Risk of Gastric Cancer with PPI Use in Observational Studies: A Systematic Review and Meta-analysis

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Background

- Several studies and systematic reviews examined the association between long-term PPI therapy and the risk of gastric cancer and arrived at mixed results.
  - Studies have used different designs, examined various definitions of PPI use and gastric cancer sites and were open to multiple sources of bias.
  - The relevance of these studies remain unclear.
- A critical re-examination of the literature is warranted

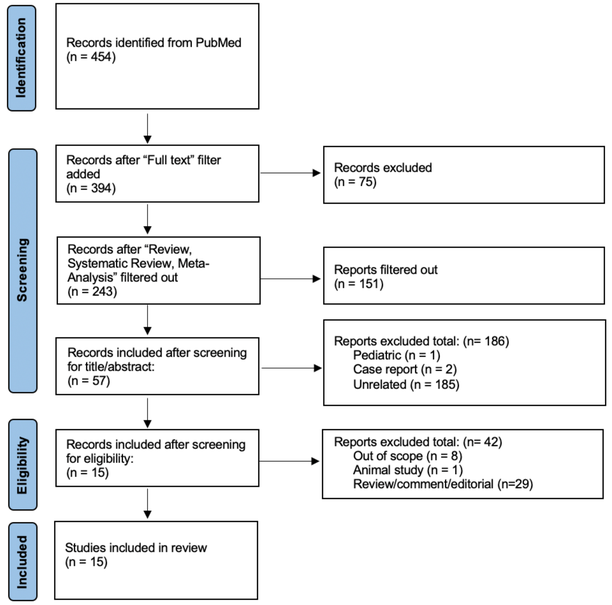

Figure 1. Study flow diagram.

Methods

- Eligibility criteria: We included observational studies.
- We accessed PubMed to identify all eligible studies published through January 2022. Three coauthors screened the records by title and abstract, and then full text for eligibility.
- We examined the effect of study design and quality, gastric cancer site (cardia, non cardia), *H pylori* infection, and PPI duration.
- We used the Newcastle-Ottawa Quality Assessment Scale with scores>6 on the 0-9 points as high quality.

Results

- A total of 15 studies met the eligibility criteria (Figure 1). 6 studies based in Asia, 6 in Europe and 3 in North America.
- **The pooled risks of cardia gastric cancer** (Figure 2)
  - Cohort studies (n=2): 0.90 (95% 0.48-1.66)
  - Case-control studies (n=5): 1.17 (95% 0.77-1.177)
  - Overall (n=7): 1.12 (95% 0.80-1.56)
  - Heterogeneity I^2: 45.1% (p=0.09)
  - No significant increase of risk in overall analysis
- **The pooled risks of non-cardia gastric cancer** (Figure 3)
  - Cohort studies (n=2): 2.03 (95% 1.17-3.53)
  - Case-control studies (n=5): 1.59 (95% 0.99-2.57)
  - Overall (n=7): 1.68 (95% 1.12-2.53)
  - Heterogeneity I^2: 80.9% (p=0.000)
  - Small significant increase of risk in overall analysis
  - Significant increase of risk in overall analysis
- **The pooled risks limited to high quality studies**
  - Cardia gastric cancer (n=5)
  - Non-cardia gastric cancer (n=5)
  - Similar findings to overall analysis (not shown)
- **Studies that accounted for *H pylori***
  - There were a few studies that systematically accounted for *H pylori* infection while examining non-cardia (n=3) or cardia cancer (n=3).
  - The study by Cheung et al. (**Hong Kong**) was the **only high quality cohort** study that examined **non-cardia cancer** and **accounted for *H pylori*** by limiting the analysis to patients who underwent *H pylori* treatment.

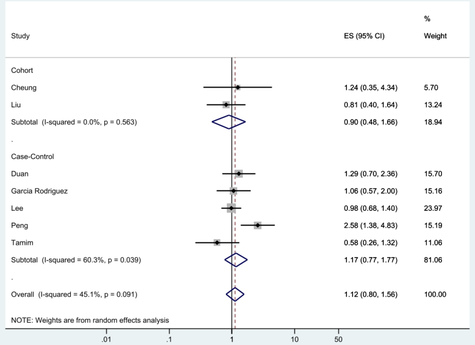

Figure 2. Pooled risk of cardia gastric cancer.

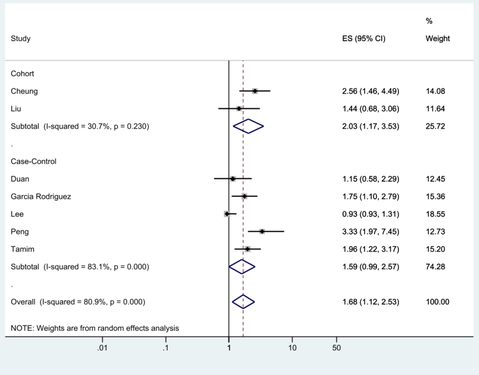

Figure 3. Pooled risk of non-cardia gastric cancer.

Summary

- No significant association between PPI use and risk of cardia gastric cancer.
- Small increase in risk of gastric cancer with PPI use, but this finding is limited by absent or weak data on:
  - Dose or duration response
  - Temporal association from cohort studies accounting for *H pylori*
  - Severity or extent of gastritis
  - Use of OTC medications
- The meta-analysis is limited by:
  - Marked heterogeneity among studies
  - Low generalizability (e.g., North America)

Conclusions

- The overall available evidence from observational studies is not supportive of an increased risk of gastric cancer with PPI use for either cardia or non-cardia gastric cancer.

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