Post-colonoscopy colorectal cancers in Lynch syndrome

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Lynch syndrome

• **Most common hereditary CRC syndrome:** 3% of all colorectal cancers

• **Cause:**
  – Germline mutations in the **MMR genes** *(MLH1/MSH2/MSH6/PMS2)* or Epcam
  – Autosomal dominant pattern of inheritance (50% probability of transmission)

• **Phenotype:**
  – High risk for CRC (30-80%) and other extracolonic tumors
  – Tumors display mismatch repair deficiency

• **Prevalence in general population:** **UNDERDIAGNOSIS** is the main issue!

### Estimated population carrier frequency for MMR genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>1 in...</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>MLH1</em></td>
<td>1,946</td>
<td>1,480-2,564</td>
</tr>
<tr>
<td><em>MSH2</em></td>
<td>2,841</td>
<td>2,101-3,846</td>
</tr>
<tr>
<td><em>MSH6</em></td>
<td>758</td>
<td>509-1,126</td>
</tr>
<tr>
<td><em>PMS2</em></td>
<td>714</td>
<td>480-1,062</td>
</tr>
<tr>
<td>Any MMR gene</td>
<td>279</td>
<td><strong>192-403</strong></td>
</tr>
</tbody>
</table>
CRC prevention: colonoscopy

Goals of colonoscopy:
- **Reduce incidence**: early detection + resection (precursors)
- **Reduce mortality**: early detection (precursors + localized CRC)

Coloscopy 1-2 years
Starting: 20-25 y-o

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Weight</th>
<th>Odds ratio M-H, random, 95% CI</th>
<th>Odds ratio M-H, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrigoni et al. 2004</td>
<td>2 199</td>
<td>5 132</td>
<td>15.3%</td>
<td>0.26 [0.05, 1.35]</td>
<td>-</td>
</tr>
<tr>
<td>Jablonska et al. 1995</td>
<td>9 364</td>
<td>146 239</td>
<td>21.3%</td>
<td>0.02 [0.01, 0.03]</td>
<td>-</td>
</tr>
<tr>
<td>Jarvinen et al. 2000</td>
<td>6 133</td>
<td>17 119</td>
<td>20.0%</td>
<td>0.28 [0.11, 0.78]</td>
<td>-</td>
</tr>
<tr>
<td>Stuckless et al. 2012</td>
<td>28 152</td>
<td>116 170</td>
<td>22.1%</td>
<td>0.11 [0.06, 0.18]</td>
<td>-</td>
</tr>
<tr>
<td>Stupart et al. 2009</td>
<td>14 129</td>
<td>13 49</td>
<td>20.7%</td>
<td>0.34 [0.15, 0.78]</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>977 709</td>
<td>709 100.0%</td>
<td>0.13 [0.04, 0.41]</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Total events** | 59 | 297 |
**Heterogeneity: Tau²=1.55; Chi²=40.15; df=4 (P=0.0001); I²=90%**
**Test for overall effect: Z=3.46 (P=0.0006)**

Incidence

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Weight</th>
<th>Odds ratio M-H, random, 95% CI</th>
<th>Odds ratio M-H, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrigoni et al. 2004</td>
<td>1 199</td>
<td>1 132</td>
<td>23.7%</td>
<td>0.66 [0.04, 10.67]</td>
<td>-</td>
</tr>
<tr>
<td>Jablonska et al. 1995</td>
<td>0 384</td>
<td>84 239</td>
<td>23.7%</td>
<td>0.00 [0.00, 0.04]</td>
<td>-</td>
</tr>
<tr>
<td>Jarvinen et al. 2000</td>
<td>0 133</td>
<td>9 119</td>
<td>23.4%</td>
<td>0.04 [0.00, 0.76]</td>
<td>-</td>
</tr>
<tr>
<td>Stupart et al. 2009</td>
<td>3 129</td>
<td>6 49</td>
<td>22.2%</td>
<td>0.17 [0.04, 0.71]</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>825 539</td>
<td>100 100.0%</td>
<td>0.06 [0.00, 0.93]</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Total events** | 4 | 100 |
**Heterogeneity: Tau²=5.95; Chi²=15.33; df=3 (P=0.002); I²=80%**
**Test for overall effect: Z=2.01 (P=0.04)**

Mortality

OR=0.13 (0.04-0.41)

OR=0.06 (0.0-0.93)

2 ESGE recommends the routine use of high definition systems and pancolonic conventional or virtual (narrow band imaging [NBI], i-SCAN) chromoendoscopy in patients with known or suspected Lynch syndrome (strong recommendation, low quality evidence).

Kaminsky et al. Endoscopy 2014

Ladabaum et al. Gastro 2015
Incident vs PCCRC

INCIDENT COLORECTAL CANCER (=PCCRC)
All CRC detected under colonoscopy screening/surveillance

INTERVAL CANCER
CRC detected before recommended screening/surveillance interval

<table>
<thead>
<tr>
<th>Incident CRC</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>PCCRC subcategories</th>
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<tbody>
<tr>
<td>Incident CRC</td>
</tr>
<tr>
<td>Non-interval type</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interval type</th>
<th>Type A</th>
<th>Type B</th>
<th>Type C</th>
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</thead>
<tbody>
<tr>
<td>Detected before recommended screening/surveillance interval</td>
<td>Detected at recommended screening/surveillance interval</td>
<td>Detected after recommended screening/surveillance interval</td>
<td>Where no screening/surveillance interval had been recommended</td>
</tr>
</tbody>
</table>

Rutter M. Gastroenterology 2018
Incident CRC under surveillance colonoscopy

- Mecklin JP et al. Gastro 2007: 35% at age 60 for males, 22% at age 60 for females.
- Engel et al. Gastro 2018: 8.4% after 10 y f-u.
- Møller P et al. Gut 2017: At age 70 y-o close to 45%.
Incident CRC under surveillance colonoscopy

Conclusions: The hypothesis that the high incidence of CRC in *path_MLH1* carriers was caused by a higher incidence in the Finnish series was not valid. We discuss whether the results were influenced by methodological shortcomings in our study or whether the assumption that a shorter interval between colonoscopies leads to a lower CRC incidence may be wrong. This second possibility is intriguing, because it suggests the dogma that CRC in *path_MLH1* carriers develops from polyps that can be detected at colonoscopy and removed to prevent CRC may be erroneous. In view of the excellent 10-year overall survival in the Finnish and non-Finnish series we remain strong advocates of current surveillance practices for those with LS pending studies that will inform new recommendations on the best surveillance interval.

Thus, one may speculate that MMR mutation carriers are capable of producing CRC not only inside an adenoma but also independently of a macroscopically visible adenoma, which in turn may rise as cancer-associated mortality, the high frequency of interval cancers in patients under regular colonoscopic surveillance with polypectomy suggests that a significant proportion of colorectal lesions are undetectable by colonoscopy and subsequently manifest as cancer within surveillance intervals.
No difference in **TNM stages** (stage IV: 1% Germany, 3% Dutch; 1% Finnish)

**Stage IV** not related with interval since last colonoscopy (overall....not case by case analysis)
Lack of association between screening interval and cancer stage in Lynch syndrome may be accounted for by over-diagnosis; a prospective Lynch syndrome database report

No difference in Stage III and IV; p=0.34

We do not have detailed information on caecal intubation rate, success of bowel preparation or previous adenoma detection rate that are acknowledged key performance indicators associated with colonoscopy quality in sporadic CRC prevention [24]. Although there is limited evidence that they may be associated with the risk of CRC in LS [25], we have no reason to assume that our observation that stage distribution is similar across the different surveillance intervals, is biased by the lack of these data.
CRC prevention in Lynch syndrome

Colonoscopy has reached its limits!

Are you doing it right?

Epidemiologist/Geneticist

Gastroenterologist
What do we know about CRC in LS?

- **Adenoma** is the main precursor, with **rapid progression to carcinoma**. Dwell-time 35.2±22.3 months for CRC (Edelstein et al. CGH 2011). >2/3 CRC occur in the proximal colon.

- **Serrated lesions** prevalence is comparable with the general population (Vleugels JLA et al. Gastro Endoscopy 2018), and do not display MMR deficiency.

- **MMR deficiency** is present in around 75% of adenomas from LS patients (Ahadova et al. IJC 2018), more frequently in the advanced ones (MMR has been seen as a non-initiating event that may accelerate progression to cancer).

- **MMR deficient crypt foci** (colonic crypts with lack of protein expression) exist in the apparently normal colon (Kloor M et al. Lancet Oncol 2012): main precursors??

  - Proximal location
  - Non-polypoid appearance: OR= 3.6 95%CI 1.9-6.8 p<0.001
  - Proximal non-polypoid appearance: OR=6.9 95%CI 2.9-16.4 p<0.001
  - Adenomas containing HGD > frequently non-polypoid
  - Overall, features that makes them difficult to identify....
Model of CRC carcinogenesis in LS

Normal mucosa → Adenoma MMR proficient → Adenoma MMR deficient → Carcinoma

ACF MMR deficient

"non-polypoid pathway"
"invisible lesions"

<3 years

Adapted from Ahadova t al. IJC 2018
Main cause of incident CRC during surveillance? Quality of colonoscopy vs. “invisible pathway”

- Unclear which factor contribute the most to the development of incident CRC in LS.
- Likely cause of interval CRC in screening colonoscopies:
  - Missed lesions: 58%
  - Inadequate exam/surveillance: 20%
  - Incomplete resection: 9%
  - New lesions: 14%

Robertson. Gut 2013
Le Clerq. Gut 2014

- Understanding how LS cancers arise will help to more effectively prevent CRC.
- Most studies focused on incidence of CRC in large cohorts of Lynch syndrome patients under surveillance have not focused on colonoscopy QUALITY.
Quality in colonoscopy: 7 domains

- Detection and resection of lesions is highly variable among endoscopist

- ADR → inverse correlation with interval cancer INCIDENCE and MORTALITY

Kaminski et al. Endoscopy 2017
Kahi et al. CGH 2011
Pohl et al. Gastroenterology 2013
Kaminski et al. NEJM 2010
Corley et al. NEJM 2014
Evidence of quality issues in LS surveillance

- **Completeness of colonoscopy**
  - Up to 30% of incident CRC in LS had either incomplete colonoscopy or missing info (Dutch registry)
  - Up to 30% of LS colonoscopies in LS are either incomplete or info is missing (Manchester Familial CRC registry)

- **Bowel preparation**
  - Up to 50% of incident CRC in LS, previous colonoscopy had either missing info or poor prep (Dutch registry)
  - Up to 25% of LS colonoscopies in LS have either poor prep or missing info (Manchester Familial CRC registry; Specialized French Network)

- **Surveillance interval**
  - Up to 40% of LS have inappropriate surveillance (Manchester Familial CRC Registry: 32%; US Cancer Genetic Clinics: 27%; Specialized French network: 37.6% of patients.
  - PLSD: 69% of incident CRC had an interval between last colonoscopy and CRC >2 years

Based on these data, it is likely that a meaningful proportion of colonoscopies in Lynch syndrome patients have poor quality....
Impact of quality in CRC incidence in Lynch syndrome under surveillance

Ariadna Sánchez, Leticia Moreira, Maria Pellisé, Evelien Dekker, Victorine Roos, Gabriel Capellà, Marta Pineda, EPICOLON researchers, Francesc Balaguer
Number of centers: 26
Total number of carriers: 1,700
Total number of CRC: 900
Total number of extracolonic tumors: 815
Total number of colonoscopies: 7,400

<table>
<thead>
<tr>
<th>Population</th>
<th>894 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>519 women (58%)</td>
</tr>
<tr>
<td>Genes</td>
<td></td>
</tr>
<tr>
<td>MLH1</td>
<td>301 (33.6%)</td>
</tr>
<tr>
<td>MSH2</td>
<td>329 (36.8%)</td>
</tr>
<tr>
<td>MSH6</td>
<td>195 (21.8%)</td>
</tr>
<tr>
<td>PMS2</td>
<td>54 (6%)</td>
</tr>
<tr>
<td>EPCAM</td>
<td>15 (1.6%)</td>
</tr>
<tr>
<td>CRC</td>
<td>344 patients (38.5%)</td>
</tr>
<tr>
<td>Other neoplasms</td>
<td>321 patients (35.9%)</td>
</tr>
</tbody>
</table>
CRC definitions

<table>
<thead>
<tr>
<th>CRC</th>
<th>344 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalent CRC</td>
<td>316 (408 tumors)</td>
</tr>
<tr>
<td>Incident CRC</td>
<td>27 (28 tumors)</td>
</tr>
</tbody>
</table>

First colonoscopy

Prevalent CRC

Incident CRC

Surveillance colonoscopies

Healthy carriers (n=577)

Timeline
<table>
<thead>
<tr>
<th></th>
<th>Prevalent CRC (n=894)</th>
<th>Incident CRC (n=577)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>316 (35.3%)</td>
<td>27 (4.6%)</td>
<td></td>
</tr>
<tr>
<td>Tumors</td>
<td>408</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>48.37 (SD ± 12.867)</td>
<td>49.29 (SD ± 8.96)</td>
<td>ns</td>
</tr>
<tr>
<td>Gender</td>
<td>143 women (45.3%)</td>
<td>16 women (55.2%)</td>
<td>ns</td>
</tr>
<tr>
<td>Genes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLH1</td>
<td>127 (40%)</td>
<td>12 (44.4%)</td>
<td>ns</td>
</tr>
<tr>
<td>MSH2</td>
<td>115 (36.4%)</td>
<td>13 (48.1%)</td>
<td></td>
</tr>
<tr>
<td>MSH6</td>
<td>46 (14.5%)</td>
<td>2 (7.4%)</td>
<td></td>
</tr>
<tr>
<td>PMS2</td>
<td>20 (6.3%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>EPCAM</td>
<td>8 (2.5%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>108 (30.3%)</td>
<td>16 (59.25%)</td>
<td>0.02</td>
</tr>
<tr>
<td>II</td>
<td>135 (37.9%)</td>
<td>6 (22.2%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>96 (26.9%)</td>
<td>5 (18.5%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>17 (4.7%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>255 (64.5%)</td>
<td>23 (82.1%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Descending</td>
<td>33 (8.3%)</td>
<td>2 (7.1%)</td>
<td></td>
</tr>
<tr>
<td>Recto-sigmoid</td>
<td>107 (27%)</td>
<td>2 (7.1%)</td>
<td></td>
</tr>
</tbody>
</table>
Lifetime CRC incidence by gene

\[ p = 0.0011 \]
CRC incidence by gene (COX)

Adjusting by:
- Age at inclusion
- Gender
- Hospital
- Patient aged 41
Colonoscopy data on surveillance (n=577)

- Number of colonoscopies per patient: **4.13 (SD 2.9)**
- Total colonoscopies: **2,145**
- Quality:
  - Complete: 2,100 (97.9%)
  - Adequate bowel prep (ABP): 1,923 (89.7%)
  - High Definition (HD): **689 (32.1%)**
  - Chromoendoscopy: **503 (23.4%)**
  - Complete + ABP: **1898 (88.5%)** → 11.5% NOT OK
  - Complete + ABP + HD or chromoendoscopy: **715 (33.3%)** → 67.3% NOT OK
- Interval between colonoscopy (mean): 18.2 months (SD 13.98)
Results (per colonoscopy)

• Total number of colonoscopies: 2,145

• Normal: 1436 (67 %)

• Polyps: 680 (31.7%)
  – Serrated lesions: 258 (12%)
  – Adenomas: 446 (20.8%)
    • 70% 1 adenoma / 15% 2 adenomas / >5 adenomas 4%
    – Advanced adenomas: 77 (3.6%)

• CRC: 28 (1.3%)
Colonoscopy in patients with incident CRC

- Number of previous colonoscopies: \textbf{4.41} (SD 3.153) (all at least 2 previous colonoscopies)
- Age at first colonoscopy: 42.26 (SD 9.77)
- Quality:
  - Complete: 24 (88.8%)
  - Adequate bowel prep (ABP): 21 (77.7%)
  - High Definition (HD): 3 (11.1%)
  - Chromoendoscopy (CE): 2 (7.4%)
  - Complete + ABP: 21 (77.7%)  $\Rightarrow$ 22.3% NOT OK
  - Complete + ABP + HD or CE: 3 (11.1%)  $\Rightarrow$ 89.9% NOT OK
- Time interval: \textbf{32.44 months (SD 45.13)}
Quality in previous colonoscopy to CRC

**Standard quality**
(complete + bowel prep ok)

- Yes: 1.5
- No: 2.9

\( p=0.15 \) OR: 1.9 (0.78 – 4.63)

**High quality**
(complete + bowel prep ok + HD/CE)

- Yes: 2.2
- No: 0.6

\( p=0.028 \) OR: 3.48 (1.05 – 11.47)
Interval between CRC and previous colonoscopy

**Previous colonoscopy performed <24 months**

\[ p = 0.001 \ \text{OR: 3.36 (1.57 – 7.18)} \]

**Previous colonoscopy performed <36 months**

\[ P < 0.0001 \ \text{OR: 6.25 (2.82 – 13.83)} \]
Quality of colonoscopy and polyp detection

**Standard quality**
(complete + bowel prep ok)

**High quality**
(complete + bowel prep ok + HD/CE)

\[ p = 0.639 \]

\[ p < 0.0001 \text{ OR } 1.64 \ (1.35 - 1.98) \]
Incident CRC stage and previous colonoscopy interval
## Incident CRC stage, previous colonoscopy interval, and QUALITY

<table>
<thead>
<tr>
<th></th>
<th>&lt;12</th>
<th>12-24</th>
<th>24-36</th>
<th>36-60</th>
<th>&gt;60</th>
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<tr>
<td>I</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>II</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>III</td>
<td>1</td>
<td>1*</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- Previous colonoscopy (13 months) bowel prep ok, but 24 months earlier 15 mm adenoma in the same segment
- Previous colonoscopy bowel prep poor

In 3/5 previous colonoscopy bowel prep poor
Conclusions

• **Quality issues** in colonoscopy surveillance in Lynch syndrome carriers exist and may explain at least in part the cause of incident CRC during surveillance (BIAS OF PREVIOUS STUDIES).

• Pending analysis:
  – Whole cohort (n=1700)
  – Multivariate analysis (age, previous adenomas, gene, ascertainment, etc).

• **Optimization** of colonoscopy performance could further **reduce the risk during surveillance**.
  ✓ Need for coordinated management (referring physician and endoscopy)
  ✓ Dedicated high-risk clinics or networks are more likely to follow high quality standards in high-risk patients
  ✓ Colonoscopy quality should be at least reach (if not exceed) the KPIs required for sporadic colonoscopy.
  ✓ Colonoscopy performed by high detectors with high-proficiency in the detection and resection of non-polypoid lesions.