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Proton pump inhibitors and carcinogenesis: a literature review

Inibidores da bomba de prótons e carcinogênese: uma revisão da literatura

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ABSTRACT: Proton Pump Inhibitors (PPIs) can have several adverse effects and, recently, the assumption that this class of drugs may favor the development of neoplasms has been discussed. The global incidence of neoplasms, especially gastric cancer, and the large-scale use of PPIs for the long-term treatment of gastric diseases prompted the development of this project. This is an exploratory and descriptive literature review, which summarized and grouped the results of scientific research. The search and collection of data in the literature was carried out through online access to the medical literature databases: PubMed; Up To Date; Virtual Health Library (VHL), which includes: Latin American and Caribbean Health Sciences Information System (LILACS), Electronic Scientific Online Library (SciELO) and Cochrane Library. The online interactive platform of the International Agency for Research on Cancer of the World Health Organization (WHO) was also used. This study aims to identify and describe studies and their lines of research that demonstrate the association between PPIs and cancer. Scientific studies report the association of PPIs with cancer but, on the other hand, innovative research suggests that this class of drugs can have a therapeutic effect in specific types of neoplasms. Therefore, it is possible to observe the growing number of medical-scientific articles and documents that confirm the therapeutic effect of PPIs on cancers. The need for larger and better-designed prospective and interventional studies to define the real roles of PPIs in the gastric microbiota is highlighted. The validity of the data and the real role of PPIs in the human body are questioned.

Keywords: Proton Pump Inhibitors. Carcinogenesis. Cancer.

RESUMO: Os Inibidores da Bomba de Prótons (IBP) são capazes de produzir efeitos adversos e, recentemente, discute-se a possibilidade de que essa classe de medicamentos possa induzir a formação de neoplasias. A incidência global de neoplasias, em especial o câncer gástrico, e o uso dos IBP em larga escala para o tratamento prolongado das enfermidades gástricas, fomentaram a realização deste trabalho. Trata-se de uma revisão bibliográfica, exploratória e descritiva, que resume e agrupa resultados de pesquisas científicas. A busca e coleta de dados na literatura realizou-se através do acesso online às bases de dados de literatura médica: PubMed; Up To Date; Biblioteca Virtual em Saúde (BVS), que agrega: Sistema Latino Americano e do Caribe de Informação em Ciências da Saúde (LILACS), Biblioteca Eletrônica Científica Online (Scielo) e Biblioteca Cochrane. Foi utilizada, ainda, a plataforma interativa online da Agência Internacional de Pesquisa sobre o Câncer, da Organização Mundial da Saúde (OMS). Buscou-se identificar e descrever os estudos e suas linhas de pesquisa que demonstram a ligação dos IBP com a indução do câncer. Estudos científicos relatam a associação dos IBP com o câncer, por outro lado, pesquisas inovadoras sugerem que essa classe de medicamentos assume ação terapêutica em tipos específicos de neoplasias. Faz-se notório, pois, o crescente volume na literatura de artigos e documentos médico-científicos ratificando o poder terapêutico dos IBP frente aos cânceres. Ressalta-se a necessidade de estudos prospectivos e intervencionistas maiores e mais bem projetados para que se definam os reais papéis dos IBP na microbiota gástrica. Indaga-se a validade dos dados e o real papel dos IBP no corpo humano.

Palavras-chave: Inibidores da Bomba de Prótons. Carcinogênese. Câncer.

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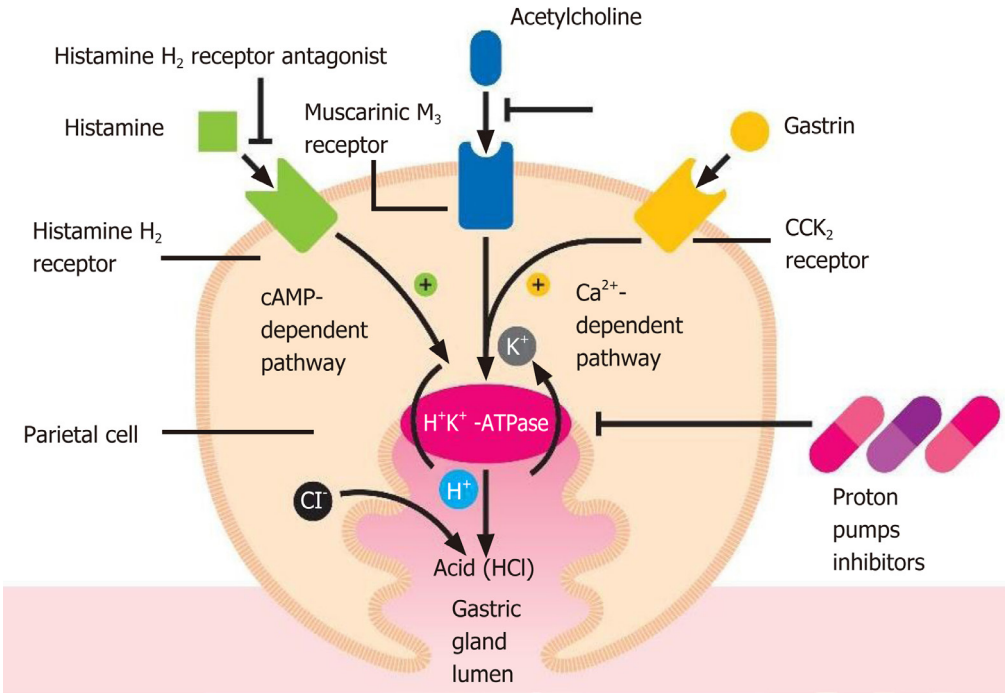
INTRODUCTION

After their discovery and launch in the world market and due to the excellent clinical response in patients with gastroesophageal symptoms, Proton Pump Inhibitors (PPIs) became frequently prescribed. In addition, the belief that these drugs were inert in the human body supported their indiscriminate use. However, it is now known that PPIs can have adverse effects and, more recently, it has been found that this class of drugs may be associated with the development of neoplasms[1].

Currently, the following PPIs are available: omeprazole, lansoprazole, dexlansoprazole, rabeprazole, pantoprazole and esomeprazole[1].

PPIs are drugs that block gastric acid secretion by irreversibly binding, through covalent bonds, to the hydrogen-potassium ATPase pump that resides on the luminal surface of the parietal cell membrane of the gastric mucosa[1,2]. This mechanism can be seen in Figure 1.



Source: Zippi et al., 2021.

Figure 1 – PPIs mechanism

The regulation of gastric acid secretion is associated with a complex system of chemical agonists that stimulate and inhibit gastric function. In short, three are the main agonists: gastrin, histamine, and acetylcholine. Gastrin is the main hormone stimulating gastric acid secretion, but it also exerts proliferative and anti-apoptotic actions on cancer cells. PPIs are indicated for the treatment of peptic ulcer disease; gastroesophageal reflux disease; Zollinger-Ellison syndrome; ulcers associated with non-steroidal anti-inflammatory drugs; and as adjunct treatment in the eradication of *H. pylori* bacteria (in combination with antibiotic therapy). Their known adverse effects are diarrheal diseases (due to *Clostridium difficile)*; malabsorption of magnesium, calcium, iron and vitamin B12; atrophic gastritis, and hypergastrinemia. The latter has been associated with gastric carcinoid tumors in rats[1,2].

"In 2006, expenditure on these drugs was £425 million (€595 million; $872 million) in England and £7 billion globally"[4]. This demonstrates the frequent prescription of PPIs, which is associated with their high level of efficacy and low toxicity. The impact of these drugs on global public health has been demonstrated, generating the need to analyze and describe studies that address their association with cancer[4].

Considering this assumption, the use of PPIs on a global scale, and the worldwide incidence of cancer, especially gastric cancer (in 2018, 5th in global incidence, and 6th in Brazil), much is discussed on the true relation between PPIs and carcinogenic effects[5].

A study about the inhibition of gastric acid secretion and its consequences stated that "the evidence so far and the exponential number of patients who do or will do a long-term treatment with PPIs, justify the continuity of this important line of research"[6]. With this purpose, this project aims to clearly identify researchers and studies that associate PPIs with carcinogenesis, analyzing the present

risk for the development of gastric neoplasms.

Therefore, this work has the purpose of sorting the scientific literature on the topic, whether in favor or against the long-term use of PPIs. This is a current subject in the scientific community, which is still uncertain on these carcinogenesis effects. This has encouraged the development of this project, with the purpose of providing the most recent discoveries.

METHODS AND MATERIALS

This undergraduate thesis is an exploratory and descriptive literature review, carried out in an organized, systematic and ethical manner, summarizing and grouping research results that contribute to the knowledge on the matter.

This literature review was developed based on previous materials, mostly scientific articles, which were compiled and described according to their main conclusions[7].

The following databases were accessed to search and collect data: PubMed; Up To Date; Virtual Health Library (VHL), which includes: Latin American & Caribbean Health Sciences Literature (LILACS), Scientific Electronic Library Online (SciELO) and Cochrane Library. The online interactive platform of the International Agency for Research on Cancer of the World Health Organization (WHO) was also used.

The content search was directed by the following descriptors: "Proton Pump Inhibitors" and "Carcinogenesis" and limited to scientific studies addressing the subject of this work. The only Boolean operator used was AND, aiming to expand the bibliographic search.

Twenty-one scientific studies that addressed the issue in the last 20 years were selected. All studies were published in the period from 2001 to 2020 and were scientifically valid. Full studies in Portuguese, English and Spanish were included.

Studies with experimental (clinical trials, randomized or not) and observational designs (case-control studies, cohort studies) were included, in addition to systematic literature reviews and meta-analyses, with the objective of enhancing the statistical significance of the data presented. The latter were reviewed carefully and selected according to their discussions on the topic.

The following studies were excluded: duplicates in the databases, studies including only pediatric population, studies published before 2001, reports, experience reports, papers in annals, newsletters, and studies with no statistical relevance.

A total of 161 scientific articles were found, of which 120 were in PubMed and 41 in the VHL. After thorough reading and verification of inclusion and exclusion criteria, 21 articles were selected for this literature review.

Current epidemiological data were retrieved from the WHO International Agency for Research on Cancer's online interactive platform. Information on biochemistry, effectiveness, use and management of PPIs was extracted from the UpToDate medical database.

RESULTS

Aiming to prove the real carcinogenic potential of PPIs, experimental studies in rats have been carried out over the last few years. Lanzoprazole has been shown to enhance the carcinogenic effect of duodenogastric reflux in rats followed for 1 year and compared to a placebo group[8]. Another study found an increased prevalence of advanced gastric neoplasia development neoplasia in rats treated with omeprazole and also tried to demonstrate the existence of gastric pancreatic acinar cell metaplasia[9].

In short-term, hypergastrinemia can cause rebound hyperacidity, while, in the long term, it causes enterochromaffin-like cell hyperplasia and carcinoids. Gastric hypoacidity can make the environment favorable to bacterial infection, and it is suggested that the broken acid barrier could favor viral and prion infections[10]. Therefore, these data suggest that chronic hypergastrinemia can lead to the development of neoplasms.

Subsequently, some researchers, through meta-analyses and systematic literature reviews, recommend that the use of PPI should be restricted in children and young adults, due to the latency of neoplasia[11,12].

In another perspective, two meta-analyses, by Eslami and Nasseri-Moghaddam[13] and Song et al.[14], assessed the long-term potential of PPIs and the risk of gastric premalignant lesions, and reached similar conclusions. Including only clinical trials, the studies found that the use of PPIs could not cause or accelerate the progression of gastric atrophy or cause enterochromaffin cell hyperplasia. They also mentioned that studies contrary to these findings presented imprecise results[13,14].

In a study with great repercussions in the scientific community, researchers analyzed more than 60,000 adults on a territory-wide health database of Hong Kong and associated long-term PPIs use with a 2.4-fold increase in gastric cancer risk in *Helicobacter pylori*-infected patients who had received eradication therapy. It was also found that the risk of gastric cancer increases with the dose and duration of PPIs use. The study suggested that physicians should exercise caution when prescribing PPIs even after eradication of *H. pylori*[15].

This study seems to have more confounding factors, as smoking and alcohol consumption were not recorded and, even more intriguingly, it is known that Asians are at a higher cancer risk than other populations, a factor directly associated with the high rate of infection by *Helicobacter pylori*[15,16]. *H. pylori* is one of the main risk factors for the development of gastric cancer, and its eradication in high-risk populations significantly reduces the chance

of developing gastric cancer[17]. It is therefore suggested that the failure to eradicate *H. pylori* may have confused the results of the Chinese study. Furthermore, it was an observational study, and thus it requires further prospective, randomized, and interventional research to obtain more precise conclusions on a subject that may change the course of PPIs prescription.

In addition, PPIs are metabolized through hepatic cytochrome P450 enzymes, with CYP2C19 having the dominant role. Genetic polymorphisms of CYP2C19 are known and most commonly found in the Asian population. As a result of these polymorphisms, the metabolism of PPIs through this pathway may be delayed, suggesting a dysfunction in the metabolism of PPIs in the Asian population, which, once again, puts in doubt the validity of the Chinese study[1].

A cohort study with 797,067 individuals on PPI therapy in Sweden found an increase in the incidence of gastric cancer. Among all adult participants of both genders, 0.28% developed gastric cancer during follow-up. This is the largest study to date on the relationship between gastric cancer and PPIs[18].

However, some criticisms to this study are also pointed out. Similarly to the Chinese study, this one lacks information on potential confounding factors, such as dietary factors, obesity, smoking and alcohol consumption, as this data were not collected in the country's health registries at the time (Sweden, 2005 to 2012). Additionally, the high prevalence of PPI maintenance use among adults in Sweden means that the large majority with risk factors for gastric cancer will have received PPI treatment at some point in their lives. This hampers assessment of PPI as an independent risk factor, which is a problem common to other study designs that address the same theme.[18].

Still in this significant research, there is also the problem of reverse causality, as the detection of asymptomatic cancer prior to the initial use of PPIs was not considered. In addition, it was not possible to be certain about the PPI dosages used by patients, due to the over-the-counter availability of these drugs.

For decades, several studies have demonstrated the protective effect of PPIs on the gastric mucosa and the possible development of neoplasms. It has been demonstrated that Pantoprazole selectively induced *in vivo* and *in vitro* apoptotic cell death in gastric cancer, suggesting that PPIs could be used for selective anticancer effects[19]. More recently, Ilaprazole, a novel Proton Pump Inhibitor, was found to show potent antitumor activities through the inhibition of TOPK-specific kinase function (T-lymphokine-activated killer cell-originated protein kinase). This study demonstrated that PPIs can directly inhibit cancer growth via a proton pump independent mechanism[20].

Recently, a systematic review on the relationship between PPI and Carcinogenesis' found that PPIs may play an adjunct role in the efficacy of chemotherapy for malignant tumors. The study found that pretreatment with PPIs would increase the sensitivity of cytotoxic drugs in several drug-resistant cancer cell lines, as PPIs alkalize the tumor microenvironment and allow the retention of weakly basic drugs within the intracellular targets (Ex: Cisplatin, 5-fluorouracil and Vinblastine). It was also found that PPIs reduce the chemoresistance of cancer stem cells by modifying anaerobic glycolysis and ATP binding cassette transporters in solid cancer cells[21]. Promising studies in the area of oncology have been using PPIs to support chemotherapy treatments.

The studies on the topic that were evaluated are summarized in Table 1.

Table 1 – Evaluated Studies

Author	Year	Title	Study design
Wolfe	2020	Proton pump inhibitors: Overview of use and adverse effects in the treatment of acid related disorders.	Systematic Literature Review
Han et al.	2015	Role of proton pump inhibitors in preventing hypergastrinemia-associated carcinogenesis and in antagonizing the trophic effect of gastrin.	Systematic Literature Review
Souza et al.	2013	Qualitative analysis of anatomopathological changes of gastric mucosa due to long term therapy with proton pump inhibitors: experimental studies x clinical studies.	Systematic Literature Review
Viste et al.	2004	Lanzoprazole promotes gastric carcinogenesis in rats with duodenogastric reflux.	Clinical Trial
Dall'Olmo et al.	2014	Role of proton pump inhibitor on esophageal carcinogenesis and pancreatic acinar cell metaplasia development: an experimental in vivo study.	Clinical Trial
Sandvik et al.	2002	Long-term safety of proton pump inhibitors: risks of gastric neoplasia and infections.	Systematic Literature Review
Ahn et al.	2013	Acid suppressive drugs and gastric cancer: a meta-analysis of observational studies.	Meta-analysis

Table 1 – Evaluated Studies *continuation*

Author	Year	Title	Study design
Waldum et al.	2018	Proton pump inhibitors (PPIs) may cause gastric cancer – clinical consequences.	Systematic Literature Review
Eslami, Nasseri-Moghaddam	2013	Meta-analyses: does long-term PPI use increase the risk of gastric premalignant lesions?	Meta-analysis
Song, Zhu e Lu	2014	Long-term proton pump inhibitor (PPI) use and the development of gastric pre-malignant lesions.	Meta-analysis
Cheung et al.	2017	Long-term proton pump inhibitors and risk of gastric cancer development after treatment for Helicobacter pylori: a population-based study.	Cohort Study
Rahman et al.	2014	Characteristics of gastric cancer in Asia.	Cross-sectional Study
Wong et al.	2014	Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial.	Clinical Trial
Brusselaers et al.	2017	Maintenance therapy with proton pump inhibitors and risk of gastric cancer: a nationwide population-based cohort study in Sweden.	Cohort Study
Feng et al.	2016	Proton pump inhibitor pantoprazole inhibits the proliferation, selfrenewal and chemoresistance of gastric cancer stem cells via the EMT/βcatenin pathways.	Clinical Trial
Fais et al.	2014	Microenvironmental acidosis in carcinogenesis and metastases: new strategies in prevention and therapy.	Systematic Literature Review
Yeo	2004	Selective induction of apoptosis with proton pump inhibitor in gastric cancer cells.	Clinical Trial
Zheng	2017	Proton pump inhibitor ilaprazole suppresses cancer growth by targeting T-cell-originated protein kinase.	Clinical Trial
Joo et al.	2019	Proton pump inhibitor: The dual role in gastric cancer.	Systematic Literature Review
Rajilic-Stojanovic et al.	2020	Systematic review: gastric microbiota in health and disease.	Systematic Literature Review

Source: Main author.

DISCUSSION

For decades, PPIs have been used in the treatment of gastrointestinal tract disorders. However, recent studies have proposed that this class of drugs may be associated with anatomopathological changes of the gastric mucosa and, consequently, with the development of gastric tumors[6].

> As treatment with proton pump inhibitors (PPIs) increases the biosynthesis and secretion of gastrin, it has been postulated that treatment with PPIs could increase the risk of cancer, especially in Barrett's esophagus, gastric carcinoids, and colorectal cancer (CRC). Some tumors produce gastrin of their own, which can act in an autocrine manner to promote tumor growth. In addition, gastrin is known to foster the tumor microenvironment[2].

Nevertheless, it is concluded that:

> The PPIs antagonized the trophic effects of hypergastrinemia. Furthermore, the blockade of proton pumps or potassium channels in cancer cells could limit the abnormal glycolytic energy metabolism of cancer cells. Apart from their suppressive effect on gastric acids, PPIs exert an anti-tumor effect through the selective induction of apoptosis as well as an anti-inflammatory effect, and they protect cells from developing chemo- or radio-therapeutic resistance. Moreover, the anti-carcinogenic actions of PPIs were augmented with PPI-induced hypergastrinemia. Together with their potential targeted killing of cancer stem cells, these effects demonstrate their potential anti-cancer actions[2].

Therefore, it is inferred that there is a balance between PPI-induced hypergastrinemia, which gives PPIs pathogenic and neoplastic power, and the "anticancer" function[2]. At this point, in addition to denying their carcinogenic effect, research claims that PPIs act as therapeutic factors for gastric cancer. As an example, it is argued that Pantoprazole may be a promising therapeutic strategy for targeting gastric cancer of cancer stem cells, as it prevents intracellular proton extrusions, which consequently reduces cancer cell survival under acidic conditions[22]. A review study confirms the specific mechanisms by which PPIs act as therapeutic factors[23]:

> PPIs can be useful in modulating tumor acidification and restoring chemotherapeutic sensitivity in drug-resistant cancer cells both

> *in vitro* and *in vivo*[23]. [...] As expected, the PPI-induced cytotoxicity is strongly enhanced in low pH culture conditions. PPIs' activity has been investigated in several human tumor histotypes, such as melanoma, B cell lymphomas, pancreatic cancer, gastric carcinoma, Ewing sarcoma, osteosarcoma, rhabdomyosarcoma, and chondrosarcoma[23]. [...] Finally, based on meta-analysis of observational studies and multicenter prospective cohort study, administration of PPIs in patients with Barrett's esophagus significantly reduces the risk of esophageal adenocarcinoma and/or high grade dysplasia[23].

The breadth of studies on PPIs still seems to be very wide. A study on the gastric microbiota in health and disease highlighted the need for larger and better-designed prospective and interventional studies to define the real roles of PPIs in the gastric microbiota and determine if they are protectors or protagonists of malignancies[24].

CONCLUSION

Scientific studies describe the association between PPIs and cancer. On the other hand, innovative recent studies do not only defend that PPIs do not induce cancer, but also suggest that this class of drugs can have a therapeutic effect in specific types of neoplasms.

The literature review showed that studies that associate PPIs and carcinogenesis, in their most varied designs, present biases and potential confounding factors, which puts their validity in doubt. Therefore, it is possible to observe the growing number of medical-scientific articles and documents that confirm the therapeutic effect of PPIs on cancers, which may explain why these drugs remain being one of the most prescribed classes of medications in the world.

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