Risk Factors and Chemoprevention of Colon Cancer in IBD

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The Incidence of CRC in UC is Declining

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>10 yrs</th>
<th>20 yrs</th>
<th>30 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eaden ‘01</td>
<td>Meta-anal.</td>
<td>1.6%</td>
<td>8.3%</td>
<td>18.4%</td>
</tr>
<tr>
<td>Winther ‘04</td>
<td>Denmark</td>
<td>0.4%</td>
<td>1.1%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Rutter ‘06</td>
<td>St. Mark’s</td>
<td>0%</td>
<td>2.5%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Lakatos ‘06</td>
<td>Hungary</td>
<td>0.6%</td>
<td>5.4%</td>
<td>7.5%</td>
</tr>
</tbody>
</table>

Nonetheless, IBD patients are still considered to be at high risk for CRC.
## CRC Risk in UC: Declining over the Decades

<table>
<thead>
<tr>
<th>Decade</th>
<th>No of Studies</th>
<th>Patient-Years</th>
<th>No of CRC cases</th>
<th>Incidence rate per 1000 py</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950s</td>
<td>3</td>
<td>4,750</td>
<td>22</td>
<td>4.29 (0.95-7.64)</td>
</tr>
<tr>
<td>1960’s</td>
<td>7</td>
<td>19,304</td>
<td>80</td>
<td>4.18 (2.67-5.68)</td>
</tr>
<tr>
<td>1970’s</td>
<td>4</td>
<td>12,909</td>
<td>40</td>
<td>3.22 (0.67-5.77)</td>
</tr>
<tr>
<td>1980’s</td>
<td>14</td>
<td>123,866</td>
<td>310</td>
<td>2.58 (1.81-3.34)</td>
</tr>
<tr>
<td>1990’s</td>
<td>12</td>
<td>87,499</td>
<td>132</td>
<td>1.53 (1.06-2)</td>
</tr>
<tr>
<td>2000’s</td>
<td>23</td>
<td>369,829</td>
<td>525</td>
<td>1.29 (1-1.58)</td>
</tr>
<tr>
<td>2010-2013</td>
<td>18</td>
<td>861,478</td>
<td>1,180</td>
<td>1.21 (0.95-1.48)</td>
</tr>
</tbody>
</table>

## Risk of CRC in IBD: Factors that \textit{Increase} Risk

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration &gt;8-10 years</td>
<td>2.4-2.8</td>
</tr>
<tr>
<td>Extent of colitis:</td>
<td></td>
</tr>
<tr>
<td>• pancolitis</td>
<td>14.8</td>
</tr>
<tr>
<td>• left-sided</td>
<td>2.8</td>
</tr>
<tr>
<td>• proctitis</td>
<td>1.7</td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
<td>4.8</td>
</tr>
<tr>
<td>Family history of colon cancer:</td>
<td></td>
</tr>
<tr>
<td>• Age &gt;50</td>
<td>2.5</td>
</tr>
<tr>
<td>• Age &lt;50</td>
<td>9.2</td>
</tr>
</tbody>
</table>

Farraye, Odze, Eaden, Itzkowitz. AGA Technical Review on the diagnosis and management of colorectal neoplasia in IBD. \textit{Gastroenterology} 138:746-74, 2010
### Risk of CRC in IBD: Factors that *Increase* Risk

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active inflammation</strong></td>
<td></td>
</tr>
<tr>
<td>• Histologic</td>
<td>3.0-5.1</td>
</tr>
<tr>
<td>• Colonoscopic</td>
<td>2.5</td>
</tr>
<tr>
<td><strong>Anatomical abnormalities</strong></td>
<td></td>
</tr>
<tr>
<td>• Foreshortened colon</td>
<td>28.4</td>
</tr>
<tr>
<td>• Stricture (UC)</td>
<td>5.7</td>
</tr>
<tr>
<td>• Pseudopolyps</td>
<td>2.1-2.5</td>
</tr>
<tr>
<td><strong>History of dysplasia</strong></td>
<td>9</td>
</tr>
</tbody>
</table>

Farraye, Odze, Eaden, Itzkowitz. AGA Technical Review on the diagnosis and management of colorectal neoplasia in IBD. *Gastroenterology* 138:746-74, 2010
Risk of CRC in IBD: Factors that *Decrease* Risk

- Surveillance colonoscopy
- Regular doctor visits (some studies)
- Chemoprevention
  - 5-ASA: Probably not
  - Immunomodulators: Probably
  - Ursodiol: Yes (in PSC patients)
  - Anti-TNFs: Insufficient data
  - Steroids: Maybe
  - Folate: Maybe
Evidence To Support Surveillance Colonoscopy in IBD

- No randomized studies
- No cohort studies (except chromoendoscopy)
- Circumstantial evidence
  - Case-Control studies
  - Decision Analysis Studies
  - Faulty comparisons of surveillance-detected vs. symptomatic cancers

Farraye, Odze, Eaden, Itzkowitz. AGA Technical Review on the diagnosis and management of colorectal neoplasia in IBD. Gastroenterology 138:746-74, 2010
AGA: Recommended Surveillance Practice 2010

- Begin at 8 years of colitis (all patients except proctitis)
  - for PSC: at time of PSC diagnosis
- Repeat colonoscopy every 1-2 years.
  - Consider shorter interval if: active inflammation,
    (+) family hx of CRC, PSC, stricture, pseudopolyps
- Representative bx’ es from each colonic segment
  - chromoendoscopy if have expertise
- Attention to polyps/raised lesions
  - Biopsy flat mucosa adjacent to polypectomy sites
- Do for Crohn’s colitis what you would do for UC

Farraye, Odze, Eaden, Itzkowitz. AGA Technical Review on the diagnosis and management of colorectal neoplasia in IBD. Gastroenterology 138:746-74, 2010
BSG 2010 IBD Surveillance Guidelines

Screening Colonoscopy at 10 Years (preferably in remission; pancelonic dye spray)

Lower Risk
- Extensive UC; inactive histo/endo inflamm.
- Left-sided colitis
- Crohn’s colitis < 50% colon

Intermediate Risk
- Extensive UC; mildly active histo/endo inflamm.
- Post-inflammatory polyps
- FH CRC age >50

Higher Risk
- Extensive UC; mod-severe histo/endo inflamm.
- Stricture in past 5 yrs
- Dysplasia in past 5 yrs declining surgery
- PSC
- FH CRC age <50

Cairns et al. Gut 59:666-690, 2010
British Society of Gastroenterology: 2010 IBD Surveillance Guidelines

• Biopsy Protocol
  – Pancolonic dye spray with targeted biopsy of abnormal areas (Grade A recommendation)
  – Otherwise, 2-4 random biopsies from every 10 cm.

• Other considerations
  – Patient preference
  – Multiple post-inflammatory polyps
  – Age
  – Co-morbidity
  – Accuracy and completeness of examination

Cairns et al. Gut 59:666-690, 2010
Problems with BSG Guidelines

• Starting at 10 yrs will miss some cancers.
  – 17% of CRC diagnosed before 10 yrs of disease (Lutgens et al. Gut, 2008)

• Interval cancers often occur approx. 2 yrs after the last colonoscopy

• Assumes that quiescent disease is low risk.

• Limited evidence to support changing the surveillance interval based on:
  – family history: only one study stratified risk based on age of FDR with CRC
  – endoscopic appearance of the colon
Chemoprevention in IBD: Mechanisms

• Medicines reduce inflammation, thereby lowering carcinogenesis
• Medicines have direct anti-tumor effect
• Mucosal healing allows better detection of dysplastic lesions by colonoscopy.
• Agents that have been most studied:
  – 5-ASA
  – Thiopurines
  – Ursodeoxycholic acid
  – Anti-TNFs
Chemoprevention in IBD: 5-ASA

• Mechanisms:
  – Promote healing (anti-inflammatory)
  – Anti-tumor effects:
    » Promote cell cycle arrest; improve DNA replication fidelity; inhibit COX-2; scavenge oxygen radicals; induce PPAR-gamma.

• Results:
  – Pooled adjusted OR: 0.95 (0.66-1.38)
  – Clinic-based studies OR: 0.58 (0.45-0.75)

Chemoprevention in IBD: Thiopurines

- **Mechanisms:**
  - Promote healing (anti-inflammatory)

- **Results: (meta-analysis)**
  - Overall: OR: 0.71 (0.54-0.94)
  - Case control studies: OR: 0.46 (0.29-0.74)
  - Cohort studies OR: 0.96 (0.94-0.98)

Gong et al. PLOS-One 8:e81487, 2014
Thiopurines to Prevent CRC: Meta-analysis

Overall: 0.71 (0.54, 0.94)
Case-Control: 0.46 (0.29, 0.74)
Cohort: 0.96 (0.94, 0.98)

Gong et al. PLOS-One 8:e81487, 2014
Chemoprevention in IBD: Anti-TNFs

• Mechanisms:
  – Promote healing (anti-inflammatory)
  – Anti-tumor effect (?)

• Results: (conflicting)
  – Dutch case-control: OR 0.09 (0.01-0.68)
  – Danish pop’n base: RR 1.06 (0.33-3.40)

SUMMARY

1. Patients with both longstanding UC and Crohn’s colitis have an increased risk of CRC.
2. Although the risk of dysplasia/CRC in IBD may be decreasing, IBD is still a high risk condition.
3. Preventing dysplasia/CRC with medications is controversial:
   • Thiopurines: probably preventive
   • 5-ASA: probably not
   • Ursodeoxycholic acid: probably (in PSC only)
   • Anti-TNF: insufficient data
4. Therefore, careful surveillance colonoscopy is important