Can We Prevent IBD-Related Colorectal Cancer with 5-ASA, AZA, or 6MP?
The Clinical Evidence

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Can We Prevent IBD-Related Colorectal Cancer with 5-ASA, AZA, or 6MP? The Clinical Evidence

<table>
<thead>
<tr>
<th>Make observation in the Lab</th>
<th>Does this observation exist in patients?</th>
<th>Test observation in patients</th>
<th>Adopt observation into clinical practice</th>
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<tr>
<td>Experimental Studies</td>
<td>Epidemiologic Studies</td>
<td>Interventional Studies</td>
<td></td>
</tr>
<tr>
<td>Animal Studies</td>
<td>“Translational” Studies</td>
<td>(Randomized Control Trial)</td>
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<td>Mechanism of Action</td>
<td>Epidemiologic Causality</td>
<td>Highest Level of Clinical Evidence to Argue Causality</td>
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Can We Prevent IBD-Related Colorectal Cancer with 5-ASA, AZA, or 6MP? The Clinical Evidence

Make observation in the Lab
- Experimental Studies
- Animal Studies

Does this observation exist in patients?
- Epidemiologic Studies
- “Translational” Studies

Test observation in patients
- Interventional Studies (Randomized Control Trial)

Adopt observation into clinical practice
- Mechanism of Action
- Biological Plausibility
- Highest Level of Clinical Evidence to Argue Causality
Can We Prevent IBD-Related Colorectal Cancer with 5-ASA, AZA, or 6MP? The Clinical Evidence

1. Make observation in the Lab
   - Experimental Studies
   - Animal Studies

2. Does this observation exist in patients?
   - Mechanism of Action
   - Biological Plausibility
   - Epidemiologic Studies
   - “Translational” Studies

3. Adopt observation into clinical practice
   - Epidemiologic Causality
   - Biological Plausibility
Can We Prevent IBD-Related Colorectal Cancer with 5-ASA, AZA, or 6MP? The Clinical Evidence

Make observation in the Lab

Experimental Studies
Animal Studies

Does this observation exist in patients?

Epidemiologic Studies
“Translational” Studies

Adopt observation into clinical practice

“Crime Scene Evidence”

“Circumstantial Evidence”

“Direct Evidence”
Confession, Eye-Witness, “smoking gun”

“Guilty?”
Background

- Six-fold increased risk of colorectal cancer in UC and Crohn’s of the colon
- 5-Aminosalicylic acid
  - Cornerstone therapy for UC and used for Crohn’s affecting the colon
- AZA/6MP
  - Related thiopurine analogues used to treat UC and CD for over 30 years

Canavan C et. al. Aliment Pharmacol Ther 2006; 25: 1097-104
Lichtenstein G et. al. Gastroenterol 2006; 130: 940-987
Definition of chemoprevention

• National Cancer Institute USA
  – The use of drugs, vitamins, or other agents to try to reduce the risk of, or delay the development or recurrence of cancer

• Examples
  – Non-IBD : ASA/ NSAIDs, Calcium
  – IBD: 5-ASA, AZA/6MP

-CCFA Consensus Conference on Colorectal Cancer Screening and Surveillance. Inflamm Bowel Dis 2005; 11(3): 314
Years covered: 1965-1983
Design: nested case-control (population cohort 3112 UC pts)
Setting: Uppsala Sweden (population)
102 CRC/UC cases vs. 196 matched UC controls

<table>
<thead>
<tr>
<th>Exposure</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3 months sulfasalazine</td>
<td>1.0</td>
<td>-</td>
</tr>
<tr>
<td>&gt; 3 months sulfasalazine</td>
<td>0.4</td>
<td>0.2-0.7</td>
</tr>
</tbody>
</table>

“Clinical trials should be initiated in patients with inactive UC to determine if continuous treatment with sulfasalazine...have an impact on dysplasia or malignant transformation”

On ASA:
“These data further support the hypothesis that aspirin has an antineoplastic effect in the large bowel. Nevertheless, the question of whether aspirin should be used to prevent large-bowel tumors would be best answered by a randomized controlled clinical trial specifically designed to address this issue”–Greenberg et al, 1993 JNCI

Pinczowski et al, Gastroenterol 107:117, 1994
Adherence to 5-ASA reduces the risk of CRC

Years covered: 1972-1981
Design: cohort (175 pts with CUC)
Setting: Leicestershire UK (community)
152 compliant vs. 16 non-compliant

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<tr>
<th>Exposure</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noncompliant sulfasalazine</td>
<td>1.0</td>
<td>-</td>
</tr>
<tr>
<td>Compliant sulfasalazine</td>
<td>0.1</td>
<td>0.02-0.3</td>
</tr>
</tbody>
</table>

“This is the first study to demonstrate that UC patients that do not comply with sulfasalazine [or MD’s stopped therapy] are more likely to develop colorectal cancer than their compliant counterparts”

“The benefits of life-long sulfasalazine are likely to apply to newer 5-ASA compounds, although prospective trials are needed”

Adherence to 5-ASA reduces the risk of CRC

Years covered: 1980s
Design: case control
Setting: cases: consultant GIs across England and Wales; controls: Leicestershire IBD patient database (community)
102 UC/CRC cases vs. 102 UC controls

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<thead>
<tr>
<th>Exposure</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not regular 5-ASA use</td>
<td>1.0</td>
<td>-</td>
</tr>
<tr>
<td>Regular 5-ASA use over 5-10 years</td>
<td>0.5</td>
<td>0.2-1.0</td>
</tr>
</tbody>
</table>

“Colorectal cancer risk in patients with UC can be substantially reduced by taking 5-ASA therapy on a regular basis”

Adherence to 5-ASA reduces the risk of CRC

Years covered: 1987-2001
Design: nested case control (General Practice Research Database)
Setting: National sample UK (population)
76 UC/CRC cases with any 5-ASA use 6 months prior to diagnosis vs.
399 UC controls also with 5-ASA exposure

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<tr>
<th>Exposure</th>
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<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Irregular use 0-12 months prior</td>
<td>1.0</td>
<td>-</td>
</tr>
<tr>
<td>Regular 5-ASA use</td>
<td>0.6</td>
<td>0.4-1.0</td>
</tr>
</tbody>
</table>

“There was good concordance between regular use in the one year before CRC diagnosis and the preceding years”

“While a randomized clinical trial would clearly be the most reliable method of assessing the effects of 5-ASA therapy on CRC risk...such a trial [would be] an impossibility”

Van Staa et al, Gut 54:1573, 2005
Negative Studies of 5-ASA and Risk of CRC in CUC

**Lashner 1997-Cohort**
- **Setting:** Cleveland Clinic USA (Referral)
- Use of 5-ASA for at least 6 months vs. < 6 months
  - 29 pts UC/D-CRC cases vs. 69 UC controls
  - OR 1.0 (0.3-2.7)

**Lindberg 2001-Cohort**
- **Setting:** Stockholm Sweden (Referral)
- Surveillance colonoscopy cohort (n=143)
  - Use of 5-ASA for at least 6 months vs. < 6 months
  - 51 pts with UC/D-CRC vs. 92 UC controls
  - OR 0.6 (0.3-1.7)

**Bernstein 2003-Case-control**
- **Setting:** Manitoba, Canada (population)
  - Linked population-based pharmacy database
  - Studied 5-ASA use in patients with 2 months of use within 2 yrs of CRC diagnosis
  - 11 pts UC/CRC vs. 155 UC controls
  - OR 1.22 (0.3-4.6)

**Rutter 2004-Nested case-control**
- **Setting:** St Mark's Hospital UK (referral)
  - Surveillance colonoscopy group
  - Use of 5-ASA < 3 months vs. > 10 yrs
  - 68 cases UC/D-CRC vs. 136 UC controls
  - OR 2.1 (0.6-6.9)
Effect of Duration or Adherence of 5-ASA on CRC risk in CUC

A. Any use of at least 2-6 months

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Definition</th>
<th>Neoplasia</th>
<th>No Neoplasia</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lashner (1997)</td>
<td>&gt; 6 mo</td>
<td>26/29 (90)</td>
<td>52/68 (91)</td>
<td>0.95 (0.34-2.70)</td>
</tr>
<tr>
<td>Lindberg (2001)†</td>
<td>&gt; 6 mo</td>
<td>42/50 (84)</td>
<td>82/92 (89)</td>
<td>0.64 (0.24-1.69)</td>
</tr>
<tr>
<td>Pinczowski (1994)</td>
<td>&gt; 3 mo</td>
<td>48/102 (47)</td>
<td>140/196 (71)</td>
<td>0.38 (0.20-0.69)</td>
</tr>
<tr>
<td>Van Staa (2003)</td>
<td>&gt; 6 mo</td>
<td>NR</td>
<td>NR</td>
<td>0.54 (0.35-0.86)</td>
</tr>
<tr>
<td>Bernstein (2003)</td>
<td>&gt; 2 mo</td>
<td>5/11 (45)</td>
<td>34/155 (25)</td>
<td>1.22 (0.32-4.60)</td>
</tr>
<tr>
<td>Rutter (2004)†</td>
<td>&gt; 3 mo</td>
<td>55/68 (96)</td>
<td>122/135 (90)</td>
<td>2.05 (0.61-6.94)</td>
</tr>
</tbody>
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Adjusted summary odds ratio
P value for homogeneity

B. Any use between 2-20 years

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<tbody>
<tr>
<td>Moody (1996)†</td>
<td>Up to 20 yrs</td>
<td>5/10 (50)</td>
<td>147/158 (93)</td>
<td>0.08 (0.02-0.29)</td>
</tr>
<tr>
<td>Eaden (2000)</td>
<td>5-10 years</td>
<td>51/102 (50)</td>
<td>84/102 (82)</td>
<td>0.47 (0.22-1.00)</td>
</tr>
<tr>
<td>Van Siaa (2003)</td>
<td>&gt; 2 yrs</td>
<td>NR</td>
<td>NR</td>
<td>0.51 (0.30-0.87)</td>
</tr>
<tr>
<td>Rutter (2004)†</td>
<td>&gt;10 yrs</td>
<td>49/63 (72)</td>
<td>85/135 (63)</td>
<td>2.38 (0.67-8.54)</td>
</tr>
</tbody>
</table>

Adjusted summary odds ratio
P value for homogeneity

Velayos et al, Am J Gastro 2005; 100:1345
### Effect of Dose of Risk of CRC/Dysplasia

"More studies are needed to answer clinically important questions such as what is the chemopreventive effect of 5-ASA in different risk subgroups, when to initiate therapy, what is the dose, duration, and frequency of therapy required for an anti-tumor effect, and how long this effect lasts after discontinuing therapy."


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<th>Neoplasia</th>
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<tr>
<td>Eaden (2001)†</td>
<td>S C 2 gm/d</td>
<td>31/82 (38)</td>
<td>32/50 (64)</td>
<td>0.85 (0.32-2.26)</td>
</tr>
<tr>
<td>Eaden (2001)‡</td>
<td>M C 1.2 gm/d</td>
<td>11/61 (18)</td>
<td>38/56 (68)</td>
<td>0.19 (0.06-0.61)</td>
</tr>
<tr>
<td>Rubin (2003) †</td>
<td>M C 1.2 gm/d</td>
<td>5/26 (19)</td>
<td>49/96 (51)</td>
<td>0.28 (0.09-0.85)</td>
</tr>
</tbody>
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*Adjusted summary odds ratio*

*P value for homogeneity*
Subsequent Published Studies of 5-ASA and Colorectal Neoplasia in UC

Velayos FS et al. Gastroenterol 2006
Setting: Referral population University Setting
188 Patients with CUC-CRC and 188 controls CUC
Use >1 year 5-ASA vs. <1 year OR 0.4 (0.2-0.9)

Setting: UC Referral patients in University Setting
26 pts UC/D-CRC vs. 96 pts UC alone
Use > 1.2 gm mesalamine vs. <1.2 gm OR 0.28 (0.1-0.9)

Terdiman et al. Inflamm Bowel Dis J 2006. Nested Case-Control (ingenix database 20 million lives)
2000-2003
Setting: National sampling USA Database claims
IBD Increases risk CRC 6-7 fold
364 UC/CD-CRC; 1172 controls UC/CD
Number prescriptions 12 months prior to dx CRC: OR-0.97 (0.8-1.2)

Jess et al Am J Gastro 2007; Nested Case-Control (1940-2002)
Setting: Combined Crohn’s/CUC; Dysplasia/Cancer; Copenhagen/Olmsted Counties
43 pts UC/CD/D-CRC cases vs. 115 UC/CD controls
Sulfasalazine >2gm/d vs. <2gm/day: OR 1.0 (0.3-2.9)
Mesalamine > 1.2 gm/d vs. <1.2 gm/d OR 2.3 (0.6-9.4)
Subsequent Unpublished Studies of 5-ASA and Colorectal Neoplasia in UC

- Setting: Mt Sinai NY USA (referral)
  - 313 patients with UC without dysplasia at surveillance
  - 53 UC/D-CRC
  - $>2 \text{ gm/d mesalamine equivalents vs. } < 2 \text{ gm/d}$
  - OR 0.9 (0.5-1.8)

**Aharoni ACG 2005-Cohort (122 pts with UC or CD)**
- Setting: Maimonides/Mt Sinai NY USA (Referral)
  - 4 pts with dysplasia
  - Mean mesalamine dose Co: 2.6 gm vs. Ca: 0.8 gm ($p=0.003$)

**Smith DDW 2006 Cohort (1995-2005)**
- Setting: St Louis Univ USA (Referral)
  - 24 Patients with PSC and IBD (80% UC) already on UDCA
  - 2 pts dysplasia, 7 indefinite dysplasia
  - Any mesalamine vs. no mesalamine
  - OR 0.5 (0.2-1.6)

**Rubin DDW 2006-Case-Control**
  - 59 UC/D-CRC vs. 141 UC controls
  - Any sulfasalazine vs. none OR 0.7 (0.4-1.5)
  - Any mesalamine vs. none OR 0.3 (0.2-0.7)
Results: Primary Analysis
5-Year survival by category of prior use of 5-ASA

Velayos et al, DDW 2006
Subsequent Studies of 5-ASA and CRC in Crohn’s

Strevel EL et al-WCOG 2005
Setting: St Michael’s, Sunnybrook and Women’s Health Center-Ontario, Canada (hospital discharge 1993-2003)
65 pts (1351 CD) with cancer (26 CRC) matched 2:1 by site, duration
Overall AZA reduced risk cancer; 5-ASA no effect

Siegel et al IBD J 2006 Case-Control
Setting: Massachusetts General Hospital USA (referral)
27 pts CD-CRC cases vs.. 27 CD controls
Regular 5-ASA use vs.. not regular
OR 0.3 (0.1-1.2)
## Relationship between AZA and 6MP and Odds of CRC in CUC

<table>
<thead>
<tr>
<th>Study</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
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<tr>
<td>Rutter 2004</td>
<td>0.3</td>
<td>0.2-0.9</td>
</tr>
<tr>
<td>Croog 2005</td>
<td>0.9</td>
<td>0.5-1.8</td>
</tr>
<tr>
<td>Velayos 2006</td>
<td>3.0</td>
<td>0.7-13.6</td>
</tr>
<tr>
<td>Rubin 2006</td>
<td>0.3</td>
<td>0.1-0.7</td>
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Rutter M et al. *Gastroenterology* 2004; 126:451  
Velayos F.et al. *Gastroenterology* 2006; 130:1941  
Rubin D et al, *DDW* 2006
Can We Prevent IBD-Related Colorectal Cancer with 5-ASA, AZA, or 6MP based on the clinical evidence

Make observation in the Lab

Does this observation exist in patients?

Adopt observation into clinical practice

1. Experimental Studies
   - Animal Studies

2. Epidemiologic Studies
   - “Translational” Studies

3. Dose? Duration?
   - When to start?
   - Subgroups? AZA, too?
   - Types of future studies?

- Higher quality exposure and clinical variable source needed.

Keeping disease in remission with regular 5-ASA therapy will likely yield secondary benefit reduced CRC. Possible AZA/6MP