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Helicobacter pylori infection and esophageal adenocarcinoma: a review and a personal view

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Abstract

Esophageal adenocarcinoma (EAC) is etiologically associated with gastroesophageal reflux disease (GERD). There is evidence to support the sequence GERD, Barrett's esophagus (BE), dysplasia, and finally EAC, with *Helicobacter pylori (H. pylori)* being implicated in each step to EAC. On the other side of this relation stands the hypothesis of the protective role of *H. pylori* against EAC. Based on this controversy, our aim was to review the literature, specifically original clinical studies and meta-analyses linking *H. pylori* infection with EAC, but also to provide our personal and others' relative views on this topic. From a total of 827 articles retrieved, 10 original clinical studies and 6 meta-analyses met the inclusion criteria. Original studies provided inconclusive data on an inverse or a neutral association between *H. pylori* infection and EAC, whereas meta-analyses of observational studies favor an inverse association. Despite these data, we consider that the positive association between *H. pylori* infection and GERD or BE, but not EAC, is seemingly a paradox. Likewise, the oncogenic effect of *H. pylori* infection on gastric and colon cancer, but not on EAC, also seems to be a paradox. In this regard, well-designed prospective cohort studies with a powered sample size are required, in which potential confounders should be taken into consideration since their design.

Keywords *Helicobacter pylori*, esophageal adenocarcinoma, Barrett's esophagus, gastroesophageal reflux disease

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Introduction

Helicobacter pylori (*H. pylori*) is a common bacterium and infects almost half of the global population [1], being strongly associated with upper gastrointestinal morbidity. Its prevalence is still high in most countries; there were approximately 4.4 billion individuals with *H. pylori* infection worldwide in 2015, and *H. pylori* remains highly prevalent in certain ethnic populations and in migrants moving from high prevalence countries [1]. The primary pathogenic role of *H. pylori* in peptic ulcer formation is supported by robust evidence [2], and *H. pylori* was recognized as a true class I carcinogen for gastric cancer by the International Agency for Research on Cancer [3] and the World Health Organization in 1994. On top of this, numerous studies claim to have implicated *H. pylori* in a long list of systemic disorders, including cardio-cerebrovascular [4,5], degenerative [6-8], and metabolic syndrome (MetS)-related conditions [4,9]. Likewise, the accumulated oncology literature suggests an etiological relation of *H. pylori* with extra-gastric neoplasms, such as pancreatic [10], colorectal [11-13], and esophageal cancers, at least in some subpopulations [14].

Esophageal cancer is among the most frequent neoplasms, a main cause of cancer-related deaths worldwide and a clinically challenging disease requiring a multidisciplinary approach [15]. Esophageal cancer is divided into two histological types: esophageal squamous cell carcinoma (ESCC), associated mostly with environmental risk factors (e.g., smoking and alcohol consumption), and esophageal adenocarcinoma (EAC) located close to the gastroesophageal junction, etiologically coupled with gastroesophageal reflux disease (GERD). In the westernized population, the incidence of EAC increased sharply, displacing ESCC, the latter accounting for most of the incidence of esophageal cancer 50 years ago [16,17].

Current evidence for the protective or harmful effect of *H. pylori* on EAC is conflicting. On this basis, we aimed to review the literature, specifically original clinical studies and meta-analyses linking *H. pylori* infection with EAC, but also to provide our personal and others' relative views on this topic.

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Conflict of Interest: None

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Literature review

Materials and methods

A literature search was carried out in the PubMed database using the following query, developed from a combination of MeSH and non-MESH terms: [(*Helicobacter pylori*) OR (*Hp*) OR (*H. pylori*)] AND [(esophageal neoplasm) OR (esophageal carcinoma) OR (esophageal cancer) OR (esophageal adenocarcinoma)]. Additional studies were identified by hand search from references of the eligible articles and commentaries on the current topic ("hand searching"). The search was completed on June 25, 2017. The selection process was performed independently by two researchers (CZ and JK).

Eligibility was based on the following inclusion criteria: clinical studies or meta-analyses reporting on the association between *H. pylori* and EAC; and histological confirmation of EAC. Exclusion criteria were: studies in languages other than English, abstracts of conferences; reviews; commentaries; editorials; and experimental studies.

Subsequently, a quality evaluation of the eligible original studies was conducted. For the purposes of the quality assessment, the Methodological Index for Non-Randomized Studies (MINORS) was used. MINORS is a validated and established index for evaluating the methodological quality of non-randomized studies. This index involves 12 criteria, 8 of which have been designed for non-comparative studies, whereas the other 4 criteria apply to comparative studies. These criteria are scored on a scale developed by Slim *et al* [18]: 0 (not reported), 1 (reported but inadequate), and 2 (reported and adequate). The maximum score for comparative studies is 24 and for the 8-item index is 16, while the minimum score is 0.

The aforementioned two reviewers (CZ and JK) independently evaluated each study according to the MINORS index and any scoring differences were discussed until consensus was reached. With regard to the 12-item index, a score greater than 16 was indicative of well-designed studies [19,20]. No threshold is currently proposed for the 8-item index. We aimed to evaluate the randomized controlled trials (RCTs) with the Cochrane tool, but no RCT was retrieved.

Results

Selection process

The initial search in PubMed resulted in the retrieval of 607 articles. Through manual searching, 220 articles were added, bringing the total to 827. After the initial screening on the basis of their title and/or abstract, 784 articles were excluded and the full text of 43 articles was evaluated for eligibility. Finally, 10 original studies and 6 meta-analyses were selected. A flowchart illustrating the selection process is presented in Fig. 1.

No RCTs fulfilling the eligibility criteria were identified. This was not unexpected, since the preferred study design for investigating prognostic and risk factors is the cohort study, followed by the case control study in evidence-based medicine (www.cebm.net/ocebm-levels-of-evidence).

Methodological quality

The MINORS 8-item index applied to all selected original studies and the results of the MINORS scoring are presented in Table 1. MINORS scores ranged from 3-11. The major limitations on the methodology of the selected studies were a retrospective design and a non-calculated or small sample size. Cohen's kappa coefficient, measuring the inter-rater agreement (CZ and JK) for each MINORS item, ranged between 0.84 and 0.92 (all $P<0.01$).

Summary of original studies included

Among the selected original studies, five reported an inverse relation between *H. pylori* infection and EAC [21-25], whereas the other five reported no association between *H. pylori* infection and EAC [26-30]. Notably, the studies scored higher suggested a neutral relationship between *H. pylori* and EAC [26,30]. Siman *et al* observed no association between EAC and *H. pylori* seropositivity, cytotoxin-associated gene A (CagA) seropositivity or CagA seropositivity among *H. pylori* seropositive subjects [26]; however, the study may possibly have been underpowered.

Summary of included meta-analyses

The first meta-analysis of the association between *H. pylori* infection and EAC was published in 2007 [31]. Another four later meta-analyses of observational studies were retrieved on the same topic [32-35]. All the meta-analyses reported lower rates of EAC in *H. pylori*-positive compared with *H. pylori*-negative individuals. Furthermore, all meta-analyses showed lower

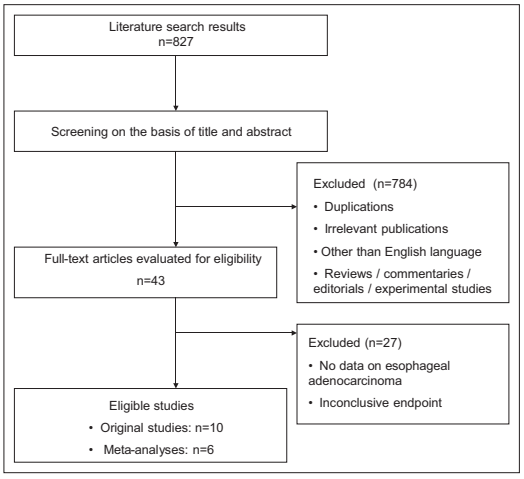

Figure 1 A flowchart presenting the literature search process, according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement

Table 1 MINORS score applied to the selected original studies

Reference	Clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of study endpoints	Follow-up period appropriate to aim of study	Loss to follow up<5%	Prospective calculation of study size	SCORE
Whiteman [21]	2	0	0	2	1	0	0	0	5
Fruh [22]	2	0	0	2	1	0	0	0	5
Anderson [23]	2	0	0	2	1	0	0	0	5
de Martel [24]	2	0	0	2	1	0	0	1	6
Ye [25]	2	1	0	2	1	0	0	0	6
Siman [26]	2	1	2	2	1	2	1	0	11
Wu [27]	2	1	0	2	1	0	0	0	6
El Omar [28]	2	1	0	2	1	0	0	0	6
Vieth[29]	1	0	0	1	1	0	0	0	3
Peek [30]	2	2	2	2	1	0	0	0	9

rates of EAC in *H. pylori* CagA-positive individuals compared with controls (*H. pylori*-negative individuals). *H. pylori* CagA-negative individuals and controls (*H. pylori*-negative individuals) had similar EAC rates, as shown in one meta-analysis [33]. As expected, there was overlap of the included studies in all meta-analyses. Although there was heterogeneity in some of the meta-analyses, meta-regression to assess the source of heterogeneity was not performed in any of them.

Personal view

Although some studies and all meta-analyses reported an inverse association between *H. pylori* infection and EAC, interpreted as a protective effect by some authors, our personal relative consideration and those of others do not agree. Our position starts from a simple question: would a physician propose the potential contamination of *H. pylori* infection in high-risk populations (e.g., obese, cigarette smokers, consumers of high quantities of red or processed meat), so as to protect them from EAC? In our opinion, a randomized controlled trial would never be assigned to answer this question, since it would transgress certain ethical considerations. In this regard, Prof. David Y. Graham maintained that *H. pylori* is not and never was "protective" against anything [36]. Fig. 2 summarizes the main results of the review, but also the main points of our consideration.

The principal hypothesis posed by most authors of the aforementioned meta-analyses and a critical review on esophageal cancer epidemiology [37] is that *H. pylori* infection, with concomitant atrophy of the gastric corpus and loss of parietal cells, results in a reduction in reflux acidity and consequently in reflux esophagitis, Barrett's esophagus (BE), and EAC development.

There is evidence supporting the sequence GERD → BE → dysplasia → EAC and the implication of *H. pylori* separately in each single step to EAC, at least in certain subpopulations. BE is a complication of long-standing GERD and a well-known precursor lesion of EAC [38,39]; GERD plays an essential role in the pathophysiology and the clinical identification of BE, which represents the only known complication derived from GERD [38,39]. The effect of *H. pylori* on BE varies according to geographic location. We showed that *H. pylori* infection is common in Greek patients with GERD, even in those without endoscopically proven reflux disease [40], and *H. pylori* eradication results in adequate control of GERD symptoms and improves esophagitis [41]. Consistent findings were reported by Schwizer *et al* [42], who also observed improvement in GERD symptoms after *H. pylori* treatment. Interestingly, other authors, previous supporters of the hypothesis that *H. pylori* "protects" against GERD, relented, claiming that *H. pylori* therapy does not cause or protect against GERD, and recommending *H. pylori* eradication in GERD [43]. Moreover, there are epidemiologic studies supporting our and others' data: a large-scale study (approximately 21,000 cases) reported that the decline in *H. pylori* infection parallels the reduction in peptic ulcer prevalence, and that the rise in GERD and/or reappearance of GERD following *H. pylori* therapy is rare. Contrary to expectations, patients

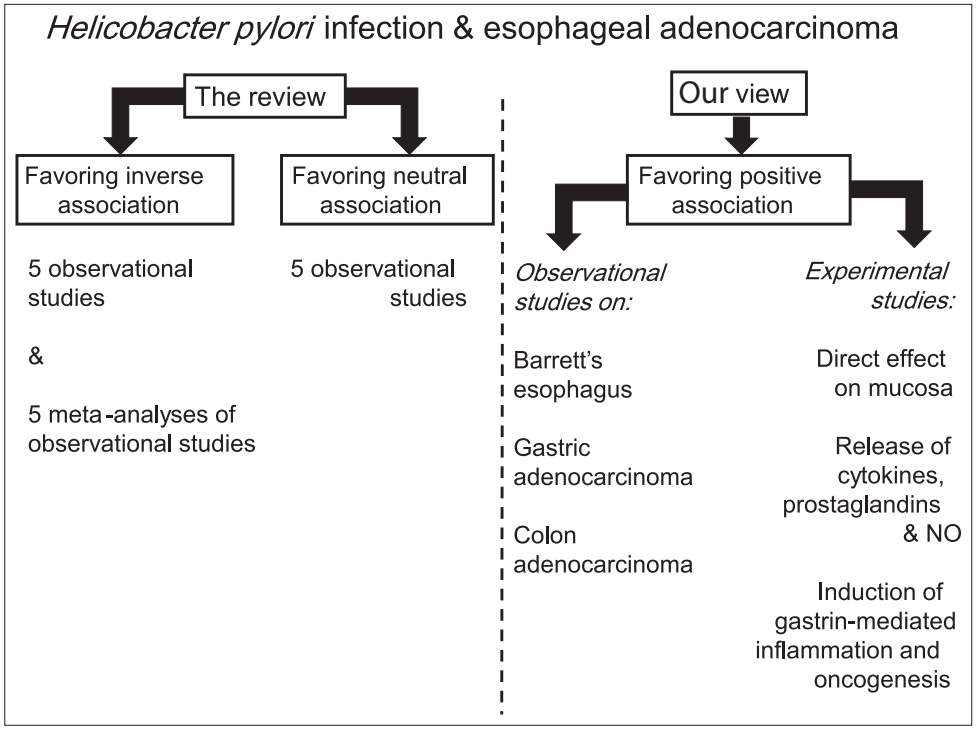

Figure 2 A synopsis of the review and our view. Five original studies and existing meta-analyses favor an inverse association between *Helicobacter pylori* infection and esophageal adenocarcinoma, whereas another five original studies favor a neutral association. On the other hand, our view is based on either clinical data linking *H. pylori* infection with Barrett's esophagus, and gastric and colon adenocarcinoma, or experimental studies showing a direct effect on esophageal mucosa or an indirect effect on inflammation and oncogenesis via mediators, including gastrin

hospitalized with duodenal ulcers (approximately 61,500 cases), apparently attributed to *H. pylori* infection, had a 70% increased risk of EAC [44]. Malaysians, who for a long time have had a low prevalence of *H. pylori* infection, also show a low incidence of GERD, BE and distal esophageal cancers, signifying that *H. pylori* infection is not protective against the abovementioned conditions and its absence may be beneficial [45]. The prevalence of EAC with persistent *H. pylori* infection is higher than that of EAC after eradication therapy [36,38]. Evidence further potentiates the consideration that *H. pylori* is not "protective" against anything, including GERD [36] and possibly its complications BE and EAC.

Apart from *H. pylori,* a number of other environmental agents (e.g., upper gastrointestinal microbiota) seem to play a role in GERD and BE pathogenesis; the presence of esophageal nitrate-reducing *Campylobacter* species in BE patients might suggest a connection with BE induction, maintenance, or exacerbation [41].

Beyond epidemiologic data, *H. pylori* might be involved in GERD pathophysiology via diverse mechanisms, such as: a) induction of mediators, cytokines and nitric oxide, which might disturb the lower esophageal sphincter (LES); b) direct injury of the esophageal mucosa by bacterial products; c) augmented release of prostaglandins that sensitizes afferent nerves and decreases LES pressure; and d) increased acidity due to gastrin induction that aggravates GERD [40].

At the molecular level, gastrin, caused by *H. pylori* infection, is an oncogenic growth agent that promotes upper and lower gastrointestinal tract oncogenesis. Specifically, gastrin appears to play an important role in neoplastic progression in BE. Gastrin stimulates proliferation via Janus Kinase (JAK)2 and Akt-dependent nuclear factor-kappa B (NF-κB) activation in Barrett's EAC cells, displays an anti-apoptotic effect via upregulation of Bcl-2 and survivin, and induces mitogenic and oncogenic cyclo-oxygenase (COX)-2 expression [38,39]. In this regard, *H. pylori* infection activates NF-κB, an oxidant-sensitive transcription regulator of inducible expression of inflammatory genes, including COX-2 that regulates gastrointestinal neoplasm cell growth and proliferation. Specifically, *H. pylori* infection promotes the expression of NF-κB and COX-2 in esophageal epithelial cells, playing a role in the inflammatory process associated with BE and esophageal oncogenesis [38].

Upon colonizing the esophagus, *H. pylori* increases the severity of esophageal inflammation and the BE prevalence [38], as could be derived from the following data: a) *H. pylori* infection prevalence is high in BE; b) neither *H. pylori* infection nor *H. pylori* infection by CagA positive strains decreases the risk of BE in some populations that have a high incidence of *H. pylori* infection; c) *H. pylori* infection might induce specific molecular changes (genetic instability, E-cadherin methylation, monoclonal antibody Das-1) linked with BE pathophysiology; and d) *H. pylori* promotes Ki-67 expression and greater Ki-67 esophageal expression was reported in BE patients compared with GERD controls. A progressive Ki-67 proliferation fraction was observed in the normal esophageal epithelium → BE → dysplasia → EAC sequence [38,39].

Insulin resistance (IR), the key MetS component [46], is connected with GERD, BE and EAC [4]. Since relative data indicate a relationship between *H. pylori* and IR [46] and other parameters of MetS [4], *H. pylori*-related MetS may contribute to the GERD → BE → EAC sequence in some ethnic populations [9]. Recent data show that lower serum adiponectin levels are associated with BE progression, while experimentally adiponectin induces an antitumor effect in Barrett's cell lines and prevents growth-factor signaling [4]. *H. pylori* therapy leads to an increase in levels of serum total adiponectin and its isoforms, thereby displaying a possible protective effect against malignant progression of BE [4].

Several studies support an association between BE and colonic neoplasms, including adenomas and adenocarcinomas [47-49]. It is conceivable that BE and colorectal neoplasms share a common, unidentified factor promoting the oncogenesis of BE-associated EAC and colorectal neoplasms. A potential association of both pathological conditions may be attributed to genetic predisposition or common environmental risk factors. *H. pylori* infection might promote both diseases [50]. Both *H. pylori* infection and BE are linked with an increased risk of the development of colorectal adenoma (CRA) and colorectal cancer (CRC) [12,50-52]. *H. pylori* infection appears to contribute to the GERD → BE → EA and CRA → CRC sequences, at least in certain populations, and its eradication may abrogate these oncogenic properties [12,51,52]. Specifically, active *H. pylori* infection appears to be involved in the pathogenesis of the normal colon epithelium → CRA → CRC sequence [12]. Excessive nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity and the production of reactive oxygen species (ROS) may promote oncogenic signaling, driving colorectal oncogenesis [13]. Likewise, in the *H. pylori*-related GERD → BE → EAC sequence, NADPH activation and NADPH-derived ROS may cause DNA damage, thereby contributing to the progression from BE to EAC [13].

In conclusion, existing epidemiologic studies provided inconclusive data on an inverse or a neutral association between *H. pylori* infection and EAC, whereas meta-analyses of observational studies favor an inverse association. A particular drawback of most original studies is confounding factors, i.e., multiple factors that were not taken into consideration in the study design or the analysis of data, but may possibly contribute to the pathogenesis of EAC. This might have affected the results of the meta-analyses, since they included original studies that did not adequately adjust for potential confounders. Furthermore, the source of heterogeneity, when it was observed, was not evaluated in the meta-analyses. In this regard, well-designed prospective cohort studies with a powered sample size are required, in which potential confounders should be taken into account. This may resolve the paradox of the positive association of *H. pylori* infection with GERD or BE, but not with EAC, as well as the paradox of the oncogenic effect of *H. pylori* infection on gastric cancer and CRC, but not on EAC. Metabolomics may also prove helpful in this direction in the near future, as the *H. pylori*-related metabolites may provide further data.

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