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THE EFFECTS OF HELICOBACTER PYLORI ERADICATION THERAPY ON THE INCIDENCE OF GASTRIC ADENOCARCINOMA

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ABSTRACT

INTRODUCTION: Helicobacter pylori is the major risk factor for the development of gastric adenocarcinoma, and may increase its risk by two times. Thus, in the last twenty years, many studies have investigated whether eradicating this agent reduces the risk of gastric cancer. However, the results were initially inconsistent. Therefore, this systematic review was carried out to identify the impact of H. pylori eradication on the incidence of gastric adenocarcinoma. METHOD: Using the Pubmed, Cochrane, Medline, and LILACS databases, a systematic review of studies involving H. pylori eradication treatment and the incidence of gastric adenocarcinoma was carried out from 2019 to 2024. Meta-analyses, reviews, systematic reviews, clinical trials, and randomized controlled trials in English, involving humans, were included in the review. RESULTS: 12 studies were included. All of them showed that the eradication of H. pylori reduced the incidence of gastric adenocarcinoma in individuals without preneoplastic lesions, so that this decrease ranged from 43% to 76% among the articles (CI=95%). DISCUSSION: Gastric adenocarcinoma is unlikely to develop in those not infected with H. pylori. Thus, investigating the effects of the eradication of this bacterium is of great interest to public health. Many factors interfere with the relationship between H. pylori and host and, therefore, with the development of gastric cancer. To mention, the socioeconomic condition and specific virulence factors. Another challenge in the issue of H. pylori is the treatment of the infection, due to the variety of strains and antimicrobial resistance, making it difficult to eradicate. In countries where H. pylori infection and gastric cancer are very prevalent, strategies aimed at analyzing the susceptibility of certain strains to antimicrobials and identifying which genes are responsible for this resistance may be the key to controlling the infection and, therefore, to reducing gastric cancer cases. CONCLUSION: Eradication of H. pylori decreases the incidence of gastric adenocarcinoma. Thus, screening and treating these infections in populations with a high prevalence of H. pylori is beneficial to prevent gastric cancer, with public health in mind.

Keywords: Gastric Neoplasms. Eradication of Helicobacter Pylori. Cancer Prevention.

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INTRODUCTION

Gastric adenocarcinoma consists of a malignant neoplasm of the cells of the glandular epithelium of the stomach and can be divided into two histological subtypes according to Lauren's classification, which are the intestinal type and the diffuse type (1).

Gastric cancer is the third most deadly malignant neoplasm in the world and the fifth most prevalent (2), and its incidence is approximately twice as high in men as in women. In addition, its occurrence is more common in developing countries (60% of cases), citing countries in the Far East, Eastern Europe, Central America, and South America. On the other hand, the lowest incidences are observed in North America, Australia, South Asia, and North Africa (1).

Infection with the *Helicobacter pylori* It is one of the most common chronic bacterial infections, so it is estimated that more than 50% of the world's population has this condition (1). In recent studies, Africa has the highest prevalence of infection (70.1%), followed by Latin America (63.4%) and Asia (54.7%). On the other hand, North America had one of the lowest prevalences (37.1%) (3). It has been observed that the risk of acquiring *H. pylori* It is more present in vulnerable populations, who have a worse socioeconomic condition during childhood, due to low access to water treatment and poor hygiene. In this sense, in developing countries, the infection is more commonly acquired in younger individuals, when compared to developed countries (1).

It is known that infection by the *Helicobacter pylori* It is the main cause for the development of gastric adenocarcinoma (1). This bacterium is classified as a class 1 carcinogen by the World Health Organization, so it confers a risk for the development of gastric adenocarcinoma of 0.1-3% (4).

Or *H. pylori* is a spiral gram-negative bacterium capable of surviving the acidic pH of the stomach. This tolerance to the environment is mainly due to its flagella, which allow the bacteria to move through the gastric mucosa, protecting it from the acid, in addition to the production of urease, an enzyme capable of converting urea into ammonia and carbon dioxide, which culminates in a higher pH of the medium (1). The bacterium initially affects the superficial layers of the mucosa, typically causing chronic active gastritis (1). However, 10 to 15% of infected individuals may develop more serious conditions such as peptic ulcer disease (gastric or duodenal), MALT gastric lymphoma, or gastric adenocarcinoma, the latter developing in 2 to 3% of those infected (1). The factors that determine the development of these complications of chronic infection are the virulence factors of the

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bacteria, host factors, such as the genes that regulate the immune response, and environmental factors (1).

It is estimated that 780 thousand cases of gastric cancer related to gastric cancer are detected annually *H. pylori* Around the world (4). Due to the importance of gastric adenocarcinoma worldwide and since gastric adenocarcinoma infection *H. pylori* is the greatest risk factor for its development, which can be treated, the objective of this systematic review is to evaluate the impact of the eradication of the *H. pylori* on the incidence of gastric adenocarcinoma.

METHOD

A systematic review was conducted in the Pubmed, Cochrane, Medline, and LILACS databases between May 2023 and April 2024. The search strategies were: 1) Indexing words: "stomach neoplasms AND *Helicobacter pylori* eradication AND cancer prevention"; 2) Articles in English; 3) Filter of the last five years; 4) Types of study: meta-analyses, reviews, systematic reviews, clinical trials, and randomized controlled trials. The inclusion criteria used were: 1) The relationship between the treatment of *H. pylori* infection and the incidence of gastric adenocarcinoma; 2) Individuals without precancerous gastric lesions. The exclusion criteria were: 1) Studies that did not meet the inclusion criteria; 2) Studies related to the treatment of *H. pylori* alone; 3) Studies based on animal model or in vitro.

RESULT

In all, 129 articles were initially identified in the databases. Of these, 37 were excluded because they were duplicates. Of the remaining 92 articles, 42 were excluded after reading their titles, as they did not fit the inclusion criteria. Of the remaining 50 articles, 33 were excluded after reading their abstracts because they met the exclusion criteria. The remaining 17 articles were selected to be read in full, and 5 of them were excluded because these were studies with a lack of statistical significance for the results found (n = 3) and because they were not found in full (n = 2). In total, 12 articles were selected for the literature review. Figure 1 illustrates a PRISMA flowchart for the selection procedure.

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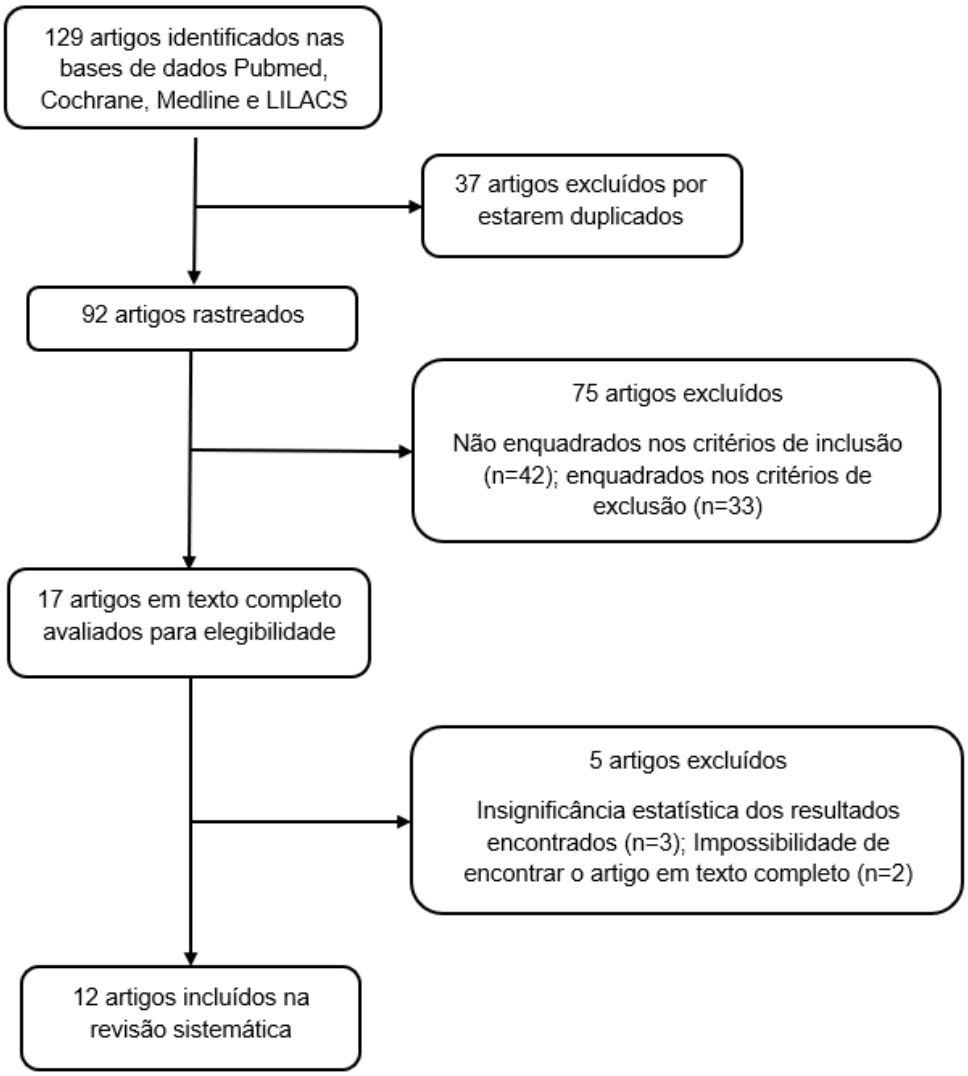
Figure 1. Flowchart of the article selection process



The detailed basic characteristics of the twelve studies used for the review are presented in Table 1. All articles were published between 2019 and 2024. As for provenance, the studies were conducted in different countries, including China, the United States, Japan, Taiwan, South Korea, Finland and Colombia. Of these twelve articles analyzed, there are four systematic reviews, three meta-analyses, three cohort studies, and two randomized controlled trials.

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Table 1. Characteristics of the studies included in the systematic review

Study	Type of study	Total number of patients	Incidence of gastric cancer after eradication	Gastric cancer mortality	Countries
Duan, 2019 (5)	Meta-analysis	40.740	IRR = 0.52 (95% CI 0.41 - 0.65)	It does not address	China, South Korea, Finland and Japan
Liou, 2020 (6)	Systematic review	8834	RR = 0.55 (95% CI 0.42 - 0.74)	It does not address	China, Colombia, South Korea and Japan
Ford, 2020 (7)	Meta-analysis	8323	RR = 0.54 (95% CI 0.40 - 0.72)	RR = 0.61 (95% CI 0.40 - 0.92)	China, Colombia, South Korea and Japan
Choi, 2020 (8)	Randomized controlled trial	1676	HR = 0.45 (95% CI 0.21 - 0.94)	It does not address	South Korea
Chiang, 2021 (9)	Cohort	6512	RR = 0.47 (95% CI 0.30 - 0.69)	RR = 0.75 (95% CI 14% - 51%)	Taiwan
Kumar, 2020 (10)	Cohort	371.813	HR = 0.24 (95% CI, 0.15–0.41; P<0.001)	It does not address	United States
Lin, 2021 (11)	Meta-analysis	63.833	RR = 0.34 (95%, CI: 0.25–0.46)	It does not address	Japan
Chiang, 2022 (12)	Systematic review	17.856	ARR ranging from 0.42% - 3.37%	It does not address	China, South Korea, Japan and Taiwan
Hu, 2022 (13)	Systematic review	2258	OR = 0.48 (95% IC = 0,32 - 0,71)	It does not address	China
Yan, 2022 (14)	Randomized controlled trial	1630	HR = 0.57 (95% CI, 0.33–0.98)	Statistically insignificant	China
Li, 2023 (15)	Cohort	716.567	HR = 0.37 (95% CI 0.14 - 0.97)	It does not address	United States
Chivu 2024 (16)	Systematic review	1838	HR = 0.45 (95% CI 0.21 - 0.94)	It does not address	Not specified

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The type of gastric cancer considered in all studies was adenocarcinoma, including both intestinal and diffuse types. The diagnostic method was histological examination after upper gastrointestinal endoscopy with biopsy.

On the other hand, the diagnosis of *H. pylori* infection was made by several methods, such as urease test, histological examination, culture, H. *pylori* serology, and urea breath test. In addition, the treatment of bacterial infection involved the use of different therapeutic regimens, among them were used Amoxicillin, Clarithromycin, Metronidazole, Proton Pump Inhibitors, 5-nitroimidazole, Bismuth Citrate and Ranitidine.

All studies showed that the eradication of *H. pylori* decreases the incidence of gastric cancer in individuals without preneoplastic lesions, so that this decrease ranged from 43% to 76% among the articles (CI = 95%). Only three of these studies addressed mortality due to gastric adenocarcinoma, so that two of them indicated that the eradication of the bacterium reduces mortality by 25% to 39% (CI = 95%), while in the other there was no statistical significance (p value = 0.421).

DISCUSSION

Gastric adenocarcinoma is the fifth most prevalent malignant neoplasm in the world and the third leading cause of cancer-related mortality worldwide, and much of this is due to the fact that the diagnosis of the neoplasm is made in advanced stages (2). Thus, given the impact of this disease on health worldwide, the prevention of gastric cancer has been increasingly studied in the last 10 years.

It is known that infection by the *Helicobacter pylori* It is the main cause for the appearance of gastric adenocarcinoma and that this disease is difficult to develop in individuals not infected by this bacterium (17), so that a study carried out in Japan showed that the prevalence of gastric adenocarcinoma in these patients is less than 1% (17). Thus, investigating the effects of the eradication of *H. pylori* on the incidence of gastric cancer is of great interest to public health.

In this sense, the results found by this systematic review strongly indicate that the eradication of *Helicobacter pylori* exerts a protective effect on the incidence of gastric adenocarcinoma, so that the current literature is unanimous regarding this result.

Among the articles included in this review, there are 2 cohort studies conducted in the United States. Both studies were carried out with patients of different ethnicities (whites, blacks, Asians, Hispanics) and concluded that the eradication of the *H. pylori* significantly

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decreases the risk of developing gastric adenocarcinoma (HR = 0.24 (95% CI, 0.15 - 0.41) (10); HR = 0.37 (95% CI 0.14 - 0.97) (15)). Thus, it is possible to observe that even though some ethnicities are more affected by gastric cancer, such as blacks, Hispanics and Asians (1,10), eradication was beneficial in all of them, showing the importance of implementing policies for tracking and treating the infection by *Helicobacter pylori*, aiming to improve public health.

Regarding mortality due to gastric adenocarcinoma, the 2 articles that addressed this issue and obtained statistically significant results include Asian populations, and therefore at high risk for gastric adenocarcinoma infection. *H. pylori*. Both studies concluded that the eradication of *H. pylori* decreases the number of deaths caused by gastric cancer (RR = 0.61 (95% CI 0.40 to 0.92) (7); RR = 0.75 (95% CI 14% - 51%) (9)). In other words, in addition to definitively decreasing the incidence of this type of cancer, there is a moderate amount of evidence showing that the proper eradication of *H. pylori* It is also capable of promoting lower mortality due to gastric adenocarcinoma, which is very important in locations with a high prevalence of gastric adenocarcinoma. *H. pylori*, thinking about public health policies.

However, to carry out the eradication of *H. pylori* It is not simple, since numerous factors interfere in the relationship between this bacterium and the host, and consequently in the development of gastric adenocarcinoma. As an example, it is noted that certain regions have higher rates of infection by the bacterium and cancer mortality, as is the case of Africa, Latin America and Asia, than others, such as countries in North America. One of the explanations for this is that the risk of acquiring *H. pylori* It is associated with living conditions and socioeconomic status, especially during childhood. Thus, we can observe that in developed countries such as Switzerland (prevalence of 18.9%), Norway (30.7%), Denmark (22.1%) the prevalence of infection by the *H. pylori* it is much lower than in developing countries, such as Brazil (71%), South Africa (77.6%) and Colombia (80%) (18,19).

In this sense, it is possible to observe that, although gastric cancer is the most prevalent and the one with the highest mortality in Japan, currently only 2% of individuals born after the 2000s are infected with gastric cancer. *H. pylori*, while about 80-90% of those born until the 1950s are colonized by this bacterium. This drastic reduction in the incidence of *H. pylori* It is mainly due to better hygiene conditions, especially before the age of 5 (20).

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Making a parallel with our country, about 50% of children between 2 and 5 years of age are infected by the *Helicobacter pylori* and about 70-90% among those aged 5 to 10 years (21). In addition, in a meta-analysis conducted to estimate the global prevalence of *H. pylori*, a prevalence of 71% was observed in Brazil (18). However, in individuals with better schooling, better sanitary conditions and better socioeconomic status, the prevalence of infection with the *H. pylori* is smaller. This was observed by a study conducted in the Southeast region of Brazil with 4604 patients, in which 63.1% of them came from the private health system and, therefore, had better socioeconomic conditions than the majority of the Brazilian population. Of this total number of people, only 1459 (31.7%) were infected with the *H. pylori*, that is, a much lower percentage than the overall prevalence of the country (22).

Thus, as the infection is more common to be acquired at a younger age and socioeconomic and sanitary conditions have such an impact on the prevalence of *Helicobacter pylori* infection, another way to aim at the prevention of gastric adenocarcinoma is by improving the living conditions of the population in developing countries. Thus, fewer individuals would be infected by *H. pylori* and the policies to eradicate the bacterium, which would eventually be implemented, would need to cover fewer people and the effect of this would be beneficial, in view of the current difficulty in carrying out the adequate treatment of this infection due to antimicrobial resistance, which will be discussed below.

VIRULENCE FACTORS

Certain strains of *H. pylori* are known to be more pathogenic than others due to their virulence factors, which contribute to the development of cancer.

Gastric colonization by the *H. pylori* It depends on special mechanisms to occur. Thus, when it reaches the stomach, the bacterium uses its flagella to reach the gastric mucosa. The bacterium has a group formed by four to eight flagella at one or both ends, which have different properties and forms of locomotion depending on the environment in which they are found. Several studies have shown that mutations in genes that decode flagella-specific proteins such as fliD, FlaA, and FlaB can impair the motility of the *H. pylori*, which can decrease and even prevent gastric colonization (23).

The bacterium also depends on the chemotactic response to different molecules such as mucin, sodium, bicarbonate, urea, sodium chloride and some specific amino acids.

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At least ten genes of the bacterium are related to the reception, transduction, and processing of the chemotactic stimulus, as well as some chemotactic bacterial receptors have been described (T1pA, B, C, and D) (23).

The relationship between the bacterium and the host is influenced by the adhesion molecules of the *H. pylori* and surface receptors of gastric cells. For example, bacteria with high expression of blood group antigen-binding adhesin A (BabA) are more virulent and more related to gastric adenocarcinoma. Another example is HopQ adhesin, present in the outer membrane of the bacterium, which binds to CEACAMs (cell adhesion molecules related to carcinoembryonic antigen) 1, 3, 5 and 6, giving rise to cell signaling that allows the translocation of CagA, the main virulence factor of this bacterium, increasing pro-inflammatory mediators in the host cell (23).

The virulence of *H. pylori* is closely related to the presence of the cag pathogenicity island (cagPAI), a region that encodes the CagA oncoprotein and a type IV secretion system. The CagA protein leads to specific modifications in the morphology of gastric epithelial cells, so that changes that occur in the cytoskeleton of these cells in gastric adenocarcinoma are related to this oncoprotein. In the host cell, CagA undergoes phosphorylation at the EPIYA site. This site is variable and can be composed of different segments (EPIYA-A, EPIYA-B, EPIYA-C and EPIYA-D), so that the EPIYA-A and EPIYA-B segments are commonly found in the strains of *H. pylori* CagA-positive, and those with EPIYA-D segments or at least two EPIYA-C, are associated with a higher risk of developing cancer. For example, a study done in Brazil showed that first-degree relatives of patients with gastric cancer tend to be infected by strains of *H. pylori* containing two or more EPIYA-C segments (23,24).

These factors may be the explanation for the fact that some countries, despite having a prevalence of HIV infection, *H. pylori* relatively low, have high mortality from gastric cancer, such as in Japan (prevalence of 51.7% and 11.47 deaths per 100 thousand inhabitants) (25), China (prevalence of 55.8% and 20.55 deaths per 100,000 population) (26) and South Korea (prevalence of 54% and 9.13 deaths per 100,000 inhabitants) (27) and countries with similar prevalence of this infection, as in the case of Finland (56.8%) (5), but with low mortality (3.37 per 100,000 inhabitants). Thus, the virulence factors of the *Helicobacter pylori* present in these places can cause the effects of gastric infection by the bacteria to be more aggressive and cause more cancer than other strains from other regions of the world. Therefore, it is possible that future treatments will be based on the

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specific virulence factors of the most prevalent strains in these regions, constituting a more effective treatment than what is currently available.

TREATMENT OF *HELICOBACTER PYLORI INFECTION*

As mentioned earlier, another challenge in the issue of *H. pylori* today is the treatment of the infection itself. This is due to the wide variety of different strains that exist and the different antimicrobial resistances among populations, making it difficult to establish a treatment that is effective for everyone.

There is no effective monotherapy for the treatment of infection by *H. pylori*. As in the studies involved in this review, generally, the treatment of choice involves the use of two antibiotics (amoxicillin; and clarithromycin, metronidazole, or levofloxacin) in addition to a proton pump inhibitor (28).

Most of the therapies of choice are based on comparison between randomized controlled trials. However, characteristics of these studies, such as the dosages of antibiotics, the potency of the proton pump inhibitors used, and the prevalence of resistance to a given antimicrobial in each population vary greatly from one another, so that treatment recommendations include options that do not achieve acceptable cure rates (28).

Treatment should ideally last 14 days and should be based on high susceptibility or high local success rates. After treatment, the patient should be tested to assess whether therapy has been successful or failed. This helps to indicate, albeit indirectly, whether a certain therapy shows more cure or resistance, helping in the population's therapeutic choice (28).

A study conducted in 2021 in Colombia analyzed strains taken from high-risk populations for gastric cancer and low-risk populations, testing their susceptibility to various antimicrobials. Subsequently, the genes of these strains were amplified and several mutations related to certain patterns of antimicrobial resistance were found (19). Thus, in countries where infection by the *H. pylori* and gastric cancer are prevalent as Colombia itself and even Japan, strategies such as this one of analyzing the susceptibility of certain strains to antimicrobials and, in addition, identifying which genes are responsible for this resistance are extremely pertinent for the control of this infection and, consequently, for the reduction of gastric cancer cases in a targeted and specific way for each population.

However, it should be noted that gastric adenocarcinoma may develop after eradication of gastric adenocarcinoma *H. pylori*, even though this practice reduces the

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incidence of this disease. One of the hypotheses that explain this, in addition to the fact that cancer has a multifactorial etiology, is that precancerous lesions prior to eradication may not be detected by upper digestive endoscopy (17), and then develop into cancer and be diagnosed only some time later. Thus, it is assumed that the eradication of *H. pylori* does not prevent the progression of these lesions from a certain degree of dysplasia. Thus, in order for this issue to be resolved, new, more accurate diagnostic methods are needed.

Finally, the Kyoto Global Consensus and the Maastricht V Consensus support that all infections by *Helicobacter pylori* must be treated regardless of the presence of symptoms (21). The results found in this systematic review, therefore, are corroborated by these consensuses, since it was observed that the treatment of the general population infected by *H. pylori* decreases the incidence of gastric adenocarcinoma.

CONCLUSION

Helicobacter pylori *eradication therapy* decreases the incidence of gastric adenocarcinoma. Therefore, public health strategies should be implemented in order to mitigate the occurrence of infection, in addition to screening and treatment of populations with high susceptibility to this condition, which can be beneficial to prevent the development of gastric cancer.

However, it cannot be stated that mortality due to gastric cancer is impacted by *H. pylori* eradication therapy, since only 3 studies have addressed this issue. Thus, more studies are needed to address this relationship, as it is a subject of paramount importance worldwide.

In addition, since it is currently known that the eradication of *H. pylori* reduces the incidence of gastric adenocarcinoma, future research on the subject should be aimed at improving the treatment of the infection itself and more accurate diagnostic methods, aiming to establish the early diagnosis of preneoplastic lesions.

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