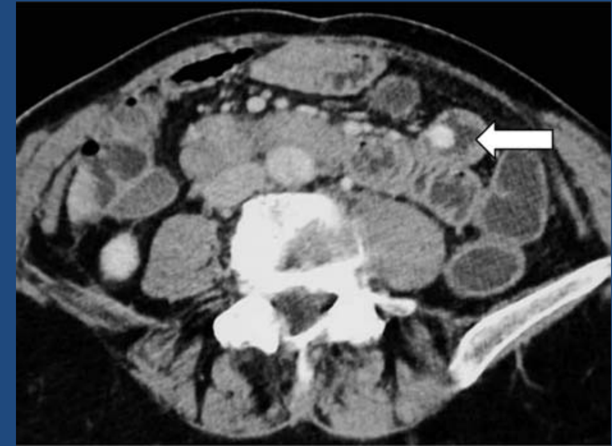
	GU (46)	**Stomach** (23)	**HPB** (20)	**SB** (16)	**Brain** (7)	**Sebaceous** (7)
Gender						
Male (457)	11.5 ± 3.0	4.8 ± 1.7	5.8 ± 2.3	5.6 ± 2.1	1.3 ± 1.0	3.5 ± 2.0
Female (578)	9.4 ± 2.2	3.4 ± 1.3	4.3 ± 1.5	1.6 ± 1.1	0.9 ± 0.6	1.6 ± 1.0
Gene						
MSH2 (534)	17.2 ± 3.1	4.8 ± 1.7	6.0 ± 1.9	2.8 ± 1.3	2.1 ± 1.1	4.2 ± 2.0
MLH1 (390)	4.3 ± 1.9	4.2 ± 1.6	4.3 ± 2.0	2.2 ± 1.6	0	0.8 ± 0.8

FGICR data:

- Males are at significantly higher risk compared to females (31% vs 19%)
- MSH2 carriers (32%) are at significantly higher risk compared to MLH1 (16%), MSH6 (14%) , PMS2 (0%) & EPCAM (0%)

Urinary tract cancer

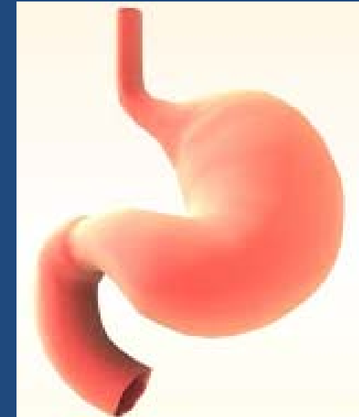
- 5-20% urethelial cell cancer of the renal pelvis & ureter
- Highest in male, MSH2 carriers
- Only 1 published study (Denmark 2008): 3,411 LS & 977 had undergone urine cytology
- Urine cytology diagnosed 2 (0.1%) asymptomatic cancer
  - 22 (1%) false positive cytologies (no cancer)
  - 5/14 cancers arose in individuals with normal cytology
- European Expert Guidelines 2013 does not recommend urothelial cancer surveillance outside of a LS clinical research



Small bowel cancer

- 5% by 70 yrs
- No evidence of family clustering
- Only 1 published study (France 2010): 35 LS, capsule endoscopy detected 2 SB adenomas & 1 SB carcinoma, while CT enteroclysis missed the 2 adenomas
- European Expert Guidelines 2013 does not recommend small bowel cancer surveillance

Gastric cancer



- 5% by 70 yrs
- No evidence of family clustering
- Only 1 published study (Finland 2002) did not support effectiveness of gastric cancer surveillance in LS
- European Expert Guidelines 2013 does not recommend gastric cancer surveillance, but does recommend testing for H pylori infection & eradication therapy if needed (Grade *C* recommendation)

H pylori → gastritis & atrophy → intestinal metaplasia → 'intestinal type' gastric cancer

Prostate cancer

- Common cancer among men, generally good prognosis
- Recent studies have revealed an increased risk of prostate cancer in LS
- USA 2013: 6.3% to 60 yrs, 30% to 80 yrs
  - 2x the population risk
- Germany & Netherlands 2012: 9% to 70 yrs
  - 2.5x the population risk
  - MSH2 18%, MLH1 0%, MSH6 4%

- No LS-specific surveillance guidelines

Cancer Care Ontario:

- PSA not recommended as a population-based screen
  - Side effects of treatment
  - Indolent course of prostate cancer

Aspirin & Lynch syndrome

- CAPP2 trial – Lancet 2011, NEJM 2008
- 1009 LS carriers
- Enteric coated aspirin 600 mg a day vs placebo
- No difference in colorectal polyps or cancer at the end of the intervention 29 mos (2-4 yr)
- Reduction of CRC & other cancers in long term follow up 4.6 yr (1-10 yr)
  - CRC: Aspirin 18/427 (4.2%) Placebo 30/434 (6.9%)
  - Non-CRC LS cancer: Aspirin 16/427 (3.7%) Placebo 24/434 (5.5%)
- Resistant starch (i.e. fiber) vs placebo did not reduce colorectal cancer risk

Aspirin & Lynch syndrome

European Expert Guidelines 2013

- Regular aspirin significantly reduces the incidence of cancer in LS (Grade *A* recommendation)
- Based on data from vascular disease clinical trials: Low dose aspirin (81 mg per day) is a reasonable option to discuss with LS gene carriers (Grade *B* recommendation)
- Discuss risks, benefits & current limitations of evidence

Summary

Colorectal cancer

- Risk higher in men vs women & MLH1/MSH2 vs MSH6/PMS2
- Colonoscopy recommended every 1-2 yrs

Endometrial cancer

- Similar lifetime risk compared to CRC

Ovarian cancer

- Risk appears to be higher in MSH2 carriers

Other Lynch syndrome cancers

- More common in men & MSH2
- No effective surveillance guidelines yet

Aspirin

- Reduces colorectal cancer risk by ~1/3
- Dose 600 mg vs 81 mg?