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Gastroesophageal reflux disease and the relationship with *Helicobacter pylori*

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ABSTRACT

After *Helicobacter pylori* was identified, and its relationship with peptic ulcer disease was exactly shown, the relationship of this bacterium with gastroesophageal reflux disease (GERD) gained momentum and discussions continue to this day. We reviewed the literature for the relationship between *H. pylori* and GERD. According to the existing data, there is no relationship between GERD and *H. pylori* presence. Successful eradication therapy does not have an impact on the emergence or exacerbation of GERD. However Barrett's esophagus and esophageal adenocarcinoma are less frequent, especially in the presence of CagA positive *H. pylori* infections. Long-term use of proton pump inhibitor (PPI) may have an impact on the development of atrophy and/or intestinal metaplasia in *H. pylori* positive patients; therefore, *H. pylori* eradication is recommended in patients that should use long-term PPI. As a conclusion, *H. pylori* screening and the eradication decision should be independent of GERD, except for patients that will use long-term PPI.

Keywords: *Helicobacter pylori*, gastroesophageal reflux disease, proton pump inhibitors, gastric atrophy, esophagus cancer, Barrett esophagus

The effects of the presence of *Helicobacter pylori (Hp)* and the eradication therapy of *Helicobacter pylori* on the progress and complications of GERD were examined under four main headings.

DOES THE PRESENCE OF HELICOBACTER PYLORI AFFECT THE PREVALENCE, SYMPTOM SCORES, SEVERITY, AND RELAPSE OF REFLUX?

Helicobacter pylori infection has been thought to play a facilitating role for the development of GERD by causing a reduction in the lower esophageal sphincter (LES) pressure, an increase in the transient relaxation of the lower esophageal sphincter, hypergastrinaemia, and a delay in gastric emptying. On the other hand, it has been suggested to be protective from GERD because it leads to a reduction in acid secretion and provides acid neutralization due to the gastritis type it creates. With the implementation of eradication therapies, a decrease has occurred in the prevalence of *H. pylori*; however, the frequency and complications of GERD have increased. This result supports the view that *H.pylori* may be protective from GERD. In an epidemiological study, the prevalence of *H.pylori* was reported to be lower in GERD than the non-reflux group (32.8% vs. 49.5%; OR: 0.58) (1). The first clinical trials showed that the presence of *H.pylori* reduced the need for proton pump inhibitor (PPI) (2). When compared in terms of maintaining symptomatic and endoscopic remission, *H.pylori* eradicated (*Hp* negative, *Hp*-) GERD patients were indicated to need a higher dose of PPI than patients that had *H.pylori* (*Hp* positive, *Hp*+) (3). Subsequently, it was shown that erosive esophagitis developed more frequent in patients treated with *H.pylori* eradication compared to *Hp*+ patients (4). It was reported in another study that reflux esophagitis recovered synchronous in patients who underwent eradication therapy due to peptic ulcers (5). In epidemiological studies, it was seen that there were differences between the East and the

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West; but there was an inverse relationship between *H. pylori* prevalence and GERD when all the proportions were evaluated together (1).

In order to search for the answers to this controversial question, when the keywords "Gastroesophageal reflux disease [MeSH Terms]" AND "Helicobacter pylori [MeSH Terms]" were entered, a total of 293 studies were found in the systematic literature review written in English on adult subjects. Of these, 17 randomized controlled studies, consistent with the criteria, and 4 meta-analyses (covering also 17 randomized controlled studies) were evaluated. A meta-analysis, by Cremonini et al. (6), that involved 14 case-control studies and 10 clinical trials, analyzed the effect of *H.pylori* eradication among participants in terms of "de novo" reflux development and progression in the existing symptoms of reflux. It was identified that eradication therapy increased new reflux development 3.25 times (95% CI , 2.09-5.33), rebound reflux development increased 2.39 times (95% CI 1.75-3.34), and new or rebound reflux development increased 2.54 times (95% CI 1.92-3.37). Despite this meta-analysis that states the presence of *H.pylori* is protective against the development of GERD, other studies have not reached this conclusion. In the meta-analysis, by Yaghoobi et al. (7), that involved five cohort studies and 7 randomized controlled trials (RCTs), all *H.pylori*+and non-GERD patients were compared by receiving placebo vs. eradication therapy in terms of new reflux symptoms and/or reflux esophagitis development. Cohort studies and RCTs were assessed separately; the odds ratio was found as 1.22 (95% CI 0.89-1.69) for the risk of symptomatic GERD development in RCTs, 1.11 (95% CI 0.81-1.53) for the risk of erosive esophagitis development, and 1.37 (95% CI 0.89-2.12) for the risk of GERD development in cohort studies (7). In another meta-analysis, 11 RCTs were evaluated. GERD and non-GERD groups were initially included in this study; the group in which eradication was applied and *H.p*ylori persistent groups were examined in terms of the development of symptomatic reflux and/or erosive esophagitis. As a result, no difference was detected between the two groups in terms of symptomatic reflux, heartburn, and erosive esophagitis frequency. They were indicated as odds ratio: 0.88 (95% CI 0.63-1.23), 0.79 (95% CI 0.54-1.15), and 0.97 (95% CI 0.67–1.40), respectively (8). Finally, in the meta-analysis by Saad et al. (9) of 10 RCTs, the group of *Hp* therapy vs. placebo and the group in which a successful *Hp* was applied vs. persistent group were compared among themselves in terms of the development of symptomatic reflux and erosive esophagitis, and similar conclusions were reached: The odds ratio was found as 0.81 (95% CI 0.56-1.71) for the development of symptomatic reflux and as 1.13 (95% CI 0.72-1.78) for the development of erosive esophagitis. Moreover, a decrease in the rate of symptomatic reflux was found in the group with successful *Hp* eradication in comparison to the persistent group (13.8% vs. 24.9%; OR: 0.55; 95% CI 0.35-0.87) (9). When

Table 1. The relationship between *H. pylori* eradication therapy and the development of symptomatic reflux disease and erosive esophagitis

Author/Journal/Year	Study Design	Comparison Groups	"Outcome Measure"	"Outcome Patern"	Results (OR)
Cremonini et al. (6), Aliment Pharmacol Ther, 2003	Meta-analysis (14 case control 10 RCT)	*HpE tx+vs. tx- *Successful HpE tx vs. HpP *before HpE tx vs. after HpE tx	Endoscopic esophagitis and reflux symptoms	Denovo/recurrent reflux development and worsening of existing symptoms of reflux disease/progression	Denovo: 3.25 (95% CI 2.09-5.33) Rebaund: 2.39 (95% CI 1.75-3.34) Denovo + Rebaund: 2.54 (95% CI 1.92-3.37)
Yaghoobi et al. (7), Am J Gastroenterol, 2010	Meta-analysis (5 cohort study 7 RCT)	All cases Hp+ and GERD(-) HpE tx vs. Placebo	Erosive esophagitis or reflux symptoms	Denovo reflux symptoms or the development of reflux esophagitis	Symptomatic GERD for RCT: 1.22 (95% CI 0.89-1.69) Endoscopic GERD for RCT: 1.11 (95% CI 0.81-1.53) GERD for cohort study: 1.37 (95% CI 0.89-2.12)
Quian et al. (8), Helicobacter, 2011	Meta-analysis (11 RCT)	Baseline patients with and without GERD HpE tx vs. HpP	Symptomatic reflux disease, erosive esophagitis	Development or progression denovo and recurrent reflux disease	Incidence of symptomatic reflux: 0.88 (95% CI 0.63-1.23) Incidence of heartburn: 0.79 (95 % CI 0.54-1.15) Incidence of erosive esophagitis: 0.97 (95 % CI 0.67-1.40)
Saad et al. (9), Scand J Gastroenterol, 2012	Meta-analysis (10 T)	-HpE tx vs placebo -Successful HpE tx vs. unsuccessful HpE tx	Symptomatic reflux disease, erosive esophagitis	Recurrent reflux disease and erosive esophagitis	Development of symptomatic reflux: 0.81 (95% CI 0.56-1.71) Development of erosive esophagitis: 1.13 (95 % CI 0.72-1.78)

HpE tx: *H. pylori* eradication theraphy, HpP: *H. pylori* persistent

Table 2. The comparison between the group with successful *H. pylori* eradication therapy and persistent groups in terms of symptomatic reflux disease and erosive esophagitis incidence

META-ANALYSIS	OR (95% CI)						
					Incidence of GERD according to disease		
Author/Publication date	incidence of symptomatic	incidence of hearthburn	incidence of reflux esophagitis	incidence of endoscopic esophagitis	Peptic Ulcer	Functional Dyspepsia	GERD
Yaghoobi et al. (7) 2010	1.22* (0.88-1.69			1.17 (0.89-2.12)	1.26* (0.88-1.80)	0.61* (0.28-1.32)	
					2.04** (1.88-3.85)	0.84** (0.44-1.58)	
Quian et al. (8) 2011	0.88 (0.63-1.23)	0.79 (0.54-1.15)	0.97 (0.67-1.40)		1.0 (0.7-1.42)	0.93 (0.32-2.74)	2.57 (0.64-10.22)
Saad et al. (9) 2012	0.81 (0.56-1.17)		1.13 (0.72-1.78)				
Cremonini et al. (6) 2003	1.34 (1.15-1.55)				1.79 (1.26-2.54)	2.28 (1.52-3.45)	

*data of RCT ** data of cohort study

a subgroup analysis was made in these four meta-analyses in terms of the disease groups in which *Hp* eradication was performed, the rate of GERD development after *Hp* eradication was found higher in the group that was given eradication therapy due to peptic ulcers than the group that was given eradication therapy due to functional dyspepsia (6,7) [In the study of Yaghoobi et al. (7), OR: 1.26, 95% CI 0.88-1.80 for RCT and OR: 2.04, 95% CI 1.88-3.85 for cohort studies and in the study of Cremonini et al. (6) OR: 1.79; 95% CI 1.26-2.54] was detected.]

According to the existing data, there is no relationship between GERD and *H. pylori* presence. Successful eradication therapy does not have an impact on the emergence or exacerbation of GERD. However, the development of GERD after eradication can be considered in patients with peptic ulcers. All the data of the above-mentioned studies are summarized in Table 1 and Table 2.

DOES THE RISK OF ATROPHIC GASTRITIS INCREASE IN THE PRESENCE OF HELICOBACTER PYLORI IN GERD PATIENTS USING LONG-TERM PPI? DOES *HELICOBACTER PYLORI* ERADICATION AFFECT THE RISK IN THESE PATIENTS?

Proton pump inhibitor (PPI) treatment alters the distribution of *H.pylori* in the stomach and causes corpus-fundus dominant gastritis with decrease in gastric acid secretion. While the annual development of atrophy was 10.9% in *H.pylori* + patients using PPI, this rate was found 0.9% in *H.pylori* - patients (10). In another study including patients not using a PPI, while this rate was 1.8% in *H.pylori* + cases, it was found 0.3% in *H.pylori* - cases (11). A search was made by entering the keywords "proton pump inhibitors [MeSH Terms]" AND "atrophic gastritis [MeSH Terms]" OR "Helicobacter pylori [MeSH Terms]" in the PubMed search, and a total of 7 RCTs were found qualified enough to answer the question above. While the groups that were taking PPI and underwent anti-reflux surgery (ARS) were compared in three of these studies, the groups in which *H.pylori* eradication was and was not received were compared in the others. In the RCT of Kuipers et al. (12), PPI therapy was given to 105 patients with GERD and ARS was applied in 72 patients. At the end of the 84-month follow-up, while the rate of atrophic gastritis development for *H.pylori*+ cases was 31% in the omeprazole arm, it was found 3% in the ARS arm. In *H.pylori*- cases, whereas the same rate was 4% in those using omeprazole, it was found to be 0% in the ARS arm. In the study of Lundell et al. (13), 155 patients in whom GERD was proven endoscopically were given omeprazole and ARS was applied in 155 patients. At the end of a 36-month follow-up, a mild progression was seen in glandular corpus atrophy in *H.pylori*+patients, and similar results were observed in the two arms in term of intestinal metaplasia. In the study of Lundell et al. (14) in 2006, omeprazole was administered in 98 of a total of 215 GERD patients, and ARS was applied in 117. It was shown that glandular atrophy developed in 5 of the 13 *H.pylori*+patients using omeprazole and in 3 of the 12 patients who underwent ARS at the end of a 84-month follow-up. In the prospective randomized case-control study of Schenk et al. (15), 57 *H.pylori*+and 26 *H.pylori* - GERD patients receiving omeprazole vs. placebo were followed for 12 months after eradication therapy; the rate of atrophy in corpus was observed not to have changed in the eradication arm. In another prospective double-blind RCT, omeprazole vs. placebo treatment was given to patients with 15 GERD with *Hp*+ omeprazole vs. eradication therapy was applied to another patients with 15 GERD with *Hp*+ , and patients with 11 GERD without *Hp* were received placebo as a control group. Whereas a slight atrophy in corpus occurred in 5 of the 11 patients who completed a one-year follow-up in the omeprazole arm, atrophy was seen in none of the 8 patients to whom eradication therapy was given (p=0.02) (16). In the RCT of Kuipers et al. (17) involving 231 *H.pylori* + GERD patients, omeprazole was given to 120 patients and *H.pylori* eradication therapy was applied to 111 patients; maintenance therapy was provided with omeprazole for 24 months. Atrophy in corpus was observed to regress in the eradication arm compared to the *H.pylori* + omeprazole arm (p=0.001), and no change occurred in intestinal metaplasia. In the study by Yang et al. (18), which involved 325 GERD patients (105 *H.pylori* + were given eradication treatment, 105 *H.pylori* + were followed without treatment, and 115 *H.pylori* - were in the control group) who were followed up24-month period after eradication therapy or placebo, the prevalence of atrophic gastritis was found to be 5.4% in the *H.pylori* eradication arm, 15.7% in the arm without treatment, and 0% in the control group. Intestinal metaplasia was reported as 19.4% in eradica-

Table 3. The application of eradication therapy can prevent the development and progression of gastric atrophy and intestinal metaplasia

Author/ Publication date	Study Design	Group of Patient	Methods of Treatment	Hp + / -	Fw-up period (month)	Results AG / IM	Corpus Gastritis
Kuipers et al. (12) NEJM, 1996	RCT	GERD	105 OMP 72 ARS	OMP 59/105 ARS 31/72	84	rate of AG for Hp + group - OMP 31% (18/59) - ARS 3% (1/31) rate of AG for Hp – group - OMP 4% (2/46) - ARS 0%	Increased
Lundell et al. (13) Gastroenterology, 1999	RCT	GERD	155 OMP 155 ARS	OMP 40/155 ARS 53/155	36	Similar results in terms of IM Hp + patients in both arms slight progression in the corpus glandular atrophy in Hp + patients	Minimal increased
Schenk et al. (15) Gut, 2000	RCT prospective randomized case control	GERD 57 Hp + 26 Hp -	HpE vs. Hp placebo followed by maintenance with OMP	Hp +/+ : 24 Hp +/- : 33 Hp - : 26	12	Decreased in antral atrophy in HpE tx group but no change corpus atrophy	Increased
Moayyedi et al. (16 Helicobacter, 2000	RCT prospective, double-blind	GERD	OMP vs Placebo:15 OMP vs HpE tx 15 Hp – control:11	Completed follow-up n=11 n= 8 n=12	12	OMP: 5/11 minimal corpus atrophy HpE tx: 0/8 no atrophy (p=0.02)	Increased
Kuipers et al. (17) Gut, 2004	RCT	231 Hp + GERD 120 OMP vs. 111 HpE No control Hp-	Maintenance theraphy with OMP for 2 years		24	HpE vs Hp+ OMP rate of antral IM and AG: no change rate of corpus atrophy: decrease (p=0.001) rate of IM in corpus: no change	Increased
Lundell et al. (14) APT 2006	RCT	215 GERD	98 OMP 117 ARS	OMP 39/98 ARS 53/117	84	Number of patients (Hp+) completed follow-up OMP: 13 ARS: 12 Glandulary atrophy: 5/13 vs 3/12	Increased
Yang et al. (18) Am J Gastroenterol 2009	RCT	325 GERD 105 HpE tx 105 HpE tx - 115 Hp (-) control group	After eradication or plasebo theraphy on-demand or continue PPI therapy	Completed follow-up n=83 n=83 n=100	24	Prevelance of expanded corpus atrophy Hp E tx: 5.4% (5/93) Hp+ without treatment: 15.7% (13/83) Hp – control: 0% IM Hp E: 19.4% (18/93) Hp+ without treatment: 36.2% (30/83) Hp- control: 2% (2/100)	Increased

OMP: omeprazo;l ARS: anti-reflux surgey; HpE: *H. pylori* eradication theraphy; IM: intestinal metaplasia AG: atrophic gastritis

tion arm, as 36.2% in the arm without treatment, and as 2% in *H.pylori* - control arm. In all studies, an increase in corpus gastritis was observed in the *H.pylori*+ groups using long-term PPI.

In light of this data, long-term use of PPI therapy in *H.pylori* + patients can lead to the development of corpus predominant gastritis. The application of eradication therapy can prevent the development and progression of gastric atrophy and intestinal metaplasia (Table 3).

DOES THE PRESENCE OF *HELICOBACTER PYLORI* AFFECT THE FREQUENCY OF BARRETT'S ESOPHAGUS (WITH OR WITHOUT DYSPLASIA)?

The incidence of esophageal adenocarcinoma has been increasing gradually in developed countries over the last three decades. Barrett's esophagus (BE) is a precancerous lesion for esophageal adenocarcinoma and the incidence is <2% in the general population (19). The relationship between *H.pylori* and BE development seems somewhat complicated. In the literature, there are studies that reach different results on this issue; in addition to the studies reporting that the presence of *H.pylori* is a risk factor for BE development, there are studies reporting that it does not influence the development of BE or it prevents BE development (20-29). In the study by Vaezi et al. (29), it was found that being infected with *H.pylori* had a protective effect for development of BE and its malignant complications. This effect was more apparent in the infection with the CagA+ (positive) strain. In the study by Thrift et al. (30), the risk of BE development was reported to be lower, 80% in *H. pylori*+GERD patients in comparison to *H.pylori* - reflux patients (OR: 2.6 vs. 8.24) (30).

Table 4. The presence of *Hp* seems to be protective from BE development and the protective effect is more evident in CagA+ patients

Author/Publication date	Study design	Comparison groups	"Outcome measure"	Results	Results (RR/OR)
Fischbach et al. (31) Helicobacter, 2012	Meta-analysis (44 case control study 5 cross sectional study	*H. pylori* prevelance in control groups and with BE patients	*H. pylori* prevelance in with BE patients and BE prevelance in cagA+ patients	*H. pylori* is protective for development BE more protective effects in cagA+ patients	RR: 0.73 (95% CI 0.60-0.88) Homogeneous 4 studies were analyzed separately: RR: 0.46 (95% CI 0.35-0.60) cagA+ group: 7 study: RR: 0.38 (95% CI 0.19-0.78)
Wang et al. (32 Am J Gastroenterol, 2009	Meta-analysis (12 case control study)	550 with BE patients 2979 control groups (endoscopically normal blood donors)		Prevelance of *H. pylori* 42.9% (236/550) vs. 43.9% (1308/2979)	OR: 0.74 (95% CI 0.40-1.37)

BE: Barret esophagus

Table 5. The presence of *Hp*, and especially the infection with the CagA+ strain, show a protective effect against esophageal adenocarcinoma. The relationship between *Hp* and esophagus squamous cell cancer is not clear

Author/Publication date	Study design	Comparison groups	Outcome measure	Results	Results (RR /OR)
Islami et al. (35) Cancer Rev Pres 2008	Meta-analysis (19 study) Adeno Ca: 13 study: 848 patients/2890 control group Squamous Ca: 9 study: 921 patients/2743 control group	Hp+ vs. Hp- cagA+ vs. cagA-	Risk of Adeno Ca or Squamous Ca	*H. pylori* reduces the risk Adeno Ca, this phenomenon more pronounced rate in cagA + Hp does not affect the risk of squamous Ca. No relationship with the cagA.	ADENO CA Overall OR: 0.56 (95% CI 0.46 -0.68) cagA+ OR: 0.41 (95% CI 0.28-0.62) cagA- OR: 1.08 (95% CI 0.76-1.53 SQUAMOUS CA Overall OR: 1.1 (95 % CI 0.78-1.55) cagA+ OR: 1.01 (95% CI 0.80-1.27) cagA- OR: 1..41 (95% CI 1-1.97)
Xie et al. (36) W J Gastroenterol, 2013	Meta-analysis (27 study) Adeno Ca: 15 study Squamous Ca: 16 study	Hp+ vs. Hp- cagA+ vs. cagA- East / West study	Risk of Adeno Ca or Squamous Ca	Hp reduces the risk of adeno Ca Rate of Hp+ in Adeno Ca: 35.96% (479/1332) vs. in control groups 44% (2070/4705), OR: 0.71 (0.63-0.81) Hp generally does not risk of squamous Ca affect the cagA+ OR: 0.90 (95% CI 0.78-1.05) *East OR: 0.77 (95% 5 CI 0.65-0.92) *West OR: 1.26 (95% CI 0.97-1.63)	Adeno Ca Overall OR: 0.59 (95% CI 0.51-0.68) Squamous Ca Overall OR: 0.83 (95% 0.63-1.03) Reduces the risk of squamous Ca CagA + Hp in Eastern studies

In order to examine the subject, a search was made using the keywords "Barrett esophagus [MeSH Terms]" AND "Helicobacter pylori [MeSH Terms]" and a total of 176 trials were found. Two meta-analyzes among them were included in the evaluation. In the research of Fischbach et al. (31), 44 case-control studies and 5 cross-sectional studies were included in the evaluation. Whether the *H.pylori* prevalence in patients with Barrett's esophagus and protective effect of being infected with the CagA+ strain for BE was investigated. The presence of *H.pylori* was shown to be protective for BE development (RR: 0.73, 95% CI 0.60-0.88) and this effect was higher in patients infected with the CagA+ strain (RR: 0.38, 95% CI 0.19-0.78). In the meta-analysis of Wang et al. (32), 12 case-control studies were evaluated. 550 BE patients were compared with 2979 volunteers consisting of healthy blood donors with normal endoscopic examination. While the *H.pylori* prevalence was 42.9% (236/550) in the group of Barrett's esophagus while it was found to be 43.9% (1308/2979) in healthy volunteers (OR: 0.74, 95% CI 0.40-1.37).

According to the available data, the presence of *H.pylori* seems to be protective for BE development and this effect is more evident in CagA+ patients. This data is summarized in Table 4.

DOES THE PRESENCE OF *HELICOBACTER PYLORI* AFFECT THE INCIDENCE OF ESOPHAGEAL CANCER?

The persistent *H.pylori* infection in GERD has been reported to be a risk factor for a subtype of esophageal squamous cell carcinoma (33). On the other hand, it has been suggested that the presence of *H.pylori* protects from the development of esophageal adenocarcinoma through various mechanisms (hypoacidity, decrease in gastric ghrelin secretion, affected gastric and esophageal microbiota, and it leads to changes in gastric T-cell compartments) (34). In the search that was conducted to investigate this issue, the keywords "esophagus cancer [MeSH Terms]" AND "Helicobacter pylori [MeSH Terms]" were used and of a total of 142 studies that were obtained. Two meta-analyses meeting the criteria were included in the assessment. The first meta-analysis was published in 2008 and it consisted of 19 studies. The majority of them were community-based and large-scale case-control studies; 13 of them include adenocarcinoma patients (848 patients/2890 control) and 9 of them include squamous cell carcinoma patients (921 patients/2743 control). The patients and controls in this study were grouped in term of *Hp* positivity and *Hp*+ patients were also grouped in terms of CagA+/CagA- strains. It was shown that *H.pylori* positivity reduced the risk of adenocarcinoma [overall OR: 0.56 (95% CI 0.46-0.68)] and the protective effect was more evident in CagA+ cases [CagA+OR: 0.41 (95% CI 0.28–0.62) and CagA- OR: 1.08 (95% CI 0.76-1.53)]. However, the presence of *H.pylori* does not affect the risk of squamous cell carcinoma [Overall OR: 1.1 (95% CI 0.78-1.55)]. Similarly, it has also been found that being infected with CagA+ or CagA- strains does not have an association with the development of squamous cell carcinoma [overall OR: 1.1 (95% CI 0.78-1.55)] (35). In the meta-analysis by Xie et al. (36), a total of 27 community and hospital based studies (15 studies with adenocarcinoma and 16 with squamous cell carcinoma) were assessed. In this study as well, the relationship between the development of cancer in the esophagus and *H.pylori* was examined, and it was shown that *H.pylori* positivity reduced the risk of adenocarcinoma development [overall OR: 0.59 (95% CI 0.51-0.68)]. While the rate of *H.pylori* positivity was 35.96% (479/1332) in the group of adenocarcinoma, it was 44% (2070/4705) in the control group. Similar to the aforementioned meta-analysis, it was determined that the presence of *H.pylori* did not usually affect the risk of squamous cell carcinoma [Overall OR: 0.83 (95% CI 0.63-1.03)] and being infected with the CagA+ strain was shown in Eastern studies to reduce the risk of squamous cell carcinoma development more than in Western studies: Eastern CagA+OR: 0.77 (95% CI 0.65-0.92) and Western cagA+OR: 1.26 (95% CI 0.97-1.63).

In the light of the data presented, the presence of *H.pylori*, and especially the infection with the CagA+ strain, show a protective effect against esophageal adenocarcinoma. The relationship between *H. pylori* and esophagus squamous cell cancer is not clear. The data is summarized in Table 5.

RECOMMENDATIONS

- There is no relationship between *H. pylori* and GERD (Level of evidence: 1a).
- *H. pylori* eradication does not have any effects in the emergence or exacerbation of GERD, except for patients with peptic ulcers (Level of evidence: 1a).
- Long-term use of PPI may have an impact on the development of atrophy and/or intestinal metaplasia in *H. pylori* positive patients; therefore, *H. pylori* eradication is recommended in patients that should use long-term PPI (Level of evidence: 1b).
- Barrett's esophagus and esophageal adenocarcinoma are less frequent, especially in the presence of CagA positive *H. pylori* infections (Level of evidence: 3a).
- *H. pylori* screening and the eradication decision should be independent of GERD, except for patients that will use long-term PPI (Level of evidence: 5).

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