



The latest research in Lynch syndrome

Robert Gryfe MD, PhD, FRCSC
Mount Sinai Hospital, University of Toronto



colorectal cancer

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Lynch syndrome colorectal cancer

- Lynch syndrome is the most common hereditary CRC syndrome
- ~2-3% of all CRCs
- Lifetime risk = 30-70%
- FGICR:

Risk to 70yr	MSH2	MLH1	MSH6	PMS2
Male	68.9 ± 6.4	84.7 ± 6.9	40.7 ± 25.2	25.0 ± 21.7
Female	53.0 ± 5.9	46.0 ± 6.2	43.4 ± 18.8	28.6 ± 17.1

- Colorectal cancer risk:

Men > Women

MLH1 ≈ MSH2 > MSH6 > PMS2

Cumulative Risk to 80 years:

MLH1 = 49% (29-85%)

MSH2 = 52% (31-90%)

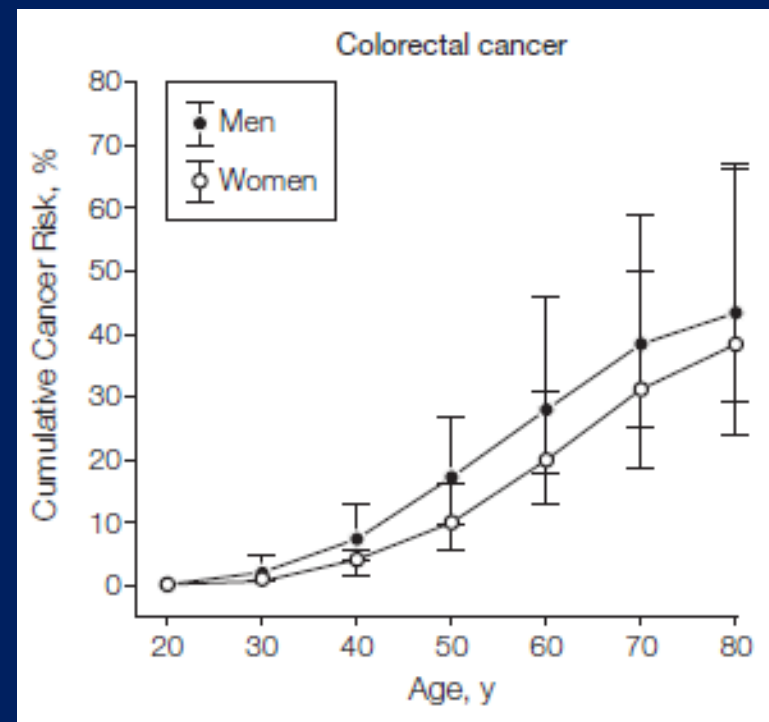
MSH6 = 18% (13-30%)

Bonadona JAMA 2011; 305:2304

Cumulative Risk to 70 years:

PMS2 = 11-19% (2-30%)

ten Brooke JCO 2015; 33:319



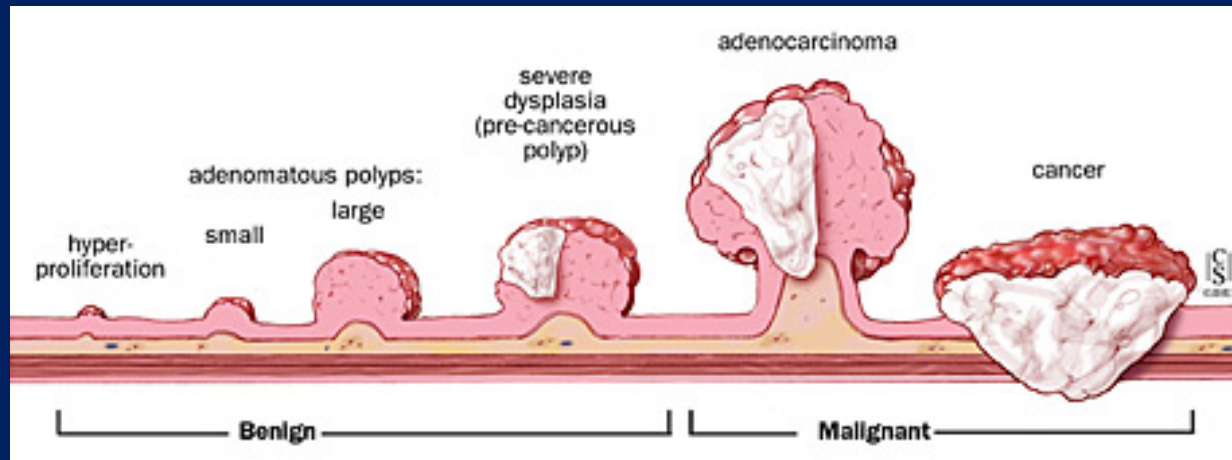
Reducing Lynch syndrome CRC risk

- Talk to your family!



- At-risk family members need:
 - genetic counseling
 - genetic testing
 - clinical recommendations

Accelerated dwell time



	Advanced adenoma (mo)	Colorectal cancer (mo)
Mean \pm standard deviation (range)	33.0 \pm 16.2 (12-56)	35.2 \pm 22.3 (7-96)

Normal \rightarrow polyp \rightarrow cancer
 \approx 3 years

Sporadic colorectal cancer \approx 10-15 years

Edlestein, Clin Gastro & Hep 2011; 9:340

Colonoscopy

Colonoscopy screening every 1-2 years:

- Reduces CRC incidence
- Reduces CRC stage
- Reduces CRC mortality

Jarvinen, *Gastroenterology* 2000; 118:829

Vasen, *Gastroenterology* 2010; 138:2300

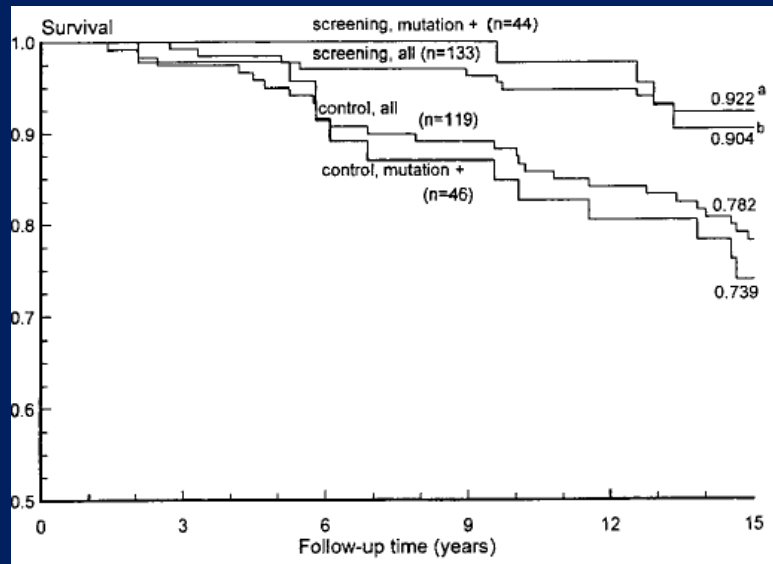
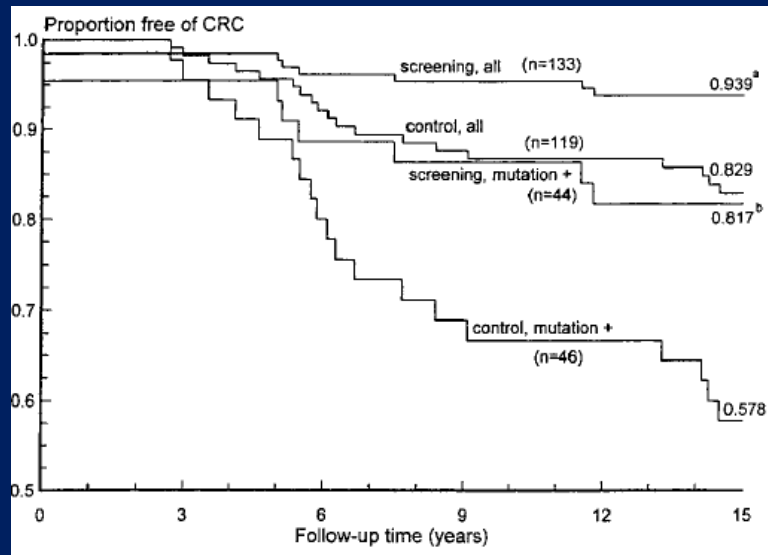


Table 1. Stage Distribution of CRC Cases

Stage ^a	Study group (n = 133)	Control group (n = 119)
A	3	3
B	5	7
C	—	1
D	—	8
Total	8	19

Colonoscopy is the 'gold standard'
but it is not perfect

Don't ignore symptoms

Aspirin chemoprevention



CAPP2

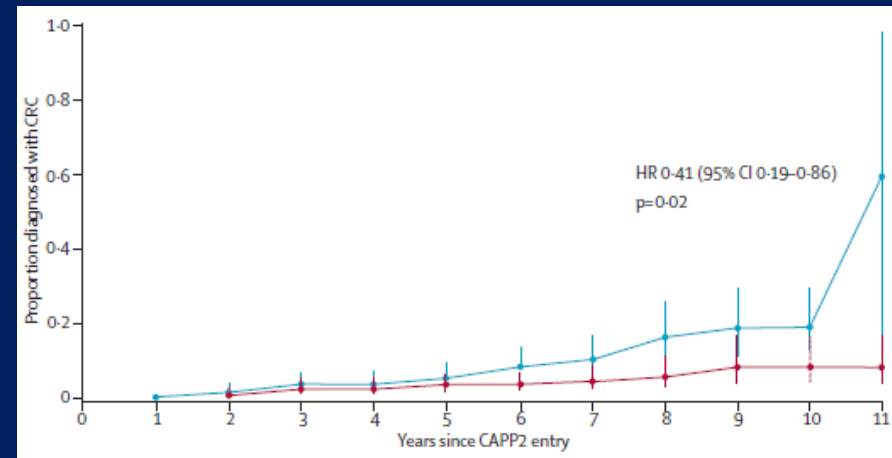
- Aspirin 600mg/d vs placebo
- No difference in CRC rates:
 - First 2 years
 - Evaluating all subjects
- 60% CRC risk reduction after ≥ 2 years of aspirin
- No \uparrow adverse events

Burn, Lancet 2011; 378:2081

- One RCT
- High dose of aspirin
- Substitute end point
- Clinical guidelines: "aspirin may be considered"

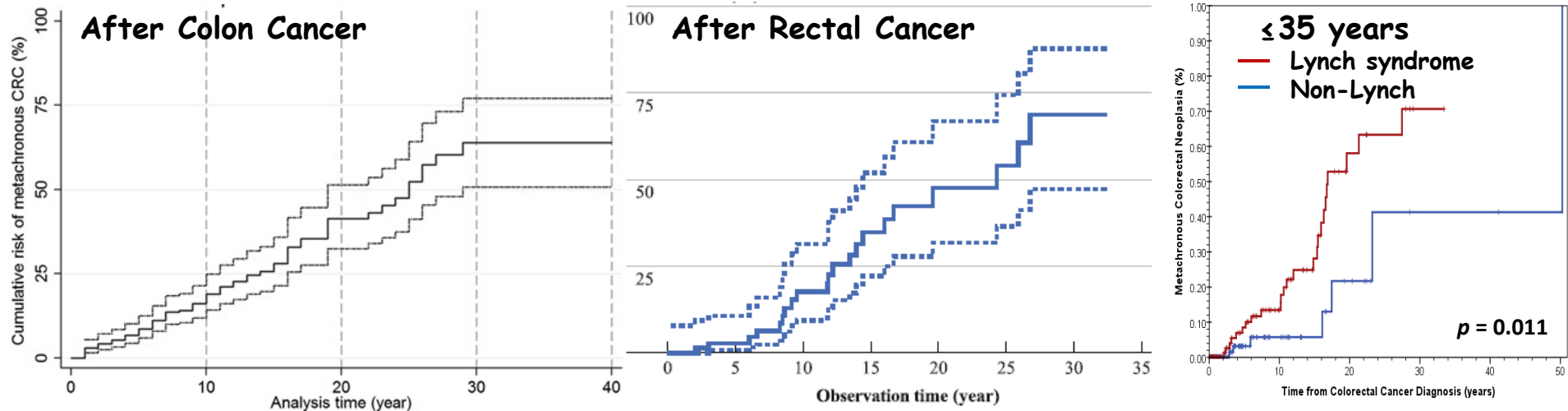
CAPP3

- Aspirin 100mg, 300mg & 600mg



Metachronous Lynch syndrome CRC

Risk of another CRC after Lynch syndrome CRC



Cumulative risk:

10 years after surgery 16% (10-25%)
20 years after surgery 62% (50-77%)

Parry, Gut 2011; 60:950

19% (9-31%)
47 (31-68%)

Win, Ann Surg Oncol 2013; 20:1829

16.1% ± 5.2%
59.2% ± 9.8%

Aronson, DCR 2015; in press

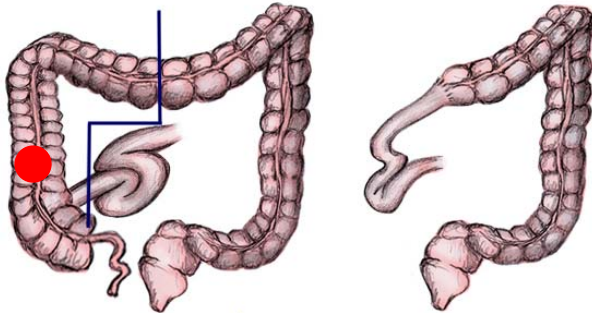
Lynch syndrome CRC surgery

Practice guidelines:

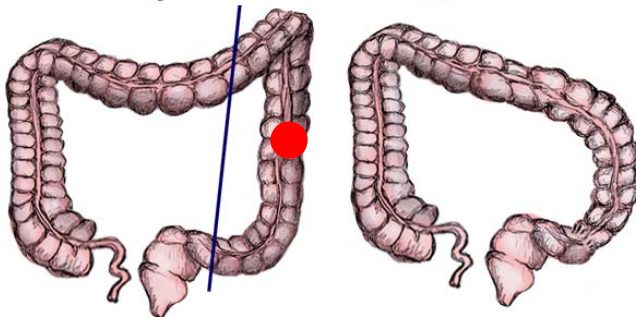
Consider extended resection for individuals with Lynch syndrome undergoing colorectal resection

- Extent of resection must be balanced with:
 - surgical morbidity
 - quality of life / bowel function considerations
 - alternative risk-reducing measures: intense post-operative colonoscopic screening

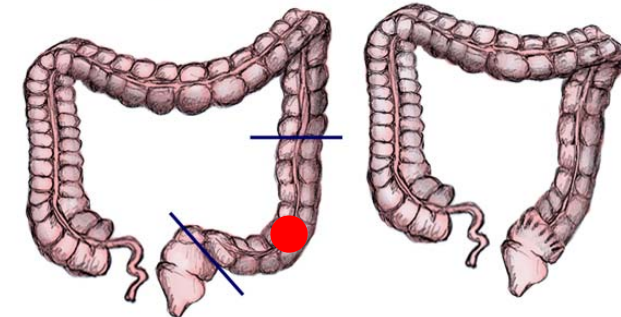
Right Colectomy



Left Colectomy

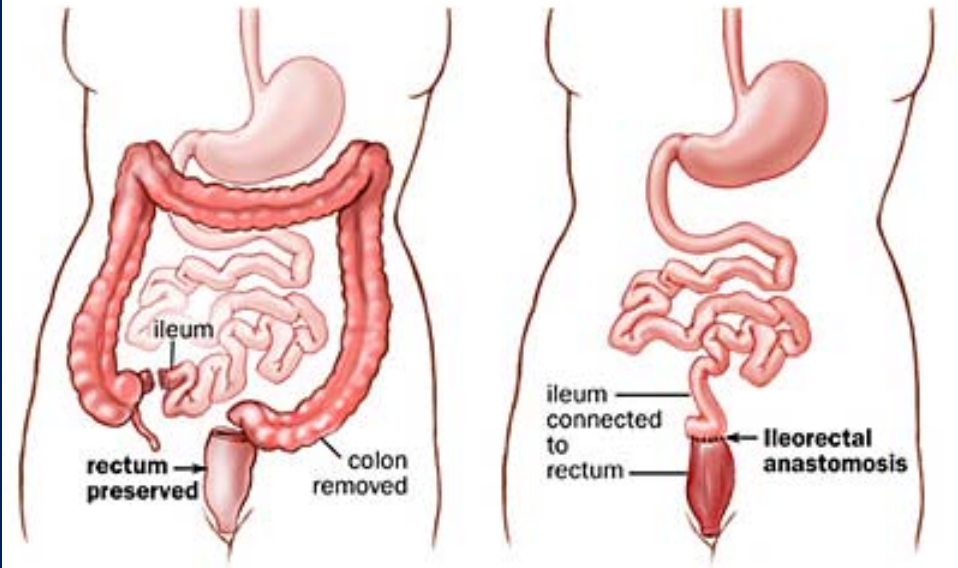


Sigmoid Colectomy



Standard Segmental Resection

Total colectomy and Ileorectal anastomosis



Extended Resection

Extended vs standard resection

Study	Patients	Segmental	Extended
Parry (2011)	332	16%	0%
Aronson (2015)	285	16%	7%
Kalady (2010)	259	25%	8%
de Vos (2002)	136	16%	3%
Natarajan (2010)	83	35%	15%

- Extended resection reduces risk of metachronous CRC in Lynch syndrome
- Metachronous CRC risk of 0-15% after extended resection
- Sigmoidoscopy surveillance still required after extended resection

Quality of life: Standard vs extended resection

SF-36 (Generic QoL)

- No differences - general health, vitality, emotional role, mental health, social functioning, bodily pain, physical role, physical functioning

EORTC QLQ CR-38 (CRC QoL)

- Extended: defecation problems
- Standard: male sexual problems
- No difference - sexual enjoyment, sexual function, future perspective, body image, female sexual problems, chemotherapy side effects, weight loss, GI-tract problems, micturation problems, stoma related problems

COREFO (Colorectal surgery QoL)

- Extended: stool frequency, social impact, stool-related aspects
- No difference - total score, need for medication, incontinence

Lynch syndrome CRC & chemotherapy

- Controversial topic
- 5-fluorouracil-based chemotherapy is recommended in stage III CRC and selective cases of stage II CRC
- Most studies have demonstrated improved survival for patients "Lynch-syndrome-like" (MSI, MMR-D) CRCs compared to sporadic CRC patients
- Several studies have demonstrated that Lynch syndrome-like CRCs do not benefit from 5-fluorouracil-based chemotherapy
- Most studies demonstrate that non-Lynch syndrome-like (MSS, MMR-I) CRCs do benefit from 5-fluorouracil-based chemotherapy

Stage III

- Generally, chemotherapy remains the standard of care, including Lynch syndrome

Stage II

- Chemotherapy is selective & individuals with Lynch syndrome are generally not treated

Summary: Lynch syndrome colorectal cancer

Colorectal cancer:

- men > woman, MLH1 \approx MSH2 > MSH6 > PMS2
- accelerated progression from normal to cancer \approx 3 years
- improved survival compared to sporadic CRC

Screening colonoscopy every 1-2 years:

- decreases colorectal cancer, cancer stage & mortality
- does not prevent all colorectal cancer

Aspirin may decrease risk of developing CRC

Increased risk of developing another CRC after initial CRC:

- risk decreased by extended resection compared to standard resection
- extended resection associated with some quality of life consequences
- screening colonoscopy/sigmoidoscopy required after resection

Adjuvant chemotherapy continues to be recommended in stage III Lynch syndrome CRC, but generally is not indicated in stage II

Talk to your family, discuss your genetic testing results & encourage them to speak with a genetic counselor

