Medical Approach to Barrett’s Esophagus

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Conflicts of Interest

• Research support: Takaeda
Goals

• Understand the role of PPI therapy in Barrett's esophagus
• Why cyclo-oxygenase inhibition in cancer prevention
• Candidates for chemoprevention
Reflux Event
Gastroesophageal Reflux

- Injury
- Metaplasia
- Esophagitis
- Restitution

Cyclooxygenase 2 induction

Acid and Bile
Salivary nitrates: Pre-carcinogens
Tobacco: Carcinogens
Oral flora: Nitrate reducing bacteria

Obesity: increased circulating insulin like growth factors

Gastric contents: Reflux of acid and pepsin

Duodenal contents: Reflux of bile and pancreatic enzymes

Chronic injury: Reflux related inflammation, oxidative stress and increased receptors for pro-growth signals

Bacterial colonization: Deconjugation of bile salts and reduction of Nitrates

H. pylori eradication: loss of esophageal protection from gastric acid injury

Gastrin: proton pump inhibitors use related Hypergastrinemia

Progression to Cancer

Normal Lining  Barrett's Esophagus  with low-grade dysplasia  with high-grade dysplasia  Invasive carcinoma
Biomarker- Clonal expansion

Barrett’s epithelial cell

Loss of p16

Loss of p53

Abnormal ploidy

COX-2 inhibitor and Barrett’s Epithelial Cells

PGE\textsubscript{2} supplementation increases the neoplastic potential of Barrett’s epithelium

\begin{figure}
\centering
\includegraphics[width=\textwidth]{chart.png}
\caption{PGE\textsubscript{2} supplementation affects proliferation and apoptosis.}
\end{figure}

*\textit{p}=0.01, **\textit{p}=0.62
Esophageal Cancer

**Number of Rats**

<table>
<thead>
<tr>
<th></th>
<th>Sulindac</th>
<th>MF-Tricyclic</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>13%</strong></td>
<td></td>
<td><strong>24%</strong></td>
<td><strong>56%</strong></td>
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</table>

* p<0.001 compared to control
** p<0.008 compared to control & p=0.245 compared to Sulindac

Inhibition of PGE2 and inflammation decrease the risk of esophageal adenocarcinoma

Gastroenterology. 122(4):1101-12, 2002
NSAID and Cancer: Mechanisms

- Inhibition of angiogenesis
- Induction of apoptosis by stimulation of pro-apoptotic genes,
- Inhibition of cancer cell growth by blocking signal transduction pathways

Chemoprevention

- Aspirin use and esophageal cancer was studied using the National Health and Nutrition Examination Survey and the National Epidemiologic Follow-up Studies (14,400 subjects)
- Occasional aspirin use associated with a 90% decreased risk
- No person classified as a regular user developed the disease.
NSAID Chemoprevention

Log-rank p=0.0003

Numbers at risk:

<table>
<thead>
<tr>
<th></th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never users</td>
<td>90  84  72  58  48  45  35  20</td>
</tr>
<tr>
<td>Former users</td>
<td>36  34  27  22  16  12  8  4</td>
</tr>
<tr>
<td>Current users</td>
<td>222 215 193 177 154 136 112 67</td>
</tr>
</tbody>
</table>

Vaughan TL Lancet Oncol 2005; 6: 945–52
Chemoprevention: Meta-Analysis of NSAID

• 9 studies combined, 1813 cancer cases
• Frequent (OR=0.55) or intermittent use (OR=0.82) of NSAIDs are protective
• Protective for adenocarcinoma (OR=.67) and squamous cell cancer (OR=.58)

Protective Association of ASA and NSAIDs With Esophageal Cancer: A Systemic Review

NSAID and Biomarkers

• 429 patients with Barrett’s esophagus
• Associations between use of NSAIDs and known biomarkers
• Odds ratios NSAID users compared with non-users:
  – 0.6 (95% CI, 0.3-1.4) for increased 4N
  – 0.6 (95% CI, 0.3-1.3) for aneuploidy
  – 0.3 (95% CI, 0.1-0.7) for 17p LOH
  – 0.7 (95% CI, 0.4-1.2) for HGD

COX-2 Inhibition

• 12 patients (11 males)
• 10 day treatment with rofecoxib

Gastroenterology. 123(1):60-7, 2002
Randomized Controlled Trial

- 100 pts with LGD or HGD
- Randomized to celocoxib 200 mg/d
- Assessed at 48 wks
  - No difference in dysplasia or cancer detected
  - No reduction in surface area of IM
  - No difference in methylation of p16, APC, and E-cadherin

Journal of the National Cancer Institute 2007;99:545-57
Cox Inhibition and Statins Effect on Progression

- Nested case-control VA population
  - 11,823 pts with Barretts
  - 116 esophageal adenocarcinoma
  - 696 matched controls
  - PPI use was almost universal (95%)

- Odds ratios, 95% CI
  - NSAID or ASA: 0.64; 0.42 - 0.97
  - Statin: 0.55; 0.36 - 0.86
Inflammatory pathway

- Membrane glycerophospholipids
- cPLA2α
- Arachidonic acid
- COX-2 and mPGES
- Prostaglandin E2 (PGE2)

NFκB
Inhibition of NF-κB activation decreases the neoplastic potential of Barrett’s epithelium.

![Graph showing inhibition of NF-κB activation and its effect on proliferation and apoptosis.](image)

- Proliferation
- Apoptosis

* p<0.001
Acid Control

N=12

Gastroenterology. 117(2):327-35, 1999
Acid Suppression and cell cycle regulation

Umansky M, Oncogene (2001) 20, 7987-7991
Acid Suppression and cell cycle regulation

Umansky M, Oncogene (2001) 20, 7987-7991
Acid Suppression and Mcm2

Acid Suppression and COX-2

Acid and Proliferation

- Two acid pulses of 3 minute duration
- Anti-proliferative effects

American Journal of Gastroenterology 2007;102:10-20
Acid and Proliferation

- Two acid pulses of 3 minute duration
- Anti-proliferative effects

American Journal of Gastroenterology 2007;102:10-20
Acid Control in Barrett’s Esophagus

- Randomized three way crossover trial
- Multi-center
- All confirmed Barrett's
- Esomeprazole
- N=31

![Bar chart showing comparison of different dosages of Esomeprazole.](chart.png)
Neoplastic Progression in Barrett's Metaplasia

Hillman, MJA 2004; 180: 387–391

[Graph showing cumulative survival over years after enrolment for PPI use (n=257) and no PPI use (n=42).]
Neoplastic Progression in Barrett’s Metaplasia

El-Serag, AJG 2004, 99 (10), 1877-83
Best Candidates for Chemoprevention in Barrett’s Esophagus?

• Factors
  – Anticipated Survival
  – Chemoprevention:
    • Low risk of cancer
    • Low risk of adverse events
    • Secondary medical need for therapy

• Best agents
  • NSAID/ASA: Pts with vascular disease,
  • PPI: Symptomatic control