Intake of Proton-Pump Inhibitors and Gastric Cancer within the Stomach Cancer Pooling (StoP) Project

Michele Sassano[1,2], Marco Mariani[2], Claudio Pelucchi[3], Nuno Lunet[4,5,6], Samantha Morais[4,5,6], Vicente Martín[7,8], Victor Moreno[8,9,10,11], Maria Paula Curado[12], Emmanuel Dias-Neto[12], Marcis Leja[13,14,15,16], Evita Gašenko[14,15,16], Carlo La Vecchia[3], Stefania Boccia[2,17], and Roberta Pastorino[17]

ABSTRACT

Background: A potential association between proton-pump inhibitors (PPI) and gastric cancer remains undefined. Thus, we aimed to evaluate such association within the Stomach cancer Pooling (StoP) Project.

Methods: Data from five case–control studies of the StoP Project were included (1,889 cases and 6,517 controls). We assessed the impact of different exposure definitions, specifically any reported use of PPIs and exposure definitions based on the duration of PPI intake. Additionally, we modeled the dose–response relationship between the cumulative duration of PPI intake and gastric cancer.

Results: Significant associations between PPI intake and gastric cancer, both overall and in the stratified analyses, were limited to exposure definitions based on short durations of intake. The overall odds ratio (OR) for any reported PPI intake was 1.78 [95% confidence interval (CI): 0.76–4.14]. In the dose–response analysis, the ORs of gastric cancer were found to be higher for short durations of PPI intake (6 months: OR 3.26; 95% CI: 2.40–4.42; one year: OR 2.14; 95% CI: 1.69–2.70; 2 years: OR 1.50; 95% CI: 1.22–1.85; 3 years: OR 1.27; 95% CI: 1.03–1.56), with the association becoming not significant for durations longer than 3 years.

Conclusions: Our findings suggest that the observed association between PPIs and gastric cancer might be mainly due to reverse causality.

Impact: The results of this study suggest that PPIs are a safe therapeutic choice regarding their effect on the occurrence of gastric cancer.

See related commentary by Richman and Leiman, p. 1127

Introduction

Gastric cancer represents the fifth most common type of cancer and the fourth leading cause of cancer death worldwide, with an estimated 1.1 million new cases and around 770 thousand deaths due to gastric cancer in 2020 (1).

Research has focused on the effect of specific medications on the risk of gastric cancer (2, 3). Among them, acid-suppressive agents may play a role by modifying gastric pH and interfering with the gastric microbiota (4), as well as by leading to hypochloridria and hypergastrinemia and therefore to an increased risk of gastric cancer (4–6).

Since their introduction, proton-pump inhibitors (PPI) have been the most popular acid-suppressive agents and have also been among the most commonly prescribed drugs (7). The use of PPIs has previously been associated with an increased risk of gastric cancer (4, 8, 9). However, it has been suggested that such association could be mainly due to protopathic bias, i.e., reverse causality occurring when the treatment under investigation is used to treat symptoms of the disease (10, 11). In this context, PPIs could be associated with gastric cancer as they might be used to treat initial symptoms of the disease. This hypothesis is based on mainly the observation that the association is stronger for a shorter duration of use of PPIs (9, 12). Indeed, when taking into account the duration of therapy with PPIs (9, 12), results become more conflicting.

Our aim was to investigate the association between the use of PPIs and gastric cancer by considering the duration of intake, using data on risk factors for gastric cancer provided by the "Stomach Cancer Pooling (StoP) Project," an international consortium of case–control studies (13).

Materials and Methods

Study population

Information regarding the StoP Project, a consortium of epidemiologic studies on gastric cancer, is reported in detail elsewhere (13).

Briefly, the consortium was founded in July 2012 by identifying case–control and nested case–control studies on gastric cancer using different search methods, such as electronic databases, manual search of citations, and contact with experts. Eventually, principal investigators of these

[1]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy. [2]Section of Hygiene, University Department of Life Sciences and Public Health, Università Cattolica del Sacro Cuore, Rome, Italy. [3]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy. [4]EPIUnit - Instituto de Saúde Pública, Universidade do Porto, Porto, Portugal. [5]Laboratório para a Investigação Integrativa e Translacional em Saúde Populacional (ITR), Porto, Portugal. [6]Departamento de Ciências da Saúde Pública e Forenses e Educação Médica, Faculdade de Medicina, Universidade do Porto, Porto, Portugal. [7]Faculty of Health Sciences, Department of Biomedical Sciences, Area of Preventive Medicine and Public Health, Universidad de León, León, Spain. [8]Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP), Madrid, Spain. [9]Oncology Data Analytics Program, Catalan Institute of Oncology (ICO), Barcelona, Spain. [10]Colorectal Cancer Group, ONCOBELL Program, Institut de Recerca Biomedica de Bellvitge (IDIBELL), Barcelona, Spain. [11]Department of Clinical Sciences, Faculty of Medicine, University of Barcelona, Barcelona, Spain. [12]Centro Internacional de Pesquisa, A. C. Camargo Cancer Center, São Paulo, Brasil. [13]Digestive Diseases Centre GASTRO, Riga, Latvia. [14]Institute of Clinical and Preventive Medicine, University of Latvia, Riga, Latvia. [15]Faculty of Medicine, University of Latvia, Riga, Latvia. [16]Riga East University Hospital, Riga, Latvia. [17]Department of Woman and Child Health and Public Health–Public Health Area, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy.

S. Boccia and R. Pastorino contributed equally as senior authors.

Corresponding Author: Michele Sassano, Department of Medical and Surgical Sciences, University of Bologna, Via Pelagio Palagi, 9, Bologna, Italy. Phone: 3906-3015-4396; E-mail: michele.sassano3@unibo.it

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studies were invited to join the consortium. Participating studies utilized different study protocols and adopted different questionnaires to collect data; thus, data harmonization was performed by the coordinating center in Milan for a set of core variables (such as age, sex, education/socioeconomic status, smoking and alcohol drinking habits, family history of gastric cancer, selected dietary variables, and—if available—markers of *Helicobacter pylori* infection). However, for each specific study, additional relevant data (i.e., intake of PPI in the current analysis) are harmonized by the proponent team.

The current study is based on version 3.2 of the StoP Project data set, including 34 case–control or nested within cohorts case–control studies, for a total of 13,121 gastric cancer cases and 31,420 controls. Based on data availability regarding PPI intake, data from five studies of the StoP Project were included in the current analysis, with 1,889 and 6,517 included cases and controls. In detail, we included one study each from Italy (14), Spain (15), Portugal (16), Latvia (17), and Brazil (ref. 18; Supplementary Table S1).

Study procedures were conducted in line with the principles outlined in the Declaration of Helsinki. Each study contributing data to the present analysis obtained written informed consent from all participants and was approved by the local ethics committee. In addition, the StoP Project received ethical approval from the University of Milan Review Board (reference 19/15, April 1, 2015).

Study outcome and exposure definition

The outcome of interest of the current study is histologically confirmed gastric cancer. The studies reported information on the different subsites (cardia, noncardia, and unspecified) and Lauren histologic classification (intestinal, diffuse, and others, including mixed, undifferentiated, and unclassified type) of gastric cancer.

Exposure to PPIs and information on covariates were assessed using structured questionnaires. Further information regarding questionnaires is reported in Supplementary Table S2. As for exposure definition, firstly, study participants were considered exposed if they reported intake of PPIs in any form, regardless of its duration or intensity. Secondly, in order to minimize the risk of protopathic bias and to assess how different exposure definitions modify the association with the outcome of interest, we adopted a time-based exposure definition based on the cumulative duration of intake of PPIs. Thus, study participants were considered exposed only if they reported cumulative intake of PPIs that lasted for a period equal to or longer than a specified cutoff (6 months, 1 year, 2 years, 5 years, 10 years, 15 years). In all analyses, participants were considered not exposed if they did not report intake of PPIs.

In addition, we also considered the duration of PPI intake as continuous to model the dose–response relationship with gastric cancer, as described below.

Statistical analysis

A two-stage model was adopted for the analysis. In particular, in the first stage, study-specific odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were computed using unconditional logistic regression for each exposure considered. According to data availability (proportion of missing values <30%) and feasibility, the following covariates were included in the logistic regression models (Supplementary Table S1): sex, age, socioeconomic status (low, intermediate, or high, according to study-specific definitions based on education, income, or occupation), body mass index (BMI), smoking status (never, former, and current), alcohol drinking status (never, former, and current drinker), family history of gastric cancer, and history of peptic ulcer. In addition, for covariates with up to 10% missing values, we performed multiple imputations using full chained equations, generating 10 imputed data sets for each study. Each imputation model included the same set of covariates and outcome as the analysis model, and imputation results were combined using Rubin's rule (19, 20). Thus, study-specific ORs and 95% CIs were pooled in the second (pooling) stage using the Mandel–Paule random-effects model, with heterogeneity between studies assessed through I^2 statistics (21). In addition, we repeated the analysis by omitting one study at a time to assess whether our findings were dependent on estimates from a single study.

We also carried out stratified analyses according to the following categorical variables: sex, age (≤60 years, >60 years), *H. pylori* infection, socioeconomic status (low, intermediate, and high), smoking status (never, former, and current), and alcohol drinking (never, former, and current). Moreover, we carried out a sensitivity analysis by restricting the analysis to all cases, regardless of history of *H. pylori* infection, and controls with a history of infection only (13). Information regarding the history of *H. pylori* infection was available for four studies and was determined serologically for three of them, specifically enzyme-linked immunosorbent assay (ELISA; Portugal, Latvia; refs. 16, 17), western blot (Portugal; ref. 16), or multiplex serology (Spain; ref. 15). For one study (Brazil), different methodologies were used to assess participants' history of *H. pylori* infection, including rapid urease test and histologic examination of tissue samples. We used multinomial logistic models to obtain study-specific ORs and the corresponding 95% CIs in relation to gastric cancer subsite (cardia and noncardia) and histologic type (intestinal, diffuse, and others, according to Lauren classification), which were then pooled as described above (pooling stage).

In addition, we computed the relative excess risk due to interaction (RERI; ref. 22) from a one-stage mixed-effects logistic model to assess the occurrence of additive interaction between the exposure, defined by any reported intake of PPIs, and the following covariates: sex, age (≤60 years and >60 years), *H. pylori* infection, socioeconomic status (low and high), smoking status (never and ever), drinking status (never and ever).

We modeled the dose–response relationship between the duration of PPI intake (months, continuous) and gastric cancer with a one-stage logistic mixed-effects model. Thus, we examined the shape of the relationship, with linearity assessed by including the exposure variable as continuous in the model and nonlinearity by using first- and second-order fractional polynomials. The same set of covariates described above was included in the model, and missing values of covariates were retained in the analysis, either grouped in a separate category for categorical variables or replaced with the study-specific median values among controls for continuous variables. Dummy variables indicating replacements were also included in the model for the latter. The best-fitting model, which means the model with the lowest deviance difference compared with the linear model, was selected (23). Only studies with detailed information on duration of intake of PPIs (15, 18) were included in the dose–response analysis.

Results were considered significant if $P < 0.05$, and all statistical analyses were carried out using Stata software version 14 (StataCorp LP).

Data availability

The data generated in this study are not publicly available due to approval requirements for data sharing from each center contributing with data to the present analysis but are available upon reasonable request from the corresponding author.

Results

The main characteristics and the distribution of the exposure among study participants are reported in **Table 1** and Supplementary Table S3, respectively. Cases (57.0%) more frequently reported a lower socioeconomic status compared with controls (42.6%). Furthermore, cases had slightly lower proportions of never smokers (48.3% vs. 49.1%) and never drinkers (19.0% vs. 22.3%) than controls. Higher proportions of cases than controls reported a history of peptic ulcer (6.9% vs. 5.8%) and a family history of gastric cancer (15.0% vs. 5.3%) and had history of *H. pylori* infection (54.7% vs. 51.1%). When considering any reported intake of PPIs, the proportion of exposed

Table 1. Main characteristics of individuals included in the analysis.

Characteristics	Controls (%) *n* = 6,517	Cases (%) *n* = 1,889	Total (%) *n* = 8,406	*P* value
Study				
Italy	444 (6.81)	160 (8.47)	604 (7.19)	
Portugal	1,667 (25.58)	692 (36.63)	2,359 (28.06)	
Spain	3,440 (52.79)	441 (23.35)	3,881 (46.17)	
Latvia	228 (3.50)	228 (12.07)	456 (5.42)	
Brazil	738 (11.32)	368 (19.48)	1,106 (13.16)	
Type of controls				
Hospital-based	1,410 (21.64)		1,410 (21.64)	
Population-based	5,107 (78.36)		5,107 (78.36)	
Sex				<0.0001
Male	3,473 (53.29)	1,120 (59.29)	4,593 (54.64)	
Female	3,044 (46.71)	769 (40.71)	3,813 (45.36)	
Age, mean (SD)	61.18 (12.84)	62.86 (12.79)	61.56 (12.84)	<0.0001
History of *H. pylori* infection				<0.0001
No	578 (8.87)	301 (15.93)	879 (10.46)	
Yes	3,327 (51.05)	1,034 (54.74)	4,361 (51.88)	
Missing	2,612 (40.08)	554 (29.33)	3,166 (37.66)	
Socioeconomic status				<0.0001
Low	2,775 (42.58)	1,076 (56.96)	3,851 (45.81)	
Intermediate	1,697 (26.04)	316 (16.73)	2,013 (23.95)	
High	1,518 (23.29)	187 (9.90)	1,705 (20.28)	
Missing	527 (8.09)	310 (16.41)	837 (9.96)	
Smoking status				0.868
Never	3,197 (49.06)	913 (48.33)	4,110 (48.89)	
Former	1,984 (30.44)	585 (30.97)	2,569 (30.56)	
Current	1,194 (18.32)	346 (18.32)	1,540 (18.32)	
Missing	142 (2.18)	45 (2.38)	187 (2.22)	
Alcohol drinking status				<0.0001
Never	1,450 (22.25)	358 (18.95)	1,808 (21.51)	
Former	618 (9.48)	375 (19.85)	993 (11.81)	
Current	3,462 (53.12)	791 (41.87)	4,253 (50.59)	
Missing	987 (15.15)	365 (19.32)	1,352 (16.08)	
Family history of GC[a]				<0.0001
No	4,675 (71.74)	1,265 (66.97)	5,940 (70.66)	
Yes	347 (5.32)	284 (15.03)	631 (7.51)	
Missing	1,495 (22.94)	340 (18.00)	1,835 (21.83)	
BMI, mean (SD)	26.91 (4.55)	26.42 (4.88)	26.80 (4.63)	<0.0001
History of peptic ulcer				0.013
No	5,530 (84.85)	1,471 (77.87)	7,001 (83.29)	
Yes	379 (5.82)	131 (6.93)	510 (6.07)	
Missing	608 (9.33)	287 (15.19)	895 (10.65)	
Subsite				
Cardia		242 (12.81)	242 (12.81)	
Noncardia		1,259 (66.65)	1,259 (66.65)	
Unspecified		149 (7.89)	149 (7.89)	
Missing		239 (12.65)	239 (12.65)	
Histologic type				
Intestinal		671 (35.52)	671 (35.52)	
Diffuse		470 (24.88)	470 (24.88)	
Other/mixed/undifferentiated/unclassified		181 (9.58)	181 (9.58)	
Missing		567 (30.02)	567 (30.02)	

Abbreviations: BMI, body mass index; GC, gastric cancer; SD, standard deviation.
[a]First-degree relatives.

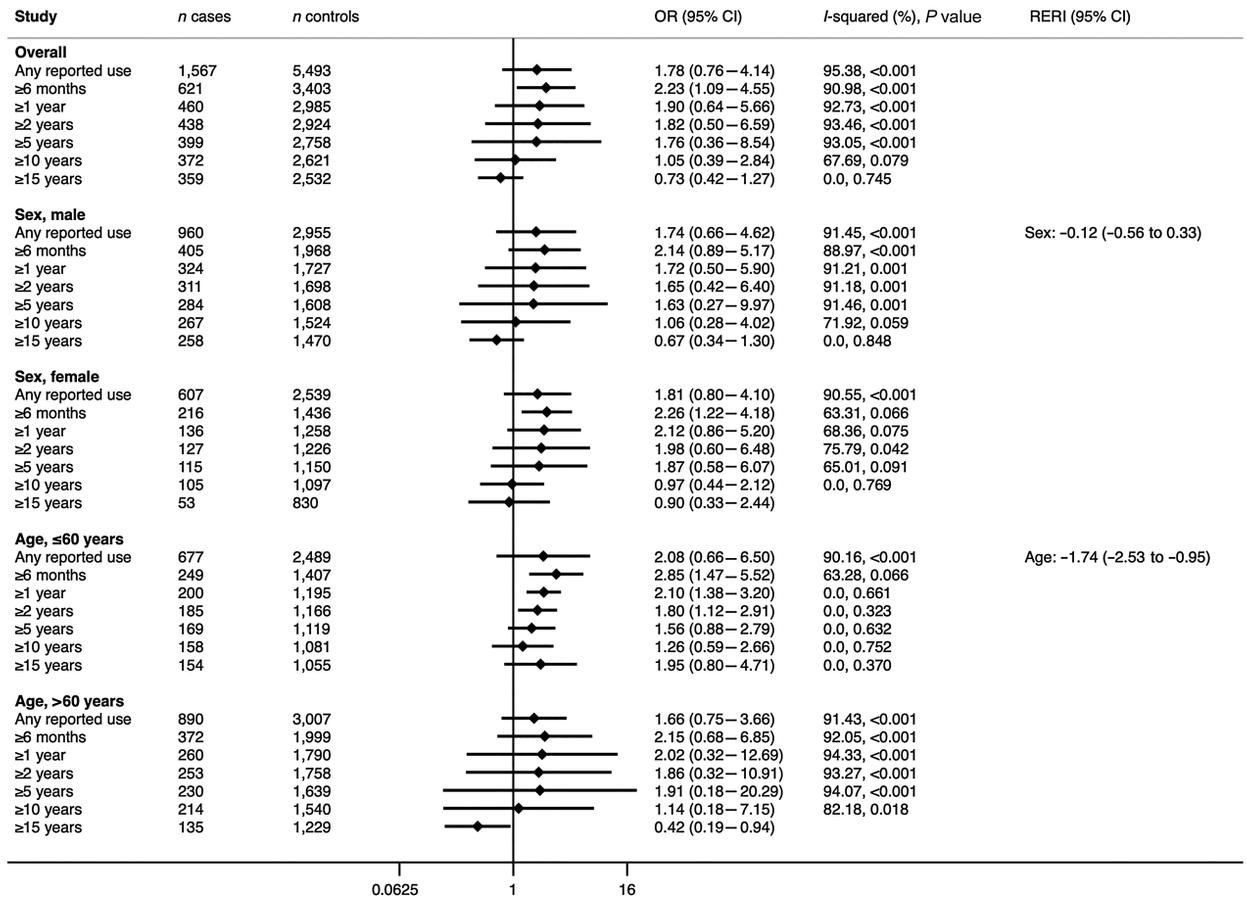

Figure 1.

Pooled adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for the association between intake of proton-pump inhibitors and gastric cancer, overall and stratified by selected study participants' demographic characteristics (sex and age). In all analyses, study participants were considered not exposed if they did not report intake of PPIs.

individuals was higher among cases (25.7%) than among controls (21.0%), whereas the opposite was observed when using time-based exposure definitions (Supplementary Table S3).

The pooled overall ORs and the corresponding 95% CIs of the association between the intake of PPIs and gastric cancer using different exposure definitions are reported in **Fig. 1**. In all cases, no significant association was found between PPI intake and gastric cancer, the only exception was observed when considering an exposure based on PPI intake for at least 6 months (OR = 2.23; 95% CI: 1.09–4.55; **Fig. 1**). In addition, after omission of the study from Latvia (17), the association between any reported intake of PPIs and gastric cancer became significant too (Supplementary Table S4).

The results of the stratified analyses confirmed the finding of no association across strata of sex, age, socioeconomic status, smoking status, alcohol drinking status, *H. pylori* infection, subsite of gastric cancer, or histologic type of gastric cancer (**Figs. 1** and **2**; Supplementary Figs. S1 and S2). However, significant associations were found among female individuals when considering an exposure based on PPI intake for at least 6 months (OR = 2.26; 95% CI: 1.22–4.18), and individuals ages 60 or younger when considering the exposure defined by PPI intake for at least 6 months (OR = 2.85; 95% CI: 1.47–5.52), 1 year (OR = 2.10; 95% CI: 1.38–3.20), or 2 years (OR = 1.80; 95% CI: 1.12–2.91). No significant association was found among male individuals and those ages 60 or older (**Fig. 1**).

When stratifying according to *H. pylori* infection (Supplementary Fig. S1), the only significant association found was among individuals without infection when considering any reported intake of PPIs (OR = 2.17; 95% CI: 1.28-3.65). However, in the sensitivity analysis including all cases and controls with *H. pylori* infection, significant associations were observed for exposures defined by a duration of intake of at least 6 months (OR = 1.38; 95% CI: 1.01–1.87) and one year (OR = 1.37; 95% CI: 1.01–1.87).

As to the stratified analyses according to smoking status or alcohol drinking, results were similar to those described above, with no consistent associations among never and current smokers and drinkers when considering exposure definitions based on short durations of intake (Supplementary Fig. S2).

Age and socioeconomic status were the only investigated factors showing additive interaction with PPI intake (**Fig. 1**; Supplementary Fig. S1). However, ORs appeared to be similar across strata of age when considering long durations of intake. Instead, we found significant associations even for exposures defined by long durations of PPI intake among individuals with high socioeconomic status, as opposed to those with low socioeconomic status (Supplementary Fig. S1).

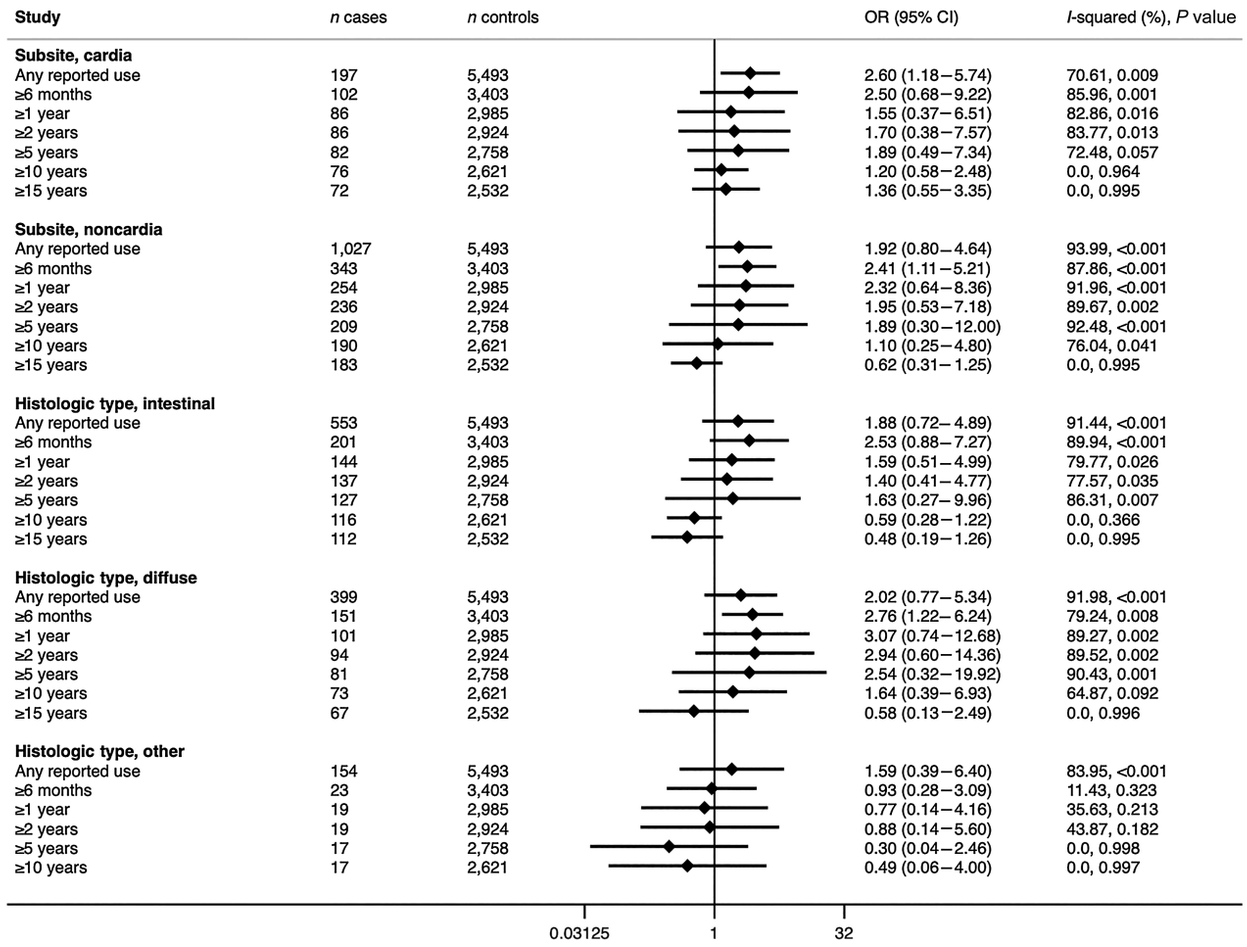

Figure 2.

Pooled adjusted ORs and corresponding 95% CIs for the association between intake of proton-pump inhibitors and gastric cancer, by subsite and histologic type. In all analyses, study participants were considered not exposed if they did not report intake of PPIs.

As for gastric cancer subsites and histologic types, associations were found with cardia gastric cancer for any reported intake of PPIs (OR = 2.60; 95% CI: 1.18–5.74), and noncardia gastric cancer (OR = 2.41; 95% CI: 1.11–5.21]) and diffuse histologic type (OR = 2.76; 95% CI: 1.22–6.24) with the exposure definition based on PPI intake lasting for at least 6 months (**Fig. 2**).

Furthermore, significant between-study heterogeneity was found in the overall and in most of the stratified analyses ($P < 0.05$, $I^2 > 40.0\%$), greatly reduced only among individuals ages 60 years or younger, among participants with a high socioeconomic status and across strata of *H. pylori* infection (**Figs. 1** and **2**; Supplementary Figs. S1 and S2).

The best-fitting dose–response model between cumulative duration of PPI intake and the odds of gastric cancer was $\ln(\text{OR}) = -4.26 \times 10^{-6} \times \text{duration}^{-2} + 0.15 \times \text{duration}^{-0.5}$ (**Fig. 3**). Increased odds of gastric cancer compared with individuals reporting no intake were observed for short-term PPI intake (up to 3 years), with the association becoming not significant in the long term. Specifically, the following OR estimates were obtained: 3.26 (95% CI: 2.40–4.42), 2.14 (95% CI: 1.69–2.70), 1.50 (95% CI: 1.22–1.85), 1.27 (95% CI: 1.03–1.56), 1.14 (95% CI: 0.92–1.42), 1.07 (95% CI: 0.85–1.33), 0.89 (95% CI: 0.70–1.14), and 0.82 (95% CI: 0.64–1.07), for durations of PPI intake of 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 10 years, and 15 years, respectively.

Discussion

Our study does not report a consistent association between the use of PPIs and gastric cancer, with significant associations found only for exposure definitions based on short durations of intake. These results were confirmed in the stratified analyses, and in the one-stage analysis of the dose–response relationship between PPIs and gastric cancer. In addition, for similar durations of use, significant associations were found between PPI intake and cardia, noncardia, and diffuse gastric cancer. An interesting finding was a significant association between PPI intake and gastric cancer among individuals with a high socioeconomic status, suggesting the occurrence of effect modifications by the latter. This was observed even for exposure definitions based on long durations of intake (up to 10 years). This might be partly due to the fact that wealthier and better-educated individuals usually seek medical advice and care promptly when experiencing disease symptoms, whereas disadvantaged individuals often delay the healthcare process (24–27). In this specific case, individuals with a low to moderate socioeconomic status might be less likely to be prescribed

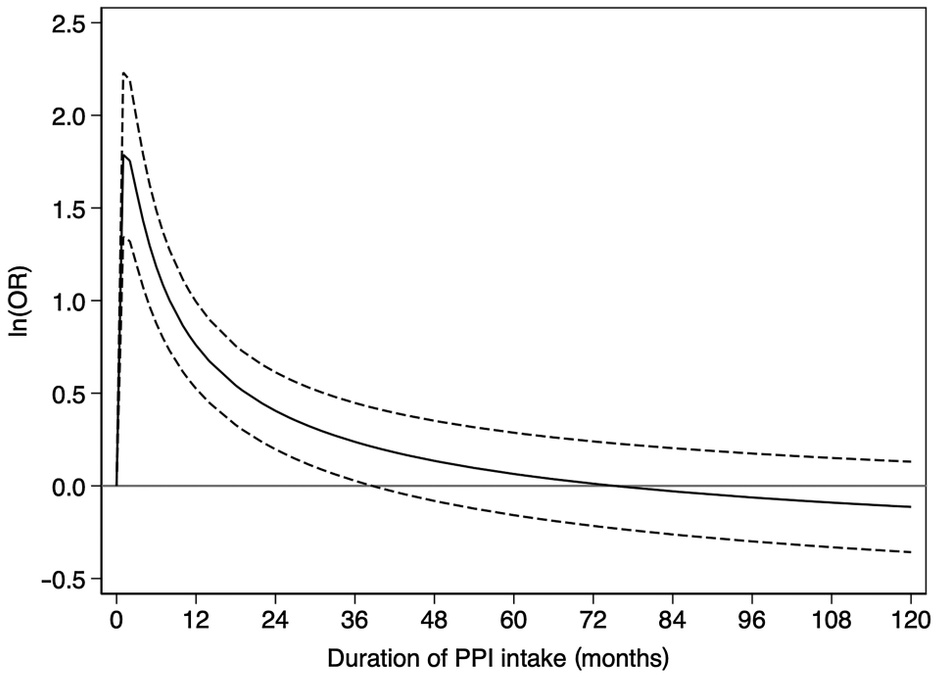

Figure 3.
Dose–response relationship between intake of proton-pump inhibitors (PPI) and gastric cancer fitted by using a one-stage logistic mixed-effects model with fractional polynomial (n = 4,575). Solid black line: log odds ratio; dashed black line: 95% confidence interval; solid horizontal gray line: odds ratio = 1.

or take PPIs when experiencing symptoms of gastric diseases, thus leading to a lower proportion of individuals with PPI intake and perhaps making its association with gastric cancer less evident compared with individuals with a high socioeconomic status. However, the observed associations among individuals with a high socioeconomic status may be due to residual or unmeasured confounding. Additionally, the dose–response analysis highlighted that the OR varies especially in the first 3 years of PPI intake, whereas the association was no longer significant after that.

Our results were broadly consistent with previous research in the field. Two meta-analyses that were conducted on randomized-controlled trials and evaluated PPI use and premalignant lesions of the stomach did not find any association between gastric cancer and PPIs, but the follow-up in these studies was relatively short, with a maximum of 36 months (28, 29). On the other hand, data from three other recent meta-analyses (8, 9, 30) conducted on observational studies showed that, overall, the use of PPI increases gastric cancer risk, but the probability of gastric cancer depends on its site (higher risk estimated for noncardia gastric cancer), on the study design (higher risk estimates in cohort studies), on the ethnicity of the population under study (higher estimates for Asian and European population), even if no relationship between the duration of PPI use and gastric cancer risk was found. In fact, these data showed that although PPIs are associated with a higher risk of gastric cancer, inconsistent results were drawn after the stratification according to the duration of PPI use (<1 year, 1–3 years, and >3 years; ref. 8). The pooled OR was only significant (OR 2.29; 95% CI, 2.13–2.47) when the duration of the PPI use was less than 1 year (compared with non-PPI users). No statistically significant association was observed for patients using PPIs between 1 and 3 years (pooled OR 1.31; 95% CI: 0.53–4.01) or for more than 3 years (pooled OR: 2.08; 95% CI: 0.56–7.77). This may underline the problem of reverse causality, with an observed association driven by individuals who are PPI users because of symptoms that arise from an undetected gastric cancer. However, a recent large cohort study found a significant association between long-term PPI intake and gastric cancer among patients who underwent *H. pylori* infection eradication therapy (31), even though time-related bias is possible (32). Recent studies that included large cohorts found significant associations between PPIs and gastric cancer. Among them, one study assessed this relationship by using data on prescriptions by general practitioners in the United Kingdom (33). However, PPIs are available over the counter in the United Kingdom, which might have led to missing data on PPI intake. In addition, the study did not take into account adherence, which could actually lead to differential misclassification of exposure between cases and noncases. Indeed, adherence might be higher among individuals with more severe symptoms and, if PPIs are taken to treat symptoms of gastric cancer, this might lead to a spurious association (i.e., protopathic bias). Another study conducted in Korea found similar results (34), but it did not assess whether the association was still significant for durations of PPI intake longer than 1 year. In addition, the association between PPIs and gastric cancer was not significant when using histamine receptor 2 antagonists as a comparator, perhaps suggesting residual bias (34). Lastly, one study carried out in Sweden similarly reported a positive association between PPI intake and gastric cancer, but the results of this study might be severely affected by unmeasured confounding as no adjustment was carried out besides standardization using the general population as reference (35). In addition, none of these studies assessed whether the relationship between PPIs and gastric cancer varies by subsite and histologic type of gastric cancer (33–35).

The mechanisms that may explain the association between PPI use and gastric cancer are far from clear. Inhibition of the secretion of gastric acid in animal models induced carcinogenesis with hyperplasia (36). Histopathologic changes in the stomach anatomy occur because of the interruption of the physiologic secretion of the gastric acid with subsequent hypergastrinemia (and following overgrowth of the gastric mucosa), hypochlorhydria, reduction of mucosal glands and their substitution by intestinal glands, and possible

gastric atrophy (28). The inhibition of acid secretion of the stomach may reduce the barrier defense that the acid pH of the stomach provides against several bacteria. This may lead to both diarrhea, a common side effect of PPIs, and growth of nongastric bacteria that may produce carcinogens as waste product (e.g., nitrosamines), plus chronic inflammation in the long term (4, 37–39).

Our study, however, provides more precise and valid evidence on the association between PPI use and gastric cancer. First, for the current analysis, we used data rigorously harmonized centrally at the StoP Project coordinating center. In addition, we were able to control for the potential confounding effect of variables such as sex, age, socioeconomic status, BMI, smoking status, alcohol drinking, family history of gastric cancer, and history of peptic ulcer when available, to conduct the analysis across different population strata, and to carry out several sensitivity analyses. However, across most strata, significant between-study heterogeneity was found and was greatly reduced only when the stratification was performed according to *H. pylori* infection. Some important risk factors, such as dietary variables, were not taken into account, thus confounding from these factors cannot be excluded. Another limitation of our study was the lack of underlying indication for PPI intake, including PPI use for *H. pylori* eradication, as information was collected from patients using questionnaires. Furthermore, data regarding the cumulative dose of PPIs among users were not available, as were also those regarding adherence to a medical prescription. Among the limitations of the study we also have to mention that only two studies were included in the dose–response modeling (15, 18), thus restraining the amount of data used for this analysis. Moreover, setting various time thresholds of exposure reduced the number of individuals included in the analyses, both among controls and cases. The recall in the use of PPI may lead to systematic errors as the accuracy and volume of memory may be influenced by subsequent events or experience data above all in case–control studies. Typically, cases can be expected to be more likely to report a specific exposure (i.e., intake of PPIs in our study) compared with controls, leading to differential misclassification of the exposure. Thus, given the null findings for long durations of PPI intake, we could hypothesize that the effect of this type of bias is actually limited in our study, and perhaps with relevant effects on our estimates for short durations of PPI intake only. On the other hand, however, for some of the studies included in our analysis, questionnaire items providing data on PPI intake were actually aimed at investigating intake of any medication, perhaps not having high sensitivity for PPIs. In this context, recall bias could be expected to lead to nondifferential misclassification (i.e., not all exposed study participants reported PPI intake, regardless of the occurrence of the outcome, thus nondifferentially), with study results biased toward the null (40). Furthermore, only the study from Brazil (18) used a rapid urea breath test and histologic examination to assess the history of *H. pylori* infection, whereas all other studies adopted serological tests. Although the former typically provide information regarding current infection, the latter can identify both current and past infection. Hence, some of the individuals from the Brazilian study (18) may have tested negative, although they actually had the infection in the past. In addition, further investigation into the mechanism of interaction between PPI intake and socioeconomic status is needed.

In conclusion, the results of our study indicate that the observed association between PPI intake and gastric cancer is driven by short-term PPI intake, with the association becoming not significant for long durations of use. Thus, our findings strengthen the hypothesis suggesting that protopathic bias may have a key role in the observed association between PPIs and gastric cancer.

Authors' Disclosures

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Authors' Contributions

M. Sassano: Conceptualization, formal analysis, visualization, methodology, writing–original draft, writing–review and editing. **M. Mariani:** Methodology, writing–original draft, writing–review and editing. **C. Pelucchi:** Resources, data curation, methodology, project administration, writing–review and editing. **N. Lunet:** Data curation, investigation, methodology, writing–review and editing. **S. Morais:** Data curation, methodology, writing–review and editing. **V. Martín:** Data curation, investigation, methodology, writing–review and editing. **V. Moreno:** Data curation, investigation, methodology, writing–review and editing. **M.P. Curado:** Data curation, investigation, methodology, writing–review and editing. **E. Dias-Neto:** Data curation, investigation, methodology, writing–review and editing. **M. Leja:** Data curation, investigation, methodology, writing–review and editing. **E. Gašenko:** Data curation, investigation, methodology, writing–review and editing. **C. La Vecchia:** Resources, data curation, investigation, methodology, project administration, writing–review and editing. **S. Boccia:** Data curation, supervision, investigation, methodology, writing–review and editing. **R. Pastorino:** Conceptualization, data curation, supervision, methodology, writing–review and editing.

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Note

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