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Review

PPIs and gastric cancer: any causal relationship?

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Abstract. Hydrochloric acid is crucial in gastric physiology. In 1978 cimetidine, the first H2 antagonist of histamine receptors on the gastric parietal cell was introduced into therapy, inducing acid. Lasting the years, several studies focused on the potential relationship between inducing hypo-achlorhydria and risk of developing gastric cancer. In 1988 omeprazole, the first proton pump inhibitor, entered therapy. In 1996, Kuipers underlined the danger of progression of chronic atrophic gastritis in subjects taking PPIs. In 2018, one paper from Korea and an another on from Sweden suggested a possible relationship between long-term PPI therapy and the development of gastric cancer. Over the years, several articles, meta-analyzes and population based focused on relationship between long-term of PPI use and the onset of gastric cancer, with conflicting results. As reported, the presence of bias in the collection of cases, in particular concerning the evaluation of the H.p. status and presence of atrophic gastritis and intestinal metaplasia in subjects treated with PPI, can lead to noticeable errors in the results and conclusions, as demonstrated in the literature by exhaustive methodological studies of pharmacoepidemiology. A possible bias in the collection of case histories is due to the fact that PPIs are often administered to dyspeptic patients, among which there are patients already carriers of gastric neoplasia: the so-called inverse causality. Literature data, amended by methodological bias (sampling errors, lack of comparative assessment of Hp status and atrophic gastritis) NOT support a causal relationship between long-term PPIs therapy and the onset of gastric cancer. (www.actabiomedica.it)

Key words: PPIs, Gastric cancer, Atrophic gastritis, Helicobacter pylori, Intestinal metaplasia

Role of acid in digestive diseases

Hydrochloric acid plays a crucial role in gastric physiology, being regulated by different positive and negative feedbacks. The dysregulation of acid production is related with the onset of various pathologies in the case of hypo-achlorhydria (chronic atrophic gastritis, gastric ulcer, gastric cancer), as well as hyperchlorhydria (GERD, duodenal ulcer, Zollinger-Ellison) (1-5).

Already in 1955 the onset of gastric cancer was linked with pernicious anemia characterized by hypo-achlorhydria (6).

Patients suffering of pernicious anemia have an increased risk of developing gastric cancer, as well as patients who have had gastric resections for peptic ulcer. To explain this relationship, several factors were hypothesized, including mucosal instability associated with atrophic gastritis leading to intraepithelial neoplasia and then gastric cancer, or bacterial growth due

to reduced gastric acidity in the stomach promoting the formation of carcinogenic nitrosamines on a substrate of ingested nitrates and nitrites (7).

The discovery of cimetidine and omeprazole

In 1978, the first H2 antagonist of histamine receptors on the gastric parietal cell named cimetidine was introduced into therapy, inducing suppression of acid production, according with the dosage (8-10).

Lasting the years, several studies focused on the potential relationship between inducing hypo-achlorhydria and risk of developing gastric cancer (11-15).

Late, in 1988 the first proton pump inhibitor, omeprazole, able to lead to complete inhibition of acid secretion, entered therapy. Since then, the literature on the correlation of PPI use and the occurrence of side effects has increased over time (16).

Proton Pump Inhibitors (PPIs) are widely used in the treatment of acid-related diseases, often continuously (17-20).

The deep and prolonged suppression of acidity has been linked with the danger of developing dangerous diseases such as gastric cancer. This perception has spread widely in recent years also among the medical profession and patients, leading to instill substantial doubts about the use of these therapies (21).

Epidemiology of gastric cancer

Gastric cancer represents the final step of a lot of change in gastric mucosa in a pathologic stomach, as William Mayo stated in 1933 (22-24). Although the gastric cancer mortality shows a decline in most countries of the world, nearly one million people are newly diagnosed with gastric cancer each year, being the most of them at an advanced stage leading to death as the third cause of cancer death (25). Gastric cancer is a recognizes different etiologies, genetic changes and phenotypes suggesting that genetic alterations could group into subclasses (26- 28).

The role of helicobacter pylori infection and gastric microbiome

H. pylori (H.p) infection is considered as the single most important risk factor leading to gastric cancer (29, 30).

The Correa cascade summarizes the change in gastric mucosa rom normal to cancer through pre-neoplastic steps such as atrophy and intestinal metaplasia (IM) (23). Recent meta-analyses demonstrated over the years the benefit of H.p. eradication to reduce gastric cancer. (31, 32). H.p. infection deeply modify the hierarchy of gastric microbiome as suggested in recent studies (33-35).

Other microbes than H.p., overgrowing in a hypochlorhydric stomach, are responsible for inflammation and production of carcinogenic molecules such as nitrosamines. Epstein–Barr virus is known as a causal factor for a subtype of H. pylori-negative gastric cancer (36-38).

Atrophic gastritis and intestinal metaplasia

The definition of 'gastritis' implies any histologically confirmed inflammation of the gastric mucosa (39).

Chronic not self-limiting gastritis recognizes different aetiologies and overlaps with H. pylori infection, for most of them (40-42).

Two histological phenotypes of gastritis are described: atrophic and non-atrophic. Gastric mucosal atrophy is defined as the loss of `appropriate' glands, and it is claimed to be related with non-hereditary gastric cancer (39, 42, 43).

Two staging systems are currently used for clinical purpose – operative link on gastritis assessment (OLGA) and operative link for gastric intestinal metaplasia assessment (OLGIM) and both distinguish four stages of gastritis (stages 0–IV) associated with a progressively increasing gastric cancer risk (44-46). In the OLGA system (46), gastritis is staged by combining the atrophy scores obtained for the oxyntic mucosa of the distal stomach and the antral/transitional proximal gastric mucosa. The stage indicates the individual risk of developing a gastric malignant neoplasia, and most

cancer cases are reported in patients with stages III and IV (47). The stage of the organic lesions correlates with serum pepsinogens, the so called 'functional serology' (48), becoming of a pivotal relevance to identify patients with atrophy in whom endoscopy with biopsies can be performed with the aim of secondary prevention of gastric cancer.

Follow-up of premalignant lesions in patients at risk for progression to gastric cancer has been investigate d by means of OLGA staging system (49, 50). Stage III/IV patients are identified as being at higher risk of developing gastric cancer and then listed for endoscopically/bioptically surveillance. The prognostic value of gastritis staging was confirmed by both the Maastricht VI Consensus Conference (51) and the Kyoto Global Consensus Meeting on H. pylori gastritis (52).

The role of hypergastrinemia

Hypergastrinemia has been claimed to be related whit both gastric and neuroendocrine tumors (53-55).

Among the other main hormone produced by the stomach is gastrin, which is secreted by G cells, predominantly located in the antrum of the stomach. It has well-known functions in regulating gastric acid secretion (56).

Gastric hypochlorhydria leads to elevated fasting serum gastrin concentrations as physiological response. Other causes of hypergastrinemia can be related whit autoimmune or H. pylori-induced chronic atrophic gastritis, as well as drug use whit inhibition of gastric acid secretion or due to an ectopic production, such as a gastrinoma. However, the peak of hypergastrinemia associated with regular use of PPIs is variable, depending on the coexistence of atrophic gastritis. Gastric microbiome could exert a role in determining hypergastrinemia and in turn to influence tumor development in the stomach (57).

In an experimental model on transgenic hypergastrinemic mice, Helicobacter pylori or H. felis infection, as well as other components of gastric microbiome, are able to improve the development of gastric cancer (57, 59, 60). Epidemiologically, H. pylori related chronic atrophic gastritis, associated with hypergastrinemia, is a well-known preneoplastic lesion of gastric cancer. Gastrin plays a pivotal stimulatory role in the development of gastric neuroendocrine tumors (NETs) (54,55).

Relationship between H2 blockers and PPI's and gastric cancer

In 1996, Kuipers published a leading article underlining the danger of the progression of chronic atrophic gastritis in subjects under continuous therapy with PPIs (61).

Lasting long-term PPIs therapy, helicobacter pylori positive patients show lower intragastric vitamin C concentrations, bacterial colonization and overgrowth of nitrate reducing bacteria (62, 63).

The so-called Waldum sequence, namely the development of NET during long-term PPIs therapy, has generally not been accepted (21).

In 2018, one paper from Korea and an another on from Sweden suggested a possible relationship between long-term PPI therapy and the development of gastric cancer (64, 65).

In the same year Niikura et al., referring to Cheung's article, published a work on 571 patients receiving PPI, focusing on the increased risk of developing gastric cancer in relation to the presence of intestinal metaplasia. The presence intestinal metaplasia (IM) in H. pylori-infected patients is an independent risk factor for gastric cancer. Previous study showed a 7.6-fold increase in the risk of development of gastric cancer in patients who have IM compared with patients who have no IM even after eradication, concluding that gastric atrophy and IM could be major confounders in estimating the risk of gastric cancer (66).

Over the years, several articles, meta-analyzes and population-based focused on relationship between long-term of PPI use and the onset of gastric cancer, with conflicting results.

For example, a meta-analysis of 16 papers found no cases of gastric cancer and NETs in subjects treated long-term with PPI.

A total of 16 studies (1,920 patients under long-term PPI therapy) was processed by meta-analytical

procedure. Mean gastrin levels increase one-to-three times and an increased prevalence of ECL cell hyperplasia was observed (+ 7.8–52.0%). Helicobacter pylori-positive patients had a significantly increased risk of developing ECL linear / micronodular hyperplasia compared with H. pylori-negative patients [OR: 2.45 (95% CI: 1.47–4.10), P = 0.0006]; without evidence of neoplastic changes. H. pylori-positive patients showed an increase risk to develop corpus atrophy in comparison whit the negative ones [OR: 11.45 (95% CI: 6.25–20.99), P <0.00001]. Not a case of gastric adenocarcinoma was reported (67).

A different meta-analysis produced opposite results leading conclusion that acid suppressive drugs such as H2R blockers or PPIs could play a role as stimulators for gastric cancer. Notably, one possible limitation of the study is linked whit the lack of information on Helicobacter pylori infection being all 11 papers observational study (68).

Another study suggested the concern that long-term PPI therapy was correlated with the onset of several digestive neoplasias: gastric, colorectal, liver, pancreatic (69).

A systematic analysis of seven papers on this topic showed in all of them an increased risk of developing gastric cancer during long-term PPI therapy, especially noncardia gastric cancer. However, some limitations (such as informations on H. pylori infection, gastric atrophy and intestinal metaplasia, evaluated as separate risk factors among long-term PPI users, and conversely aspirin or other NSAIDs as possible protective factors) in collecting data may produce bias. (70).

Figure 1 focuses on an important relationship between the number of patients who have used PPIs over the years (over 2 billion people), the number of subjects infected with helicobacter pylori (4 billion) and the number of patients who are diagnosed each year for gastric cancer (1 million - globocan 2020). The huge difference between those who use PPIs, those infected with helicobacter (billions of people) and those diagnosed with gastric cancer (one million) are on entirely different scales and suggest that it is at best a risk factor but not a direct causal link (1, 25, 71).

This is also supported by figure 2 summarizes the trends over the years of PPI intake, helicobacter infection and gastric cancer diagnosis, which shows

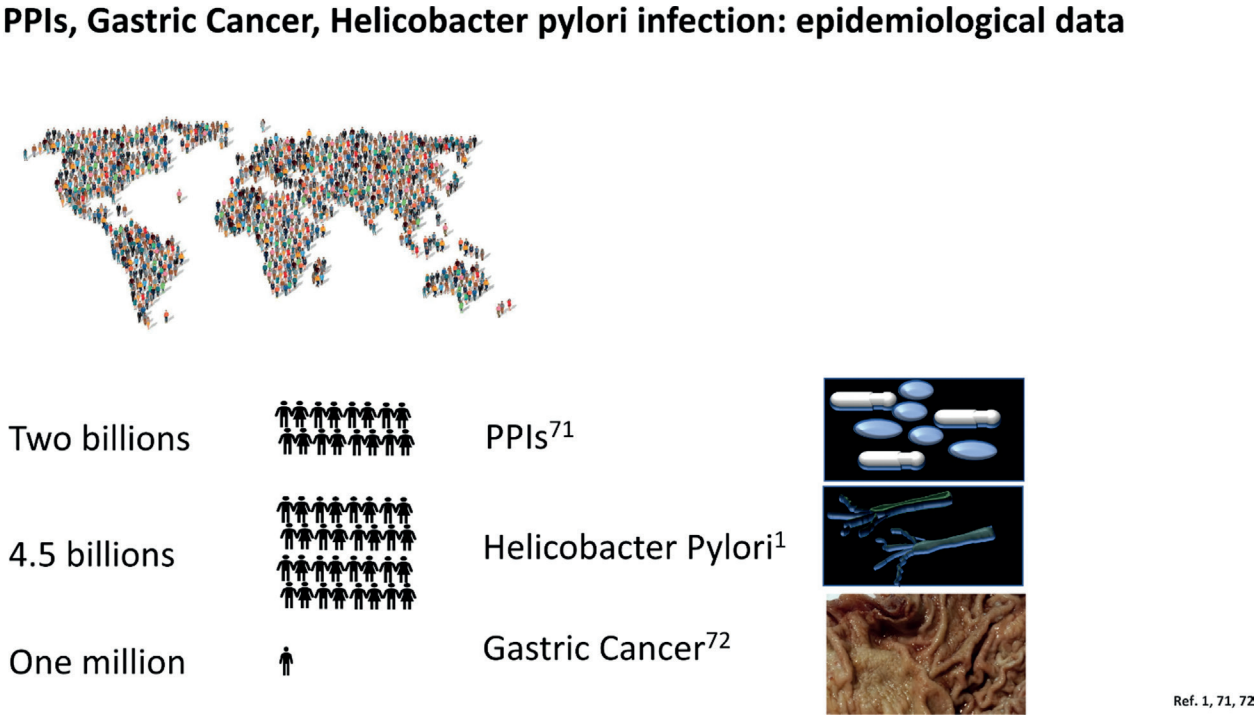

Figure 1. Relationship between the worldwide incidence of gastric cancer, H.p. infection and use of PPIs.

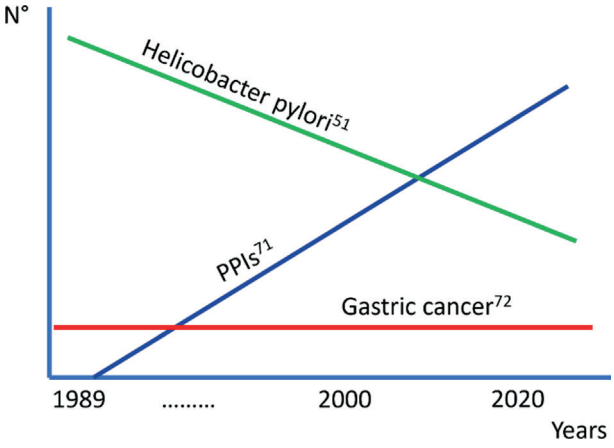

Figure 2. Lasting the years, curve trends of incidence of gastric cancer, H.p. infection and prescription of PPIs.

substantial stability over the years of the latter in the face of a decline in subjects infected with helicobacter. and an increase in the use of PPIs (25, 51, 71).

Possible bias and confounding factors

As reported, the presence of bias in the collection of cases, in particular concerning the evaluation of the H.p. status and presence of atrophic gastritis and intestinal metaplasia in subjects treated with PPI, can lead to noticeable errors in the results and conclusions, as demonstrated in the literature by exhaustive methodological studies of pharmacoepidemiology (72-74).

A possible bias in the collection of case histories is due to the fact that PPIs are often administered to dyspeptic patients, among which there are patients already carriers of gastric neoplasia: the so-called inverse causality (75).

The association between PPIs and gastric cancer risk has been investigated in observational studies, and a recent meta-analysis showed an increase in gastric cancer risk of 150% in patients with long-term PPIs therapy (76). Similarly, H2 blockers has also been shown a 40%-fold gastric cancer risk in a recent meta-analysis (77). However, some works reported in this meta-analysis did not adjust for important confounding factors, including short lag times, with three not using any lag in the analysis (65, 78, 79).

Lag times are recommended in studies of drug–cancer associations (80) because cancers (81) develop over several years, and new drug undertaken shortly before cancer diagnosis are unlikely to be causative; moreover, drugs prescribed immediately before cancer diagnosis could reflect reverse causality, being pre-discovered cancer symptoms just related the prescription of medications (82). Reverse causation could be avoided also by using short lags, but the critical lag time to influence the induction and latency period is not known (83). Some papers concern the rational of prescribing PPIs in patients (84). Therefore, two large population-based studies in the United Kingdom investigated both PPIs or H2 blockers use and increased gastric cancer risk.

The results of the studies show a relevant increase in the prescription of PPIs and/or H2 blockers immediately before gastric cancer diagnosis, suggesting a possible role of reverse causation (85). In fact, PPIs might be prescribed more frequently to patients with gastritis, just affected by dyspeptic symptoms (79).

Recommendation and conclusion

The guidelines for the appropriateness of PPIs prescribing suggested by gastroenterological scientific societies in Italy focus on the inappropriate use of these drugs in people with atrophic gastritis (86).

As stated in the work, the following conditions are not appropriate for PPIs use:

- Steroids alone
- Prophylaxis in patients taking chronically NSAIDs / ASA / COXIBs with age <65 years or without other risk factors
- Low molecular weight heparin or warfarin without risk factors
- Ticlopidine or clopidogrel use without risk factors
- Biphosphonate or SSRI alone
- Antibiotics or chemiotherapic agents
- Patients with functional heartburn
- Dyspeptic patients with functional symptoms of post-prandial distress syndrome (PDS)

- Patients with chronic liver disease and portal hypertension
- Patients with multifocal atrophic gastritis
- Patients with partial or total gastrectomy

A position paper in the pharmacological field on the risks and benefits of acid-suppressive therapy, stated that no controlled human data support the increased risk of gastric cancer (87).

A summary published in 2020 of what is known in the literature on the subject suggests that there is no correlation between gastrointestinal cancer and chronic use of PPIs for periods of more than 10 years (69).

In conclusion, the following points should be emphasized from the review of the literature:

- PPIs are important drugs and should be used in accordance with the guidelines
- The HP status must be verified as NEGATIVE before starting continuous therapy with PPIs
- The condition of atrophic gastritis should be checked BEFORE long-term PPIs therapy started.
- Literature data, amended by methodological bias (sampling errors, lack of comparative assessment of Hp status and atrophic gastritis) NOT support a causal relationship between long-term PPIs therapy and the onset of gastric cancer

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