Primary sclerosing cholangitis, colitis and cancer

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Objectives

♦ Risk factors for colorectal cancer
♦ Colitis-associated colon cancer vs sporadic colon cancer
♦ Preventive strategies
  - Surveillance
  - Surgery
  - Pharmacologic agents
    • Folic acid
    • Ursodeoxycholic acid
    • 5-ASA
Inflammatory Bowel Disease (IBD) accounts for 1-2% of all cases of Colorectal Cancer (CRC) in the general population.

CRC accounts for one in six of all deaths in IBD patients.

Irrespective of actual incidence, CRC has a profound impact on patients’ psychological well-being³,⁴

Disease Distribution at Presentation

- Pancolitis: 37%
- Left-sided: 17%
- Proctitis: 46%

n=1116

Endoscopic Spectrum of Severity
UC – Spectrum of Disease

Normal

Mild

Moderate

Severe

Risk Factors
## Risk Factors in the Development of CRC in UC

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent of disease&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>++++</td>
</tr>
<tr>
<td>Duration of disease&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>++++</td>
</tr>
<tr>
<td>Presence of PSC&lt;sup&gt;3&lt;/sup&gt;</td>
<td>+++</td>
</tr>
<tr>
<td>Young age at onset&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>++</td>
</tr>
<tr>
<td>Colonic stricture</td>
<td>++</td>
</tr>
<tr>
<td>Positive family history&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>+</td>
</tr>
<tr>
<td>Severity of inflammation&lt;sup&gt;4&lt;/sup&gt;</td>
<td>+</td>
</tr>
<tr>
<td>Psuedopolyps</td>
<td>+/-</td>
</tr>
<tr>
<td>Backwash ileitis&lt;sup&gt;5,6&lt;/sup&gt;</td>
<td>+/-</td>
</tr>
</tbody>
</table>

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PSC increases cancer risk in colitis
PSC increases cancer risk in colitis
Figure 5  Routine screening/surveillance investigations in asymptomatic patients with primary sclerosing cholangitis (PSC). IBD, irritable bowel disease; USS, ultrasonography.
Why is risk higher in PSC?

- Milder disease (paradoxical)
- Subclinical disease – less treatment
- Fewer early colectomies
- Immuno-suppression (transplant)
- Mutations that cause cancer in PSC also cause cancer in colitis
- Carcinogenic bile acids (more right sided disease)
Prevalence and Cumulative Risk of Developing CRC in UC

Overall prevalence of CRC

- Any UC patient: 4%
- Pancolitis: 6%

Cumulative Risk of CRC

- 10 Years: 2%
- 20 Years: 5%
- 30 Years: 20%

Relative Risk of CRC Based on Extent of UC

- All Cases
- Proctitis
- Left-Sided
- Pancolitis

Standardized incidence ratio
Sporadic Colon Cancer

vs.

Colitis-associated Colon Cancer
Molecular Progression of UC to CRC

- Normal Epithelium
- Inflamed Epithelium
- Indefinite Dysplasia
- Low-Grade Dysplasia
- High-Grade Dysplasia
- Cancer

- Aneuploidy
- Sialosyl-Tn

- p53
- K-ras
- C-src
- Microsatellite Instability

- APC
- Rb and Other TSG
### Sporadic Colon Cancer (SCC) vs. Colitis-associated Colon Cancer (CAC)¹

<table>
<thead>
<tr>
<th>SCC</th>
<th>CAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>♦ Only 3-5% experience multiple synchronous colon cancers</td>
<td>♦ Approximately 12% experience multiple synchronous colon cancers</td>
</tr>
<tr>
<td>♦ Mean age-60’s</td>
<td>♦ Mean age-30 to 40’s</td>
</tr>
<tr>
<td>♦ Left sided predominance</td>
<td>♦ More uniformly throughout the colon</td>
</tr>
<tr>
<td></td>
<td>♦ More right-sided in IBD pts. with PSC²</td>
</tr>
</tbody>
</table>

1 Itzkowitz SH. *Gastro Clin of NA* 1997;26:129-139  
Prevention of CRC
Prevention of CRC

♦ Secondary Prevention
  - Surveillance
  - Surgery
    - Polypectomy
    - Colectomy

♦ Primary Prevention
  - Prophylactic colectomy (rarely used)
  - Pharmacologic agents (chemoprevention)
Surveillance
Surveillance Recommendations

♦ Colonoscopy:

- UC - After 8-10 years of colitis, annually or biannually with multiple biopsies at regular intervals
- PSC – begin in patients with colitis at the first year of diagnosis then annually
- Evidence is not sufficiently strong to justify different guidelines for left-sided colitis vs pancolitis

Surveillance Recommendations

♦ Biopsies:

- Four every 10 cms from cecum to rectum
- Additional samples of the rectosigmoid area may be advocated
- Polyps should be assessed and removed separately
  - with sampling of surrounding flat mucosa.

Surveillance May Decrease the Risk or Mortality of Colon Cancer

Results from an 18 year surveillance program in the US

Limitations of Surveillance

♦ Dysplasia may be missed when obtaining biopsies

♦ Intra- and inter-observer variation in interpretation of dysplasia

♦ Patient Compliance

♦ High Cost to Benefit Ratio

Surgery
Surgery

♦ Colectomy
  - Recommended for patients with low-grade dysplasia, high-grade dysplasia, DALMs, or cancer

♦ Polypectomy
  - Adenoma-like DALM?
Pharmacologic Agents
# Prevention of Colorectal Cancer

- Pharmacologic agents (chemoprevention)

<table>
<thead>
<tr>
<th>Sporadic Colon Cancer</th>
<th>Colitis-associated Colon Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Folic Acid</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Ursodeoxycholic acid</td>
</tr>
<tr>
<td>Calcium / Vitamin D</td>
<td>5-ASA</td>
</tr>
<tr>
<td>Folic Acid</td>
<td></td>
</tr>
<tr>
<td>CEE + MPA (Prempro®)</td>
<td></td>
</tr>
</tbody>
</table>
Folic Acid


Retrospective case-control

Relative Risk

0.0 0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8

0.4 mg Folic acid 1 mg Folic acid

0.76 0.54

P=NS
Ursodeoxycholic acid (UDCA)

Relative Risk = 0.26 (95% CI, 0.06 - 0.92; p=0.034)

Ursodeoxycholic acid (UDCA)

- Less severe dysplasia – less mortality

Figure 3  Kaplan–Meier estimates of proportion of patients without dysplasia and carcinoma after taking ursodeoxycholic acid (Urso) or placebo. From Pardi et al. Reproduced with permission from Elsevier.
5-ASA
5-ASA Mechanism of Action in CRC Prevention

- Precise mechanism unknown
- Proposed mechanisms
  - Oxygen radical scavenger\(^3\)
  - Increased apoptosis, decreased proliferation\(^1,2\)
  - Inhibition of production of prostaglandins, and leukotrienes\(^3\)
  - Improvement in DNA repair\(^4\)
  - Block stem cell activation

## 5-ASA Summary

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>% Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pinczowski</td>
<td>sulfasalazine</td>
<td>62</td>
</tr>
<tr>
<td>Eaden</td>
<td>Various 5-ASAs (various doses)</td>
<td>53</td>
</tr>
<tr>
<td>Eaden</td>
<td>Mesalamine (≥ 1.2 g/day)</td>
<td>81</td>
</tr>
<tr>
<td>Rubin</td>
<td>Various 5-ASAs (≥ 1.2 g/day)</td>
<td>72</td>
</tr>
<tr>
<td>Bernstein</td>
<td>Various 5-ASAs (various doses)</td>
<td>----</td>
</tr>
</tbody>
</table>
The risk for colorectal cancer is higher in patients with PSC and colitis.

Early detection of "subclinical" disease is crucial for detection.

Patients must be monitored early and often.

Treatment with UDCA and 5-ASA likely reduces cancer risk independent of its anti-inflammatory effect.

The higher cancer risk in PSC/UC patients raises the likelihood that early colectomy will reduce the risk for colitis-induced cancer.
Forefront – Detecting activated stem cells in PSC – then preventing their activation!