Proton pump inhibitor use and the risks of fundic gland polyps and gastric cancer: a systematic review and meta-analysis

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An Tran-Duy conceptualized and designed the study, acquired and analysed data, interpreted the study results, drafted the manuscript and critically revised the manuscript for important intellectual content. Bart Spaetgens acquired and analysed data, interpreted the study results and critically revised the manuscript for important intellectual content. Arno W Hoes designed the study, interpreted the study results and critically revised the manuscript for important intellectual content. Niek J de Wit designed the study, interpreted the study results and critically revised the manuscript for important intellectual content. Coen DA Stehouwer conceptualized and designed the study, interpreted the study results and critically revised the manuscript for important intellectual content.

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ABSTRACT

Background & Aims

There has been an increasing number of case reports and observational studies on the adverse events in patients on long-term use of proton pump inhibitors (PPIs). Recently, effects of PPI therapy on the risks of fundic gland polyps (FGPs) and gastric cancer have drawn considerable attention. We performed a systematic review with meta-analyses of the existing randomised controlled trials (RCTs) and observational studies to assess the association between PPI use and the risks of FGPs and gastric cancer.

Methods

We searched PUBMED, EMBASE and Cochrane Central Register of Controlled Trials databases for relevant studies published through July 2015. Pooled odds ratio (OR) of FGPs and pooled risk ratio (RR) of gastric cancer in PPI users compared with PPI non-users were computed using both fixed- and random-effects models.

Results

We included 12 studies; one RCT reported on the effect on gastric polyps (location not specified), six cohort and one case-control studies reported on FGPs, and one cohort and three case-control studies reported on gastric cancer. Pooled OR [95% CI] of FGPs was 1.43 [1.24, 1.64] and 2.45 [1.24-4.83] from fixed- and random effects models, respectively, and pooled RR [95% CI] of gastric cancer 1.43 [1.23, 1.66] from both models. Significant heterogeneity was present across studies reporting on FGPs but absent across those reporting on gastric cancer.

Conclusions

Long-term use of PPIs (≥12 months) is most likely associated with an increased risk of FGPs. Therapy with PPIs may also increase the risk of gastric cancer, but this association can be biased due to a limited number of and possible confounding in the available studies.

Keywords: proton pump inhibitors; fundic gland polyps; gastric cancer; side effect
INTRODUCTION

Since the introduction of the first proton pump inhibitor (PPI) omeprazole in the late 1980s,\(^1\) PPIs have generally been considered to be safe and have been widely used in clinical practice. However, with an increasing number of case reports and emerging observational studies on the adverse events in patients receiving long-term PPI therapy, questions about the potential risks associated with their use have recently been raised. Currently, the most prominent concerns about the long-term PPI use relate to the risks of bone fractures, enteric infection, pneumonia and vitamin B\(_{12}\) deficiency. To a lesser extent, the effects of PPI therapy on the risks of fundic gland polyps (FGPs) and gastric cancer, of which the mechanisms are not well understood, have also drawn attention.

Fundic gland polyps are gastric mucosal lesions of small sizes (typically 2-5 mm) located in the fundus or body of the stomach.\(^2,3\) These polyps are composed of cystically dilated fundic glands lined by parietal or chief cells which arrange in a disordered fashion.\(^4,5\) They can be single or multiple,\(^2,3,5\) and be sporadic or associated with an inherited polyposis syndrome such as familial adenomatous polyposis (FAP).\(^3,6,7\) In 1992 Graham published a letter noting three cases of FGPs developed after one year of therapy with omeprazole.\(^8\) Since then, case reports describing the occurrence of FGPs in chronic PPI users have steadily emerged over time.\(^9-15\) However, the association of FGPs with the use of PPIs currently remains a topic of debate and the link between FGPs and the risk of gastric cancer is still unclear. It has been suggested that sporadic FGPs arise through activating mutations of the β-catenin gene, and FAP-associated FGPs are caused by alterations of the somatic adenomatous polyposis coli gene.\(^16,17\) Although FGPs are generally considered to be benign, some reports showed low-grade dysplasia in FGPs,\(^18,19\) and one case report describing a chronic PPI user developed FGPs which contained high-grade dysplasia.\(^20\)

Several researchers suggest that PPIs cause gastric cancer because they profoundly reduce gastric acid production and consequently lead to increased secretion of gastrin. Hypergastrinaemia as a result of acid suppression causes hyperplasia of enterochromaffin-like cells in rats\(^21\) but this phenomenon has never been reported in other species.\(^22\) Although hypergastrinaemia occurs in nearly all PPI users,\(^23\) whether or not it increases the risk of gastric cancer is controversial. In the last decade, discussion has been shifted from the isolated carcinogenic effect of PPIs to the proposed synergistic effect between PPIs and \textit{H. pylori} in
carcinogenesis; the latter augments the acid-suppressive function of PPIs,\textsuperscript{24,25} causes non-H. pylori bacterial overgrowth\textsuperscript{26} and exacerbates gastritis due to double infection with H. pylori and non-H. pylori bacterial species.\textsuperscript{27} 

H. pylori-driven gastric inflammation has been widely accepted as a risk factor of gastric cancer.\textsuperscript{28,29} Given the widespread use of PPIs, it is crucial to determine whether a relationship between PPI use and the risks of FGPs and gastric cancer exists. In this study we performed a systematic review with meta-analyses of the existing randomised controlled trials (RCTs) and observational studies to assess the association between PPI use and the risks of FGPs and gastric cancer.

METHODS

Search strategy and eligibility criteria

We searched PUBMED, EMBASE and Cochrane Central Register of Controlled Trials to identify all English-language studies published from the inception until 31 July 2015 that assessed the association between PPI use and the risk of FGPs or gastric cancer. We used the search terms “proton pump inhibitor”, “omeprazole”, “esomeprazole”, “pantoprazole”, “lansoprazole”, “dexlansoprazole”, “rabeprazole”, “fundic gland polyps”, “fundus polyps” “gastric polyps”, “stomach polyps”, “gastric cancer”, “gastric carcinoma”, “gastric adenocarcinoma”, “gastric neoplasm”, gastric neoplasia”, “stomach cancer”, “stomach carcinoma”, “stomach adenocarcinoma”, “stomach neoplasm”, “stomach neoplasia”. Detailed search queries are provided in Appendix 1. We also manually scanned the bibliographies of relevant articles for additional studies.

We included RCTs and observational studies (i.e. cohort or case-control studies) that met the following criteria: (i) studies written in English, (ii) studies reported on FGPs or gastric cancer, (iii) outcomes of PPI users were compared with those of PPI non-users, (iv) studies provided adequate data that enabled an estimation of an odds ratio (OR) or a risk ratio (RR).

Study selection and data extraction

The studies were independently reviewed by two reviewers (ATD and BS). Where there was any uncertainty about the inclusion of a study, this issue was discussed between the two reviewers to achieve a resolution. The following information was independently extracted from the included studies and jointly verified for accuracy: adjusted OR or RR of gastric polyp and cancer
(when available), first author’s surname, year of publication, country of study, type of outcome, study design, period of patient recruitment, patient inclusion criteria, number of participants and events, type and dose of PPIs, duration of PPI exposure, and age and gender of participants. We contacted authors when there was unclear information.

**Study quality assessment**

We assessed the risk of bias in RCTs using the Cochrane Collaboration’s tool,\(^{30}\) which addresses the following domains: sequence generation, concealment of allocation sequence, blinding, incomplete outcome data, selective outcome reporting and any other problems that could put the studies at risk of bias. We assessed the methodological quality of the observational studies using the Newcastle-Ottawa Scale (NOS; ranging 0-9)\(^{31}\) as recommended by the Cochrane Handbook for Systematic Reviews of Interventions.\(^{30}\) On this scale, a study is judged by giving points (stars in the NOS terminology) to items belonging to three categories: selection of the study groups, the comparability of the groups, and the ascertainment of the exposure (for case-control studies) or outcome of interest (for cohort studies) (see Appendix 2 for details).

**Outcome measures, data analysis and presentation**

ORs and RRs were selected as measures of the effects of PPI use on the risk of FGPs and gastric cancer, respectively, so that the adjusted effect estimates in the included studies could be used in the meta-analyses. Pooled ORs and RRs were computed using both fixed-effect and random-effects models. Heterogeneity across studies was tested using the Q-statistic and quantified using the inconsistency \(I^2\).\(^{32}\) When possible, subgroup analyses were performed to assess the potential impact of duration of PPI exposure, quality of observational studies (NOS ≤5 vs. NOS >5; cut-off point arbitrarily defined) and study design (RCT vs. observational studies) on the pooled effects. In a sensitivity analysis, the influence of individual studies on the summary statistics was examined by omitting one study at a time from the meta-analysis. Publication bias was assessed using funnel plots and Egger’s regression test of funnel plot asymmetry.\(^{33}\) In each funnel plot, the standard errors of the estimates were plotted on a vertical reversed scale against the effect estimates on the horizontal scale, and the triangle was centred on the pooled estimate and extending to 1.96 times the standard errors on either side. In the absence of bias, the scatter of the data points is subject to sampling variation alone and the plot resembles a symmetrical inverted funnel; in this case, the triangle should include about 95% of studies if the
fixed-effect assumption (i.e. all the studies have the same true treatment effect) is valid. The statistical analyses were performed using the R package metaphor. A P-value <0.05 was considered statistically significant.

We followed both the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement and the guidelines for Meta-analysis Of Observational Studies in Epidemiology (MOOSE) in reporting this study.

RESULTS

Figure 1 shows the flow chart of the selection of studies. The search identified 1,809 studies. After screening the titles, abstracts and full text, 12 studies were considered eligible for complete data extraction. Of these, one RCT reported on the effect on gastric polyps (location not specified), six cohort and one case-control studies reported on FGPs, and one cohort and three case-control studies reported on gastric cancer. Table 1 shows characteristics of the included studies, outcomes, characteristics of the drug treatments and study quality (for detailed quality assessment of the observational studies, see Appendix 2).

Proton pump inhibitor use and risk of gastric polyps

Pooled effect

Eight studies (one RCT and seven observational studies) reporting on the effect on FGPs were included in the analysis. Of the observational studies, three studies adjusted the effect estimates for potential confounding. *H. pylori* infection status, an important potential confounding factor, was considered in two studies only. The directions of the estimated ORs and their 95% CIs were not consistent among the studies (Figure 2A). When all the estimates were pooled, the summary OR [95% CI] in PPI users compared with PPI non-users from the fixed- and random-effects models were 1.43 [1.24, 1.64] and 2.45 [1.24, 4.83], respectively. Significant heterogeneity was present across studies (P-value <0.0001 (both models); $I^2$ equalled 92.8% and 92.7% in fixed- and random-effects models, respectively).

Sensitivity and subgroup analyses

The sensitivity analysis showed that the direction and 95% CI of the pooled effect of the use of PPIs on gastric polyps as well as and the presence of heterogeneity were not influenced by any single study in both fixed- and random-effect models (see Appendix 3, Table S3.1)
Pooled ORs [95% CI] from the fixed-effect model based on data from groups of patients receiving PPIs shorter than or equal to 12 months (two studies\textsuperscript{40,44}), longer than or equal to 12 months (three studies\textsuperscript{40,43,44}) and longer than 48 months (two studies\textsuperscript{40,41}) were 0.82 [0.59, 1.12], 3.81 [2.78, 5.24] and 4.02 [2.49, 6.48], respectively. The random-effects model produced the same results, except for the pooled OR [95% CI] in the second subgroup (≥12 months), which was 2.88 [0.97, 8.55] (Figure 3A).

Pooled ORs [95% CI] from studies with NOS ≤5\textsuperscript{38-40,44} and studies with NOS >5\textsuperscript{41-43} were 1.12 [0.96, 1.31] and 4.04 [2.92, 5.59], respectively from the fixed-effect model, and were 1.89 [0.66-5.42] and 3.54 [1.36-9.26], respectively from the random-effects model. Pooled OR [95% CI] from observation studies only was 1.42 [1.24, 1.64] (fixed-effect model) and 2.44 [1.18-5.04] (random-effects model), against the estimated OR [95% CI] of 2.67 [0.25, 28.52] from one RCT.

Publication bias

The funnel plot (Figure 4) showed that, out of eight data points, six lay outside the triangle, and six lay on the right side of the triangle altitude. The Egger's regression test of the funnel asymmetry showed highly significant publication bias (P-value <0.0001).

Proton pump inhibitor use and risk of gastric cancer

Pooled effect

Of four included studies reporting on gastric cancer, one case-control study\textsuperscript{47} reported zero PPI users among controls and thus was excluded from the analysis because an OR could not be computed. All the three remaining studies adjusted the effect estimates for the potential confounders; however, \textit{H. pylori} infection status was not considered for adjustment in any of these studies. One study\textsuperscript{46} reported ORs for gastric cancer at two subsites, namely gastric cardia adenocarcinoma and gastric non-cardia adenocarcinoma, and reported no raw data or single OR or RR for all-subsite gastric cancer. Therefore, four estimates (all from observational studies) were available to be pooled, which yielded a summary RR [95% CI] of 1.43 [1.23, 1.66] from both fixed- and random-effects models (Figure 2B). No significant heterogeneity across studies was present (both models: P-value = 0.53; \(I^2 = 0\%\)).

Sensitivity and subgroup analyses
The sensitivity analysis showed that the direction of the pooled effect of the use of PPIs on gastric cancer and of 95% CI of the pooled effect, and the absence of heterogeneity, were not influenced by any single study in both fixed- and random-effect models (see Appendix 3, Table S3.2).

Pooled RRs [95% CI] from the fixed-effect model based on data from groups of patients (in two studies\textsuperscript{45,46}) who received PPIs shorter than 12 months, longer than or equal to 12 months and longer than 36 months were 1.76 [1.24, 2.52], 1.42 [0.98, 2.07] and 2.45 [1.41, 4.25], respectively. The random-effects model produced the same results, except for the pooled RR [95% CI] in the second subgroup (≥12 months), which was 1.31 [0.79-2.19] (Figure 3B).

Publication bias

When the number of studies is small, the visual interpretation and test for asymmetry of the funnel plot of the publications are not reliable.\textsuperscript{30} With three included studies reporting on gastric cancer, we did not assess the bias of these publications.

**DISCUSSION**

Proton pump inhibitor use and risk of gastric polyps

The summary effect and its 95% CI based on the estimates from one RCT and seven observational studies showed that the use of PPIs was associated with an increased risk of FGPs. The likelihood of this association was strengthened by the fact that the pooled OR and its lower bound of the 95% CI from studies with higher quality were much larger than those from studies with lower quality and from all studies. However, the magnitude of the mean effect size remains unclear. Of the eight included studies, only three\textsuperscript{40,41,43} adjusted the effect estimates for potential confounders. The development of FGPs is known to be suppressed by *H. pylori*.\textsuperscript{49-51}

However, the status of *H. pylori* infection was considered for adjustment only in two studies.\textsuperscript{41,43} Duration of PPI use is an important factor influencing the risk of FGPs,\textsuperscript{40} but is not specifically reported in most of the studies. In general, there was diversity in the PPI exposure. Mean (range) of duration of PPI use was 37.4 (3-98) months in the study by Choudhry et al.\textsuperscript{38} and was 21.9 (1-97) months in study by Hsu et al.\textsuperscript{42} In other studies, mean or median duration of PPI use was not reported and the duration ranges varied widely from 5 to >48 months. In all the included studies, FGPs were found in patients undergoing an esophagogastroduodenoscopy (EGD), of whom a large proportion had gastroesophageal reflux disease (GERD). The effect of
PPIs in these patients might be confounded by indication, because the patients with GERD are often prescribed PPIs and might have a higher risk of FGPs. Because none of the included studies adjusted the effect estimates for a history or presence of GERD, their findings might be biased.

The sensitivity analysis showed that the study by Vieth and Stolte had a considerable impact on the pooled effect from the fixed-effect model; this is in agreement with the observation that this study had a weight far larger than those of other studies, and its effect estimate was smallest among all studies except one (see Figure 2A). However, since the exclusion of the study by Vieth and Stolte did not change the direction of the 95% CI of the pooled effect from any of the models, the likelihood of the association between PPI use and the risk of FGPs was not influenced by this study.

Because of the presence of a considerable heterogeneity across the included studies, the assumption in the fixed-effect model that the true effect is the same value in every study may not hold. Despite this, the pooled ORs and the 95% CIs obtained from both fixed- and random-effects models consistently showed that the use of PPIs was associated with an increased risk of FGPs.

The results from the analysis of the subgroups by length of PPI exposure suggest that the risk of FGPs increases with increasing duration of PPI use. This subgroup analysis suggests that the use of PPI for at least 12 months is a necessary condition for the development of FGPs. This observation is in line with the results from several studies published in the form of abstract or letter, which showed an increased risk of FGPs in patients receiving PPIs for 12 months or longer.

Despite the finding that the use of PPIs was associated with an increased risk of FGPs, the clinical significance of PPI-associated FGPs remains unclear. Benign gastric polyps have been found incidentally in 5 to 140 out of 1000 people undergoing an EGD, and 3-77% of these gastric polyps could be FGPs. In the study by Choudhry et al., no hyperplasia or dysplasia was found in the FGPs in seven PPI users. In the study by Jalving et al., one and seven patients among 19 patients with FAP-associated FGPs had high- and low-grade dysplasia in FGPs, respectively; among these eight patients with dysplasia, only two patients used PPIs.

Based on their data, the authors of the above-mentioned study suggested that the development of FGPs and/or dysplasia in FGPs in FAP patients was unlikely to be related to PPI
use. In contrast, in two studies published in abstract form, Weinstein and colleagues noted that
the use of omeprazole increased hyperplasia in the mucosa adjacent to the FGPs,\textsuperscript{60} and Hirt and
colleagues suggested that FGPs associated with PPI use exhibited a histologic difference from
the sporadic FGPs that were traditionally described.\textsuperscript{61} In another study, among patients with
FAP-associated FGPs, two patients were on long-term PPI therapy (>6 months) and both had
dysplasia; in comparison, only three out of seven patients not receiving PPIs had dysplasia.\textsuperscript{62}
Apart from these observations, there has been no large, systematic study on the association
between the PPI-related FGPs and the development of dysplasia or carcinoma.

**Proton pump inhibitor use and risk of gastric cancer**

The summary effect and its 95% CI based on the estimates from three observational studies
suggest that the use of PPIs may be associated with an increased risk of gastric cancer. This is in
agreement with the results from the study by Ahn et al.,\textsuperscript{63} which examined the association
between the use of acid suppressive drugs, including histamine H\textsubscript{2} receptor antagonists (H\textsubscript{2}RA)
and PPIs, and the risk of gastric cancer. In their meta-analysis, the authors of this study\textsuperscript{63} used
the same three studies\textsuperscript{45,46,48} as those in our study and reported a very similar summary effect of
PPIs and its 95% CI (1.39 [1.19-1.64]). Despite a slight difference in the results between our
study and the study by Ahn et al.,\textsuperscript{63} the messages are the same at the first glance. However, the
magnitude and the statistical significance of the association between PPI use and the risk of
gastric cancer remain uncertain. In the study by Ahn et al.\textsuperscript{63} the potentially biased outcomes
from the included studies were briefly mentioned, but various sources of bias and uncertainty in
the summary effect of PPIs were not discussed in great details. From the included studies, only
four values of RRs were available for the meta-analysis, of which two RRs were not significantly
different from 1. *Helicobacter pylori* infection is a major confounding factor, because it is
associated with both PPI prescription and risk of gastric cancer. The study by Poulsen et al.\textsuperscript{45}
included the history of *H. pylori* eradication as a covariate in the statistical model, but this could
not exclude the residual confounding by untreated *H. pylori* infection. Except for this study,
none of the included studies adjusted the effect estimate for the status of *H. pylori* infection.
Other potential confounding factors include early symptoms of gastric cancer similar to benign
gastric conditions like GERD and peptic ulcers, which can lead to PPI prescriptions. Except for
the study by Garcia Rodriguez et al.,\textsuperscript{46} which adjusted the effect estimates for a history of GERD,
peptic ulcer and dyspepsia, none of the included studies attempted to reduce this potential
bias. Diet (e.g. smoked foods or cured meats), inherited cancer syndromes and family history of gastric cancer are among other potential confounders, but none of them were considered in the included studies.

To the best of our knowledge, no meta-analyses of studies examining the association between PPI therapy and gastric cancer, except for those in the study by Ahn et al.\textsuperscript{63} and our study, have been carried out. In our study, a subgroup analysis of the effect of PPIs with regard to the duration of therapy was performed. This added new information to the existing literature, because in the study by Ahn et al.\textsuperscript{63} no such an analysis directed specifically at the PPI use was conducted. Our analysis showed that the pooled RR, and the lower and upper bounds of its 95% CI in patients using PPI for less than 12 months were larger than those in patients using PPI for 12 months or longer, but smaller than those in patients using PPI for more than 36 months. A speculative explanation for this observation may be that the PPI effect in the subgroup with PPI use <12 months, compared to the subgroup with PPI use ≥12 months, may be confounded to a larger extent with the effect of \textit{H. pylori} infection, because in the \textit{H. pylori} eradication procedure PPI is prescribed only for a short-term use. However, when PPIs are used for a sufficiently long time, the interaction effect between PPIs and \textit{H. pylori} may substantially increase the risk of gastric cancer as observed in the subgroup with PPI use >36 months. This interaction effect is supported by a number of studies. In a normal gastric acid environment, \textit{H. pylori} colonizes the gastric antrum,\textsuperscript{64} causing an antrum-predominant gastritis. Inflammation of the antral mucosa stimulates gastrin secretion, which maintains the normal or high acidic environment. In this case the patterns of \textit{H. pylori} colonization and gastric secretion are stable. When acid secretion is suppressed for whatever reason including the use of PPI, \textit{H. pylori} also colonizes the stomach body, causing a corpus-predominant gastritis,\textsuperscript{65} which may impair function of parietal cells. As a consequence, the acid-suppressive effect of PPIs is enhanced\textsuperscript{24,25} and this leads to overgrowth of non-\textit{H. pylori} bacteria;\textsuperscript{26} the double infection with non-\textit{H. pylori} and \textit{H. pylori} bacteria causes more severe gastritis\textsuperscript{27}, which can lead to atrophic gastritis following long-term use of PPIs.\textsuperscript{66,67} Corpus gastritis and gastric atrophy are well recognized as important risk factors for gastric cancer.\textsuperscript{28,68} It should be noted that the validity of this explanation depends also on the prevalence of \textit{H. pylori} infection in subgroups of patients, but this information was not available in the included studies. Another explanation for the inconsistency in the trend of the relationship between duration of PPI use and the risk of gastric cancer may be that the numbers
of data points included in the first subgroup (PPI use <12 months) and third subgroup (PPI use >36 months) were small, which made the estimates of the summary RRs imprecise.

Study strengths and limitations

In this review, the quality of the included studies, including the bias in their results, were rigorously assessed. We used both fixed- and random-effects model to summarize the effects of PPI use on the risk of gastric polyps and cancer, and compared the results from two types of models.

Our study has some limitations. The number of included studies reporting on gastric cancer was small and thus the pooled effects and the heterogeneity assessment may be imprecise, and the publication bias of these studies could not be adequately assessed. Because the status of H. pylori infection was only partially controlled for in one study, we could not distinguish between an isolated PPI effect and a synergistic PPI- H. pylori effect. In the subgroup analysis, we did not have enough information to classify the studies or patients based on mutually exclusive periods of PPI use; the overlap of the periods (e.g. ≥12 months and >36 months) and the unequal number of data points between subgroup did not allow a firm conclusion about the trend of change in the risk of FGPs or gastric cancer with increasing lengths of PPI exposure.

CONCLUSIONS

Long-term use of PPIs (≥12 months) is most likely associated with an increased risk of FGPs, but the clinical significance of this is currently unclear. Therapy with PPIs may also increase the risk of gastric cancer, but this association can be biased due to a limited number of available studies and possible confounding by indication and by other factors. Given the large number of patients receiving PPIs, more and higher-quality studies are needed to confirm or repudiate any causal link between PPI use and gastric cancer. In addition, the potential link between PPI-related FGPs and gastric cancer should be studied in more details.

ACKNOWLEDGEMENTS

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References


### Table 1. Characteristics of the included studies on the use of proton pump inhibitors and risks of gastric polyps and cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Outcome</th>
<th>Study design; analysis type; country</th>
<th>Period of recruitment</th>
<th>Patient inclusion criteria</th>
<th>H. pylori infection prevalence in study population</th>
<th>No. PPI users /No. PPI non-users</th>
<th>No. events in PPI users/No. events in PPI non-users</th>
<th>Mean age (SD or range)</th>
<th>% Male</th>
<th>PPI use</th>
<th>Adjustment for covariates and study quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peura et al., 2009[17]</td>
<td>Gastric polyps (location not specified)</td>
<td>RCT; Prospective; USA</td>
<td>Dec 2005-May 2007</td>
<td>No criteria regarding age, gender, life style, socioeconomic status, medication or comorbidity</td>
<td>Not reported</td>
<td>5,633/896</td>
<td>19/1</td>
<td>Patients receiving PPIs: 47.7* (13.7)† Patients receiving placebo: 48.4 (13.7)</td>
<td>19/1</td>
<td>Patients receiving PPIs: 47.9 Patients receiving placebo: 33.7</td>
<td>Type and dose: Dexlansoprazole MR 30, 60 or 90 mg d⁻¹; Lansoprazole 30 mg d⁻¹ Duration of exposure: ≤ 12 months (mean: 276 days; SD: 134 days)</td>
</tr>
</tbody>
</table>

*Sequence generation and concealment of allocation sequence were described in another article;[20] these steps were conducted using the Interactive Voice Response System (IVRS; ClinPhone Inc., Northbrook, IL, USA), of which the adequacy assessment is beyond the scope of the present study; This was an open-label extension of a triple-blind RCT; Incomplete outcome data were not adequately addressed; there was no evidence of selective outcome reporting; important potential confounders (e.g. H. pylori infection, peptic ulcer) were not taken into account in study design and analysis.
<table>
<thead>
<tr>
<th>Study</th>
<th>FGPs detected by EGD or histological examination</th>
<th>Study Design</th>
<th>Study Period</th>
<th>Patient Characteristics</th>
<th>Type and Dose</th>
<th>Exposure Time</th>
<th>Analysis Method</th>
<th>Covariates</th>
<th>NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choudhry et al., 1998&lt;sup&gt;8&lt;/sup&gt;</td>
<td>FGP detected by EGD</td>
<td>Cohort; Retrospective; USA</td>
<td>Mar 1987-Feb 1996</td>
<td>Patients undergoing EGD</td>
<td>Not reported</td>
<td>231/2,072</td>
<td>7/6</td>
<td>No adjustment; NOS = 5</td>
<td></td>
</tr>
<tr>
<td>Vieth and Stolte, 2001&lt;sup&gt;9&lt;/sup&gt;</td>
<td>FGP detected by histological examination</td>
<td>Cohort; Retrospective; Germany</td>
<td>During year 1999</td>
<td>Patients with no infection of H. pylori</td>
<td>0%</td>
<td>2,251/ 28,096</td>
<td>116/1,415</td>
<td>PPI users: 53.1* (16.4)† PPI non-users: 53.0* (17.6)‡</td>
<td>No adjustment; NOS = 5</td>
</tr>
<tr>
<td>Jalving et al., 2006&lt;sup&gt;10&lt;/sup&gt;</td>
<td>FGP detected by EGD, confirmed by histological examination</td>
<td>Cohort; Retrospective; Netherlands</td>
<td>Nov 2002-Mar 2005</td>
<td>Patients undergoing EGD</td>
<td>Not reported</td>
<td>322/277</td>
<td>75 (23.3%) / 32 (11.5%)</td>
<td>PPI users: 55.5* (21-86) PPI non-users: 51 (17-88)</td>
<td>Logistic regression was used to estimate ORs; Covariates included age, reasons for PPI use and use of other medications&lt;sup&gt;§&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ally et al., 2009&lt;sup&gt;11&lt;/sup&gt;</td>
<td>FGP detected by EGD, confirmed by histological examination</td>
<td>Cohort; Retrospective; USA</td>
<td>Mar 2007-Sep 2007</td>
<td>Patients undergoing EGD</td>
<td>12.2% (none of these developed FGPs)</td>
<td>252/133</td>
<td>33/10</td>
<td>52 (15)</td>
<td>Multiple logistic regression was used to estimate ORs; Covariates included duration of PPI use, H. pylori infection and Caucasian race</td>
</tr>
<tr>
<td>Hsu et al., 2010&lt;sup&gt;12&lt;/sup&gt;</td>
<td>FGP detected by EGD, confirmed by histological examination</td>
<td>Cohort; Retrospective; Taiwan</td>
<td>Jan 2007-Aug 2007</td>
<td>Exclusion: Patients with incomplete colonoscopy examination, inadequate bowel preparation, inflammatory bowel disease, newly diagnosed GI malignancy, and familial colon polyposis</td>
<td>PPI users: 6.6%; PPI non-users: 21.2%</td>
<td>122/137</td>
<td>60/38</td>
<td>PPI users: 61.3 (11.2); PPI non-users: 52.5 (12.9)</td>
<td>No adjustment; NOS = 7</td>
</tr>
<tr>
<td>Author, year</td>
<td>Outcome</td>
<td>Study design; analysis type; country</td>
<td>Period of recruitment</td>
<td>Patient inclusion criteria</td>
<td>No. cases/No. controls</td>
<td>Mean age (SD or range)</td>
<td>% Male</td>
<td>PPI use</td>
<td>Adjustment for covariates</td>
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<tr>
<td>Zelter et al., 2011</td>
<td>FGP detected by EGD, confirmed by histological examination</td>
<td>Cohort; Prospective; Argentina</td>
<td>Jun 2007-Aug 2008</td>
<td>Patients undergoing EGD PPI users: 18.2%; PPI non-users: 16.7%</td>
<td>313/1462</td>
<td>50.7* (14.9)†</td>
<td>41.1</td>
<td>Type and dose: Not reported; Duration of exposure: &gt; 12 months</td>
<td>Multiple logistic regression was used to estimate ORs; Covariates included age, gender and H. pylori infection; NOS = 7</td>
</tr>
<tr>
<td>Poulsen et al., 2009</td>
<td>Gastric cancer identified using a modified Danish version of ICD-7 code</td>
<td>Population-based cohort; Retrospective; Denmark</td>
<td>Jan 1990-Dec 2003</td>
<td>Patients aged 40-84 years without a history of cancer (except non-melanoma skin cancer); For patients receiving PPIs, only new users were included, i.e. all patients prescribed PPIs during 1989 (the year before the index date) or before 40 years old were excluded</td>
<td>18,790/not reported</td>
<td>62 (SD not reported)</td>
<td>47%</td>
<td>Type: Omeprazole (dominant), lansoprazole, esomeprazole, pantoprazole, rabeprazole; Dose: Not reported; Duration of exposure: Four groups, &lt; 1 year, 1 year, 2-4 years and &gt; 5 years</td>
<td>Log-linear Poisson was used to estimate incident rate ratios; Covariates included calendar period, age, gender, gastroscopy (≥ 1 year before gastric cancer diagnosis), COPD, alcohol-related admission or therapy, number of NSAID prescription, history of H. pylori eradication therapy, smoking, and alcohol-related admission or therapy; NOS = 8</td>
</tr>
</tbody>
</table>

**Case-control study**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Outcome</th>
<th>Study design; analysis type; country</th>
<th>Period of recruitment</th>
<th>Patient inclusion criteria</th>
<th>No. cases/No. controls</th>
<th>No. PPI users in cases/No. PPI users in controls</th>
<th>Mean age (SD or range)</th>
<th>% Male</th>
<th>PPI use</th>
<th>Adjustment for covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cao et al., 2014</td>
<td>FGP detected by EGD, confirmed by histological examination</td>
<td>Case-control; Retrospective; China</td>
<td>Mar 2011-Mar 2012</td>
<td>Patients undergoing EGD CASES: 22.3%; CONTROLS: 42.3%</td>
<td>328/656</td>
<td>54/136</td>
<td>CASES: 55.1 (12.6) CONTROLS: 54.9 (12.7)</td>
<td>24.1%</td>
<td>Type and dose: not reported; Duration of exposure: Three groups: 1-6 months, 6 months-1 year, and &gt; 1 year</td>
<td>No adjustment; NOS = 3</td>
</tr>
<tr>
<td>Study</td>
<td>Type of Cancer</td>
<td>Study Design</td>
<td>Country</td>
<td>Study Period</td>
<td>Cases/Controls</td>
<td>CASES:</td>
<td>CONTROLs:</td>
<td>Type and Dose</td>
<td>Exposure Time</td>
<td>ORS</td>
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<tr>
<td>Garcia Rodriguez et al., 2006</td>
<td>Gastric adenocarcinoma</td>
<td>Nested case-control; Retrospective; UK</td>
<td>Jan 1994-Dec 2001</td>
<td>For both cases and controls: Patients aged 40-84 years, enrolled with a general practitioner for at least two years, having at least on year of prescription history recorded in the database, and with no history of cancer. For cases: Patients with no another concurrent cancer</td>
<td>Not available</td>
<td>522/10,000</td>
<td>43/399</td>
<td>Mean: not reported; range: 40-84</td>
<td>Type and dose: not reported; Exposure time: three groups, &lt; 1 year, 1-3 years, and &gt; 3 years</td>
<td>Unconditional logistic regression was used to estimate ORs; Covariates included smoking, alcohol consumption, age, sex, calendar year, BMI, gastro-oesophageal reflux, hiatal hernia, peptic ulcer and dyspepsia; NOS = 6</td>
</tr>
<tr>
<td>Crane et al., 2007</td>
<td>Gastric adenocarcinoma</td>
<td>Case-control; Retrospective; USA</td>
<td>1971-2000</td>
<td>Patients without a history of cancer</td>
<td>Not available</td>
<td>121/121</td>
<td>2/0</td>
<td>74 (13)</td>
<td>Type and dose: not reported; Exposure time: &gt; 1 year</td>
<td>Unable to compute an OR as no patient in controls was exposed to PPIs; NOS = 5</td>
</tr>
<tr>
<td>Tamim et al., 2008</td>
<td>Gastric cancer identified using ICD codes</td>
<td>Nested case-control; Retrospective; Canada</td>
<td>Jan 1995-Dec 2003</td>
<td>All people living in Quebec, eligible for outpatient prescription drug benefits for at least 5 years, and with no history of cancer</td>
<td>Not available</td>
<td>1,598/12,991</td>
<td>248/1,402</td>
<td>CASES: 75.5 (9.3) CONTROLs: 75.9 (8.8)</td>
<td>CASES: 52.1 CONTROLs: 51.5</td>
<td>Type, dose and exposure time: not reported</td>
</tr>
</tbody>
</table>

BMI, biomass index; EGD, esophagogastroduodenoscopy; FGP, fundic gland polyps; GI, gastrointestinal; GP, general practitioner; GPRD, General Practice Research Database (now CPRD); ICD, International Classification of Diseases; NOS, Newcastle-Ottawa Scale; OR, odds ratio; PPI, proton pump inhibitor.

* Weighted mean.
† Pooled SD.
‡ Values available for Dexlansoprazole only.
§ Information obtained from personal communications with the authors.
‡‡ Applicable only for a subgroup of 306 patients whose biopsies were taken; of these patients, 55 received PPIs.
Total articles: \((n = 1,809)\)
- Medline: 335
- Embase: 1,258
- Cochrane Central Register of Controlled Trial: 215
- Manual search: 1

Scan of titles and abstracts by two independent reviewers

Articles requiring full-text review \((n = 32)\)

Excluded \((n = 1,777)\)
- Review, recommendation, guideline or opinion (no original clinical data): 769
- Ineligible study design/analysis (cross-sectional, cross-over): 18
- No assessment of association between PPIs and outcomes of interest: 738
- Lack of comparison between PPI and no PPI: 6
- Case report: 214
- Modelling study: 8
- Duplicated: 24

Review of full-text by two independent reviewers

Articles meeting criteria for complete data extraction \((n = 12)\)
- \((Gastric polyps: 8; Gastric cancer: 4)\)

Figure 1. Flow chart of study selection.
Figure 2. Forest plots of (A) odds ratios for gastric polyps and (B) risk ratios of gastric cancer in patients receiving proton pump inhibitors compared with subjects not receiving proton pump inhibitors. CC, case-control study; CH, cohort study; FGPs, fundic gland polyps; GC, gastric cancer; GCA, gastric cardia adenocarcinoma; GNCA, gastric non-cardia adenocarcinoma; GPs, gastric polyps; RCT, randomised controlled trial.
Figure 3. Forest plots of (A) odds ratios for fundic gland polyps and (B) risk ratios of gastric cancer in subgroups of patients receiving proton pump inhibitors for different durations compared with subjects not receiving proton pump inhibitors. FGPs, fundic gland polyps; GC, gastric cancer; GCA, gastric cardia adenocarcinoma; GNCA, gastric non-cardia adenocarcinoma; PPI, proton pump inhibitor.
Figure 4. Funnel plot for detection of possible bias of publication on the effect of proton pump inhibitor use on gastric polyps.
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Author/s:
Tran-Duy, A; Spaetgens, B; Hoes, AW; de Wit, NJ; Stehouwer, CDA

Title:
Use of Proton Pump Inhibitors and Risks of Fundic Gland Polyps and Gastric Cancer: Systematic Review and Meta-analysis

Date:
2016-12

Citation:

Persistent Link:
http://hdl.handle.net/11343/123650