Highlights from the latest research in Lynch syndrome

Familial Gastrointestinal Registry Education Night

Robert Gryfe MD, PhD, FRCSC
Mount Sinai Hospital
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)

<table>
<thead>
<tr>
<th>Colorectal Cancer</th>
<th>MSH2 (539)</th>
<th>MLH1 (384)</th>
<th>MSH6 (77)</th>
<th>PMS2 (29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (451)</td>
<td>68.9 ± 6.4</td>
<td>84.7 ± 6.9</td>
<td>40.7 ± 25.2</td>
<td>25.0 ± 21.7</td>
</tr>
<tr>
<td>Female (584)</td>
<td>53.0 ± 5.9</td>
<td>46.0 ± 6.2</td>
<td>43.4 ± 18.8</td>
<td>28.6 ± 17.1</td>
</tr>
</tbody>
</table>

**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

p < 0.0001
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)

<table>
<thead>
<tr>
<th>Cancer</th>
<th>MSH2 (315)</th>
<th>MLH1 (200)</th>
<th>MSH6 (50)</th>
<th>PMS2 (14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial (155)</td>
<td>50.7 ± 6.5</td>
<td>53.3 ± 8.5</td>
<td>65.0 ± 19.7</td>
<td>0</td>
</tr>
<tr>
<td>Ovarian (40)</td>
<td>24.3 ± 7.6</td>
<td>5.1 ± 2.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Colorectal (234)</td>
<td>53.0 ± 5.9</td>
<td>46.0 ± 6.2</td>
<td>43.4 ± 18.8</td>
<td>28.6 ± 17.1</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Amsterdam II</th>
<th>Ontario MOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Colorectal</td>
<td>• Amsterdam II</td>
</tr>
<tr>
<td>• Endometrial</td>
<td>• Stomach</td>
</tr>
<tr>
<td>• Small bowel</td>
<td>• Hepatobiliary</td>
</tr>
<tr>
<td>• Ureter &amp; transitional cell</td>
<td>(pancreas, bile duct)</td>
</tr>
<tr>
<td>kidney</td>
<td>• Brain</td>
</tr>
<tr>
<td>• Sebaceous adenoma/carcinoma</td>
<td></td>
</tr>
<tr>
<td>• Keratoacanthoma</td>
<td></td>
</tr>
</tbody>
</table>
Cumulative Lifetime Non-Gynecological Extracolorectal Cancer Risk

Risk to age 70 yrs (%)

<table>
<thead>
<tr>
<th>Gender</th>
<th>GU (46)</th>
<th>Stomach (23)</th>
<th>HPB (20)</th>
<th>SB (16)</th>
<th>Brain (7)</th>
<th>Sebaceous (7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (457)</td>
<td>11.5 ± 3.0</td>
<td>4.8 ± 1.7</td>
<td>5.8 ± 2.3</td>
<td>5.6 ± 2.1</td>
<td>1.3 ± 1.0</td>
<td>3.5 ± 2.0</td>
</tr>
<tr>
<td></td>
<td>9.4 ± 2.2</td>
<td>3.4 ± 1.3</td>
<td>4.3 ± 1.5</td>
<td>1.6 ± 1.1</td>
<td>0.9 ± 0.6</td>
<td>1.6 ± 1.0</td>
</tr>
<tr>
<td>Female (578)</td>
<td>17.2 ± 3.1</td>
<td>4.8 ± 1.7</td>
<td>6.0 ± 1.9</td>
<td>2.8 ± 1.3</td>
<td>2.1 ± 1.1</td>
<td>4.2 ± 2.0</td>
</tr>
<tr>
<td></td>
<td>4.3 ± 1.9</td>
<td>4.2 ± 1.6</td>
<td>4.3 ± 2.0</td>
<td>2.2 ± 1.6</td>
<td>0</td>
<td>0.8 ± 0.8</td>
</tr>
</tbody>
</table>

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**

- 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?