Mechanistic Studies of Aspirin and Prevention of Colorectal Cancer

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National Cancer Institute
Board of Scientific Advisors &
National Cancer Advisory Board
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## Colonoscopy: Effective but with limits

<table>
<thead>
<tr>
<th></th>
<th>No screening</th>
<th>Colonoscopy screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>All CRC</td>
<td>1.0</td>
<td>0.44 (0.38-0.52)</td>
</tr>
<tr>
<td>Distal colorectal</td>
<td>1.0</td>
<td>0.24 (0.18-0.32)</td>
</tr>
<tr>
<td>Proximal colon</td>
<td>1.0</td>
<td>0.73 (0.57-0.92)</td>
</tr>
</tbody>
</table>

Nishihara et al, NEJM 2013
## Aspirin and adenoma trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Duration</th>
<th>Dose</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baron, NEJM 2003</td>
<td>1121 prior adenoma</td>
<td>3 years</td>
<td>81 mg 325 mg</td>
<td>0.83 (0.70-0.98) 0.96 (0.81-1.13)</td>
</tr>
<tr>
<td>Sandler, NEJM 2003</td>
<td>635 prior CRC</td>
<td>3 years</td>
<td>325 mg</td>
<td>0.65 (0.46-0.91)</td>
</tr>
<tr>
<td>Benamouzig, Gastro 2003</td>
<td>272 prior adenoma</td>
<td>1 year</td>
<td>160 mg 300 mg</td>
<td>0.85 (0.57-1.26) 0.61 (0.37-0.99)</td>
</tr>
<tr>
<td>Logan, Gastro 2008</td>
<td>945 prior adenoma</td>
<td>3 years</td>
<td>300 mg</td>
<td>0.79 (0.63-0.99)</td>
</tr>
<tr>
<td>Ishikawa, Gut 2014</td>
<td>311 prior adenoma</td>
<td>2 years</td>
<td>100 mg</td>
<td>0.60 (0.36–0.98)</td>
</tr>
</tbody>
</table>
Study population

Nurses’ Health Study (n=121,700)

Health Professionals Follow-up Study (n=51,539)
Duration of aspirin use and risk of CRC

Multivariate relative risk

Years of regular aspirin use

P for trend = <0.0001

Chan et al, JAMA 2005
Aspirin use reduces risk of CRC: 18 year follow-up of WHS Trial

Cook et al, Ann Int Med 2013
Aspirin reduces CRC in Lynch after long-term follow-up

Intention-to-treat HR=0.63; p=.12
Poisson IRR = 0.56; p=.05

Burn et al, Lancet 2011
Nurses’ Health Study (n=121,700)

Health Professionals Follow-up Study (n=51,539)

N=1,279 with Stage I, II, III CRC
Aspirin use and CRC patient survival

Colorectal cancer-specific survival

Log-rank $P=.02$

Overall survival

Log-rank $P=.03$

Chan et al, JAMA 2009
Aspirin and risk of GI bleeding

P trend = <.0001

U.S. Preventative Services Task Force 2007

- Recommends against routine use of aspirin or NSAIDs to prevent CRC in average risk individuals
- “Harms outweigh the benefits for the prevention of CRC”
Can we exploit mechanism to personalize chemoprevention?

- Prostaglandin balance
- *Wnt* signaling
<table>
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<th>Non-Users</th>
<th>Regular Users</th>
</tr>
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<tbody>
<tr>
<td>All CRC</td>
<td>1.0</td>
<td>0.73 (0.62-0.86)</td>
</tr>
<tr>
<td>COX–2 positive</td>
<td>1.0</td>
<td>0.64 (0.52-0.78)</td>
</tr>
<tr>
<td>COX-2 negative</td>
<td>1.0</td>
<td>0.96 (0.73-1.26)</td>
</tr>
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*P* heterogeneity = 0.02

Chan et al, NEJM 2007
Aspirin and CRC-specific mortality among CRC patients

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<tr>
<td>All CRC</td>
<td>1.0</td>
<td>0.71 (0.53-0.95)</td>
</tr>
<tr>
<td>COX-2 negative CRC</td>
<td>1.0</td>
<td>1.22 (0.36-4.18)</td>
</tr>
<tr>
<td>COX-2 positive CRC</td>
<td>1.0</td>
<td>0.39 (0.20-0.76)</td>
</tr>
</tbody>
</table>

P heterogeneity=0.04

Chan et al, JAMA 2009
Aspirin has greater specificity for COX-2 positive cancers

Aspirin preferentially reduces the risk of CRC and the spread of tumors for which growth depends, at least in part, on COX-2 function.
Aspirin and CRC-specific mortality among CRC patients

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<tr>
<td>All CRC</td>
<td>1.0</td>
<td>0.71 (0.53-0.95)</td>
</tr>
<tr>
<td>$PIK3CA$ wildtype CRC</td>
<td>1.0</td>
<td>0.93 (0.68-1.28)</td>
</tr>
<tr>
<td>$PIK3CA$ mutant CRC</td>
<td>1.0</td>
<td>0.18 (0.05-0.60)</td>
</tr>
</tbody>
</table>

$P$ heterogeneity = 0.01

Liao et al, NEJM 2012
Aspirin and recurrence-free survival among CRC patients in VICTOR

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<tr>
<td>All CRC</td>
<td>1.0</td>
<td>0.71 (0.53-0.95)</td>
</tr>
<tr>
<td><em>PIK3CA</em> mutant CRC</td>
<td>1.0</td>
<td>0.11 (0.01-0.83)</td>
</tr>
<tr>
<td><em>PIK3CA</em> wildtype CRC</td>
<td>1.0</td>
<td>0.94 (0.59-1.24)</td>
</tr>
</tbody>
</table>

P heterogeneity=0.02

Domingo *et al*, JCO 2013
15-Hydroxyprostaglandin dehydrogenase and CRC

- Ubiquitously downregulated in CRC
- Knockout of 15-PGDH in mice
  - \( \uparrow \) PGE-2, \( \uparrow \) colon tumors, resistance to anti-tumor effect of celecoxib
- Pilot study in APC Trial
  - \( \downarrow \) 15-PGDH in normal colon = \( \uparrow \) resistance to anti-adenoma effect of celecoxib

Yan et al, PNAS 2004; Yan et al, PNAS 2009
Assessment of 15-PGDH in normal colon mucosa

- RNA extracted from normal colon in CRC resections
- RT-PCR to quantitate 15-PGDH mRNA expression

Fink et al, Dig Dis Sci 2013
### Aspirin and risk of CRC by 15-PGDH in normal colon

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<tr>
<td>All CRC</td>
<td>1.0</td>
<td>0.73 (0.62-0.86)</td>
</tr>
<tr>
<td>High 15-PGDH</td>
<td>1.0</td>
<td>0.49 (0.34-0.71)</td>
</tr>
<tr>
<td>Low 15-PGDH</td>
<td>1.0</td>
<td>0.90 (0.63-1.27)</td>
</tr>
</tbody>
</table>

P heterogeneity=0.02

Fink *et al*, Sci Trans Med 2014
Aspirin may preferentially reduce the risk of CRC among individuals with sufficient colonic 15-PGDH
Urinary PGE-M

- Urinary metabolites (PGE-M) accurately reflect systemic prostaglandin balance
- PGE-M previously associated with CRC and adenoma
**Study population**

**Nurses’ Health Study (N=121,700)**

- **Diet**
- **Aspirin**

**Urine collection**

- N=18,743

**Matching factors**

1) Age
2) Date of urine
3) Year of endoscopy
4) Reason for endoscopy

**Controls**

- N=420

**Adenoma**

- N=420

**Exclusions**

1) Prior cancer
2) IBD
3) Polyposis
Risk of advanced adenoma by urine PGE-M

Aspirin/NSAID use and risk of advanced adenoma by urine PGE-M

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<thead>
<tr>
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<th>Regular Users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any PGE-M</td>
<td>1.0</td>
<td>0.76 (0.53-0.99)</td>
</tr>
<tr>
<td>High PGE-M (Q 2,3,4)</td>
<td>1.0</td>
<td>0.65 (0.45-0.94)</td>
</tr>
<tr>
<td>Low PGE-M (Q1)</td>
<td>1.0</td>
<td>1.31 (0.62-2.76)</td>
</tr>
</tbody>
</table>

PGE-M risk-stratifies for aspirin chemoprevention

Aspirin/NSAIDs primarily → risk of advanced adenoma in those with ↑ urine PGE-M
Can we exploit mechanism to personalize chemoprevention?

- Prostaglandin balance
- $Wnt$ signaling
## GWAS hits for CRC

<table>
<thead>
<tr>
<th>Position/Gene</th>
<th>rs#</th>
<th>Minor Allele</th>
<th>MAF</th>
<th>OR (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>8q24</td>
<td>rs6983267</td>
<td>T</td>
<td>0.50</td>
<td>0.83 (0.81-0.85)</td>
<td>7x10^{-30}</td>
</tr>
<tr>
<td>18q21/SMAD7</td>
<td>rs4939827</td>
<td>T</td>
<td>0.49</td>
<td>0.85 (0.81-0.89)</td>
<td>1x10^{-28}</td>
</tr>
<tr>
<td>15q13/CRAC1 (HMPS)</td>
<td>rs4779584</td>
<td>T</td>
<td>0.18</td>
<td>1.26 (1.19-1.34)</td>
<td>4x10^{-14}</td>
</tr>
<tr>
<td>rs10318</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10p14</td>
<td>rs10795668</td>
<td>A</td>
<td>0.33</td>
<td>1.25 (1.19-1.32)</td>
<td>3x10^{-13}</td>
</tr>
<tr>
<td>8q23.3/EIF3H</td>
<td>rs16892766</td>
<td>C</td>
<td>0.07</td>
<td>0.89 (0.86-0.91)</td>
<td>3x10^{-18}</td>
</tr>
</tbody>
</table>

+ > 30 more

Pomerantz et al, Nat Genet 2009; Tuupanen et al, Nat Genet 2009
rs6983267 and risk of CRC

Nan et al, JNCI 2013
rs6983267 and MYC expression

Nan et al, JNCI 2013
Aspirin and risk of CRC risk by rs6983267 genotype

Nan et al, JNCI 2013

\( P \) for interaction = 0.01
Rs6983267 risk stratifies for aspirin chemoprevention

- T allele ↓ risk of CRC and MYC expression
- Benefit of aspirin on CRC appears limited to individuals ≥ one T allele
Summary

• Overwhelming evidence supports a benefit of aspirin on CRC development
• Aspirin may improve CRC survival
• Mechanisms by which aspirin prevents cancer can be exploited to risk-stratify for chemoprevention
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- Medical students – Navya Bezawada, Raaj Mehta