Molecular Targeting of Aspirin for the Prevention and Treatment of Colorectal Cancer

Andrew T. Chan, MD, MPH
Division of Gastroenterology
Massachusetts General Hospital

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Study population

Nurses’ Health Study (n=121,700)

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

Chan et al, JAMA 2005

Multivariate relative risk vs. Years of regular aspirin use

P for trend = <0.0001
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

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

Multivariate relative risk

0 0.5 to 1.5 2 to 5 6 to 14 > 14

Standard tablets of aspirin per week

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?
Aspirin and risk of CRC by COX-2 expression

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<tr>
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<th>Regular Users</th>
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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>
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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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<td>0.71 (0.53-0.95)</td>
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<tr>
<td>COX-2 positive CRC</td>
<td>1.0</td>
<td>0.39 (0.20-0.76)</td>
</tr>
<tr>
<td>COX-2 negative CRC</td>
<td>1.0</td>
<td>1.22 (0.36-4.18)</td>
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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><strong>PIK3CA mutant CRC</strong></td>
<td>1.0</td>
<td>0.18 (0.05-0.60)</td>
</tr>
<tr>
<td><strong>PIK3CA wildtype CRC</strong></td>
<td>1.0</td>
<td>0.93 (0.68-1.28)</td>
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\[ P \text{ heterogeneity}=0.01 \]

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

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<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>
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P heterogeneity = 0.02

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

• Ubiquitously downregulated in CRC
• Knockout of 15-PGDH in mice
  \[\uparrow\text{PGE-2}, \uparrow\text{colon tumors, resistance to anti-tumor effect of celecoxib}\]
• Pilot study in APC Trial
  \[\downarrow15\text{-PGDH in normal colon} = \uparrow\text{resistance to anti-adenoma effect of celecoxib}\]

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>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>
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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
Study population

Nurses’ Health Study (N=121,700)

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

Exclusions
1) Prior cancer
2) IBD
3) Polyposis

Urine collection
N=18,743

Diet
Aspirin

Controls
N=420

Adenoma
N=420
Risk of advanced adenoma by urine PGE-M

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

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<td>1.0</td>
<td>0.76 (0.53-0.99)</td>
</tr>
<tr>
<td><strong>High PGE-M (Q 2,3,4)</strong></td>
<td>1.0</td>
<td>0.65 (0.45-0.94)</td>
</tr>
<tr>
<td><strong>Low PGE-M (Q1)</strong></td>
<td>1.0</td>
<td>1.31 (0.62-2.76)</td>
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PGE-M risk-stratifies for aspirin chemoprevention

Aspirin/NSAIDs primarily ↓ risk of advanced adenoma in those with ↑ urine PGE-M
Summary

- Overwhelming evidence supports a benefit of aspirin on CRC development
- Aspirin may improve CRC survival
- Mechanisms by which aspirin prevents cancer, such as inhibition of prostaglandin synthesis, can be exploited to risk-stratify for chemoprevention and treatment
Acknowledgements

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• Co-investigators/Collaborators
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