HKU Finds that Long-term Use of Proton Pump Inhibitors is Associated with an Increased Risk of Stomach Cancer

Press Conference
November 13, 2017
Speakers

Professor Leung Wai-keung
Li Shu Fan Medical Foundation Professor in Gastroenterology
Clinical Professor, Department of Medicine
Li Ka Shing Faculty of Medicine, HKU

Dr Esther Chan Wai-yin
Associate Professor, Department of Pharmacology and Pharmacy
Research Lead, Centre for Safe Medication Practice and Research (CSMPR)
Li Ka Shing Faculty of Medicine, HKU

Dr Michael Cheung Ka-shing
Specialist in Gastroenterology and Hepatology
Department of Medicine
Queen Mary Hospital
Contents

• Overview of stomach cancer
• What is Proton Pump Inhibitor (PPI)?
• Our study findings
Stomach cancer
• 5th commonest cancer: 952,000 new cases (6.8%) in 2012
• 3rd leading cause of cancer death: 723,000 deaths (8.8%) in 2012
Stomach cancer: Global incidence and mortality

**Men**

- Lung
- Prostate
- Colorectum
- Stomach
- Liver
- Oesophagus
- Bladder
- Non-Hodgkin lymphoma
- Kidney
- Leukaemia
- Lip, oral cavity
- Pancreas
- Larynx
- Brain, nervous system
- Melanoma of skin

**Women**

- Breast
- Colorectum
- Cervix uteri
- Lung
- Corpus uteri
- Stomach
- Ovary
- Thyroid
- Liver
- Non-Hodgkin lymphoma
- Leukaemia
- Pancreas
- Oesophagus
- Kidney
- Brain, nervous system

**Graphs show incidence and mortality rates per 100,000.**
# Stomach cancer in Hong Kong

## Incidence in 2015 - Both Sexes

<table>
<thead>
<tr>
<th>Rank</th>
<th>Site</th>
<th>No.</th>
<th>Rel. Freq.</th>
<th>Crude rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Colorectum</td>
<td>5,036</td>
<td>16.6%</td>
<td>69.1</td>
</tr>
<tr>
<td>2</td>
<td>Lung</td>
<td>4,748</td>
<td>15.7%</td>
<td>65.1</td>
</tr>
<tr>
<td>3</td>
<td>Breast</td>
<td>3,920</td>
<td>12.9%</td>
<td>53.8</td>
</tr>
<tr>
<td>4</td>
<td>Prostate</td>
<td>1,831</td>
<td>6.0%</td>
<td>54.4</td>
</tr>
<tr>
<td>5</td>
<td>Liver</td>
<td>1,791</td>
<td>5.9%</td>
<td>24.6</td>
</tr>
<tr>
<td>6</td>
<td>Stomach</td>
<td>1,167</td>
<td>3.8%</td>
<td>16.0</td>
</tr>
<tr>
<td>7</td>
<td>Non-melanoma skin</td>
<td>1,018</td>
<td>3.4%</td>
<td>14.0</td>
</tr>
<tr>
<td>8</td>
<td>Corpus uteri</td>
<td>978</td>
<td>3.2%</td>
<td>24.9</td>
</tr>
<tr>
<td>9</td>
<td>Non-Hodgkin lymphoma</td>
<td>976</td>
<td>3.2%</td>
<td>13.4</td>
</tr>
<tr>
<td>10</td>
<td>Nasopharynx</td>
<td>876</td>
<td>2.9%</td>
<td>12.0</td>
</tr>
<tr>
<td></td>
<td><strong>All Sites</strong></td>
<td>30,318</td>
<td>100.0%</td>
<td>415.8</td>
</tr>
</tbody>
</table>

## Mortality in 2015 - Both Sexes

<table>
<thead>
<tr>
<th>Rank</th>
<th>Site</th>
<th>No.</th>
<th>Rel. Freq.</th>
<th>Crude rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lung</td>
<td>4,031</td>
<td>28.2%</td>
<td>55.3</td>
</tr>
<tr>
<td>2</td>
<td>Colorectum</td>
<td>2,073</td>
<td>14.5%</td>
<td>28.4</td>
</tr>
<tr>
<td>3</td>
<td>Liver</td>
<td>1,571</td>
<td>11.0%</td>
<td>21.5</td>
</tr>
<tr>
<td>4</td>
<td>Pancreas</td>
<td>691</td>
<td>4.8%</td>
<td>9.5</td>
</tr>
<tr>
<td>5</td>
<td>Stomach</td>
<td>669</td>
<td>4.7%</td>
<td>9.2</td>
</tr>
<tr>
<td>6</td>
<td>Breast</td>
<td>637</td>
<td>4.4%</td>
<td>8.7</td>
</tr>
<tr>
<td>7</td>
<td>Prostate</td>
<td>404</td>
<td>2.8%</td>
<td>12.0</td>
</tr>
<tr>
<td>8</td>
<td>Non-Hodgkin lymphoma</td>
<td>358</td>
<td>2.5%</td>
<td>4.9</td>
</tr>
<tr>
<td>9</td>
<td>Leukaemia</td>
<td>341</td>
<td>2.4%</td>
<td>4.7</td>
</tr>
<tr>
<td>10</td>
<td>Nasopharynx</td>
<td>327</td>
<td>2.3%</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td><strong>All Sites</strong></td>
<td>14,316</td>
<td>100.0%</td>
<td>196.3</td>
</tr>
</tbody>
</table>

*Hong Kong Cancer Registry, Hospital Authority*
Helicobacter pylori

- *H. pylori* has been classified by the International Agency for Research on Cancer (IARC) as a carcinogen in 1994.

- The prevalence of *H. pylori* infection varies, ranging from <20% in some European countries to >80% in some African countries.

- It is estimated that more than 4 billion people are infected with *H. pylori* in the world.
Pathogenesis of stomach cancer

- Normal mucosa
- Chronic active gastritis
- Gastric atrophy
- Intestinal metaplasia
- Dysplasia
- Gastric cancer

*H. pylori*

?? Proton pump inhibitors (PPIs)

What are proton pump inhibitors (PPIs)?
What are proton pump inhibitors (PPIs) ?

- Potent gastric acid suppressing agent
- Dexlansoprazole, Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, Rabeprazole, etc.

1. Bind to the cell lining of stomach
2. Inhibit gastric acid production
3. Prevent ulcers/assist healing process
What are proton pump inhibitors (PPIs) ?

- Widely used in various gastrointestinal conditions
  - Indigestion
  - Acid reflux (heartburn)
  - Peptic ulcer disease (stomach / duodenum)
  - Prevent drug related ulcers
  - *H. pylori* eradication in triple therapy
What are proton pump inhibitors (PPIs)?

- One of the top selling drug classes

Top Therapeutic Classes by Prescriptions in US in 2016

![Bar chart showing the number of dispensed prescriptions (million) for different therapeutic classes.](chart)

Source: IQVIA, National Prescription Audit, Dec 2016
What are proton pump inhibitors (PPIs)?

- One of the top selling drug classes

<table>
<thead>
<tr>
<th>Country</th>
<th>Most Popular PPI</th>
<th>No. of Prescriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>Omeprazole</td>
<td>76 million</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Top 10 prescribed medicines)</td>
</tr>
<tr>
<td>UK</td>
<td>Omeprazole</td>
<td>31 million</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Top 10 prescribed medicines)</td>
</tr>
<tr>
<td>HK</td>
<td>Pantoprazole</td>
<td>1.6 million</td>
</tr>
</tbody>
</table>

Source: QuintilesIMS Institute, National Health Service, Clinical Data Analysis and Reporting System
Adverse effects of PPIs

• Generally well tolerated
  – Mild headache
  – Constipation / diarrhoea
  – Wind (flatulence)

• Long term uses associated with
  – Bone fracture
  – *Clostridium difficile* infection
  – Pneumonia
Our Study
Research question

Will the use of PPIs increase the risk of stomach cancer even after successful *H. pylori* eradication?
Study on the association between PPIs use and stomach cancer (a population-based study)

Long-term proton pump inhibitors and risk of gastric cancer development after treatment for *Helicobacter pylori*: a population-based study

Ka Shing Cheung,¹ Esther W Chan,² Angel Y S Wong,² Lijia Chen,¹ Ian C K Wong,²,³ Wai Keung Leung¹

Methods

- PPIs use after *H. pylori* eradication therapy (year 2003 – 2012)
- Stomach cancer development (up to year 2015)
Characteristics of the study cohort

- Total patient number: 63,397
- Study observation period: 2003 - 2015
- Median follow-up: 7.6 years
- 153 (0.24%) developed stomach cancer
- Overall incidence rate: 3.2 per 10,000 person-years
- Median age at stomach cancer diagnosis: 71.4 years
- Median time from *H. pylori* therapy to stomach cancer development: 4.9 years
PPIs use and stomach cancer

- Definition of PPIs use: < weekly use
- PPIs users: 3271 (5.2%)
- Median duration of PPIs use: 2.7 years
- Incidence rate of stomach cancer: 8.1 per 10,000 person-years

- Compared with non-PPIs use, PPIs use was associated with an increased risk of stomach cancer by 2.4
- 4.3 excess stomach cancer cases per 10,000 person-years

- Use of H2-receptor antagonist, another less potent acid reducing drug, was not associated with an increase in stomach cancer risk (relative risk 0.72, statistically insignificant)
PPIs frequency and stomach cancer

Non-PPIs use
(< weekly use)

Weekly to <daily PPIs use
relative risk: 2.44

Daily PPIs use
relative risk: 4.55
PPIs duration and stomach cancer

Non-use vs Daily PPIs use

- PPIs use ≥ 1 year: relative risk: 5.04
- PPIs use ≥ 2 years: relative risk: 6.65
- PPIs use ≥ 3 years: relative risk: 8.34
Conclusion

• Long-term PPIs use is associated with an increased stomach cancer risk even after *H. pylori* eradication

• A dose-response trend in terms of frequency and duration of PPIs treatment is noted

• PPIs are effective medications to treat various gastrointestinal diseases – PPIs use should not be discouraged

• Review of indications; use with the minimal dose, frequency and duration
Since online publication on 1 Nov 2017, study findings reported by >90 media globally, including

- NY Times
- The Guardian
- Newsweek
- The Times
- American Gastroenterological Association
Acid reflux drug linked to more than doubled risk of stomach cancer - study

There are more than 50m prescriptions for proton pump inhibitors in the UK, though they have previously been linked to side-effects and increased risk of death.
New PPI Study on Gastric Cancer Generates Media Attention

AGA provides talking points to help your patients understand the science behind the PPI study.

The results of a new study about the use of proton pump inhibitors (PPIs) and their link to gastric cancer has been covered by various media outlets. This may cause your patients to question whether they should stay on or start using PPIs. Like all recent PPI studies, the information is important and interesting, but the results should not automatically alter practice, due to the limitations of the study’s methodology.

The study, "Long-term proton pump inhibitors and risk of gastric cancer development after treatment for Helicobacter pylori: a population-based study," published in Gut, concluded that even after Helicobacter pylori (H. pylori) eradication therapy, long-term use of PPIs was associated with an increased risk of gastric cancer in some patients. Steven Neumeier, MD, states that understanding the science behind a study can help patients make informed decisions about their health.
Q & A Session