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
<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

![Graph showing the relationship between years of regular aspirin use and multivariate relative risk.](image)

- 1.0
- 1.04
- 0.89
- 0.67
- 0.68

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

Burn *et al.*, Lancet 2011

Intention-to-treat HR=0.63; p=.12
Poisson IRR = 0.56; p=.05
Nurses’ Health Study (n=121,700)

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

Diet
Aspirin
BMI
Med. Hist.
Tobacco

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

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

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
- \textit{Wnt} signaling
Aspirin and risk of CRC by COX-2 expression

<table>
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<tr>
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<th>Non-Users</th>
<th>Regular Users</th>
</tr>
</thead>
<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>$PIK3CA$ mutant CRC</td>
<td>1.0</td>
<td>0.18 (0.05-0.60)</td>
</tr>
<tr>
<td>$PIK3CA$ wildtype CRC</td>
<td>1.0</td>
<td>0.93 (0.68-1.28)</td>
</tr>
</tbody>
</table>

P heterogeneity=0.01

Liao et al, NEJM 2012
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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 mutant CRC</td>
<td>1.0</td>
<td>0.11 (0.01-0.83)</td>
</tr>
<tr>
<td>PIK3CA 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
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
15-PGDH risk-stratifies individuals for aspirin chemoprevention

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
Nurses’ Health Study (N=121,700)

Study population

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

Exclusions
1) Prior cancer
2) IBD
3) Polyposis

Diet
Aspirin

Urine collection
N=18,743
Controls
N=420
Adenoma
N=420
Risk of advanced adenoma by urine PGE-M

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<thead>
<tr>
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<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
<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, rs10318</td>
<td>T</td>
<td>0.18</td>
<td>1.26 (1.19-1.34)</td>
<td>4x10^-14</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>
<tr>
<td>+ &gt; 30 more</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pomerantz et al, Nat Genet 2009; Tuupanen et al, Nat Genet 2009
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

$P_{\text{trend}} = 0.03$

Nan et al, JNCI 2013

[Diagram showing odds ratios for genotypes GG, GT, and TT]
Aspirin and risk of CRC risk by rs6983267 genotype

Nan et al, JNCI 2013
Rs6983267 risk stratifies for aspirin chemoprevention

- T allele $\downarrow$ risk of CRC and MYC expression
- Benefit of aspirin on CRC appears limited to individuals $\geq$ 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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