The relationship of *H. pylori* infection and gastric cancer

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ABSTRACT

Introduction: *The aim of this review is to assess whether there is a relationship between* Helicobacter pylori *infection and gastric cancer.*

Method: *We searched the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and the NHS Database of Abstracts of Reviews of Effectiveness; MEDLINE; EMBASE, Biological Abstracts and Science Citation Index-Expanded. We used the search terms* Helicobacter pylori *and (gastric or stomach) and (cancerS or neoplasmS) and (systematic reviewS or meta-analS), and searched for articles in all languages and limited the search to humans. Evaluation of the Level of Evidence: We used the rating system of the American Family Physician journal: Level A (randomized controlled trial/meta-analysis); Level B (other evidence); and C (consensus/expert opinion).*

Results: H. pylori *increases the odds ratio of gastric cancer in various studies.* H. pylori *is associated with the development of both types of gastric adenocarcinoma. On average only three per cent of those who carry* H. pylori *develop gastric carcinoma. The risk of gastric cancer is also increased if the individual has polymorphisms that result in the expression of higher than average levels of the cytokine IL-1*β*. There is no evidence that nutritional supplements prevent gastric cancer.*

Conclusions: *Gastric cancer is preceded by a long latency period. Infection with* H. pylori *is a primary cause of the precancerous cascade from gastritis to dysplasia, and eradicating* H. pylori *by antibiotic therapy results in a modest retardation of the cancerous process. The research to date reviewed above suggests that the best strategy is twofold. Firstly, focus on high risk individuals with known risk factors of* H. pylori *exposure treat them for* H. pylori *and screen them endoscopically for the development of early gastric cancers which can be ideally resected endoscopically. Secondly, screen younger individuals (< 45 years) at risk for* H. pylori *who have not been exposed to* H. pylori *for as long and treat them.*

Key-words: *Helicobacter Pylori; Dyspepsia; Duodenal Ulcer; Stomach Ulcer; Gastritis; Deglutition Disorders; Antibodies; Enzyme-Linked Immunosorbent Assay; Breath Tests; Serology; Serum; Feces; Saliva; Pepsinogen A; Endoscopy; Cost-benefit Analysis; Sensitivity and Specificity; Predictive Value of Tests; Mass Screening*

INTRODUCTION

Gastric cancer is the second cause of cancer deaths worldwide for males and fourth for females according to Correa[1] and to Watabe[2] and Portugal is third out of 28 European countries in rates of gastric cancer. In 2000 an estimated 876,000 individuals were diagnosed and 649,000 died from stomach cancer worldwide each year.[3] In most countries it is diagnosed after it has invaded the muscularis propria and the five-year survival is less than 20%.[4] Conventional therapy has had minimal impact on survival. The pathological precursor stage of the disease provides a long precancerous latent period. Diagnostic strategies are available to identify those with the risk factors and treat them in the precursor stage; and to identify and treat endoscopically or surgically those in the early submucosal stage of the cancer when five-year survival rates are favourable.

The incidence and mortality of gastric cancer has fallen substantially in many Western countries in the past three decades, with a decrease in well-differentiated distal non-cardia cancer but an increase in proximal diffuse adenocarcinoma of the cardia. Distal gastric cancer is related to gastric atrophy and intestinal metaplasia and predominates in developing countries and individuals with lower socio-economic status within Western societies. The proximal

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cardia tumours are related to pangastritis without atrophy and are more common in developed countries and individuals with higher socio-economic status. The main risk factor for the distal non-cardia type is *H. pylori* infection, whereas gastro-esophageal reflux and obesity play important roles in the development of cancers of the cardia. There is a ten-fold variation in gastric cancer rates worldwide, with Japan and Korea having the highest rates.[5]

Gastric cancer has a multifactorial etiology: long-term colonisation with *H. pylori*; a diet high in salt and *N*-nitroso compounds and low in fruit and vegetables; a dose-dependent relationship to tobacco smoking (OR = 2.0); and obesity for gastric cardia adenocarcinoma.[5]

H. pylori is present in the stomachs of 50% of the world's population;[6] 30% in the developed world, 60 % in the developing world, and in 85% of the Portuguese population. It is usually acquired in childhood (Level B Evidence: prospective cohort study):[7] in a study in Sapporo, Japan, of 345 pregnant females found 20% had positive serology for *H. pylori* and the researchers followed 51 of their children, of whom 11% acquired *H. pylori*, with DNA strains identical to those of their mother. It may also be transmitted between children by episodes of gastroenteritis, and colonisation is related to low socioeconomic status, overcrowding, and country of origin (Level C Evidence: expert review).[8]

The aim of this review is to assess whether there is a relationship between *Helicobacter pylori* infection and gastric cancer.

METHOD

Searches: We searched the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews, and the NHS Database of Abstracts of Reviews of Effectiveness (DARE) (all to Cochrane Library Issue 1, 2006); MEDLINE (OVID, January 1966 to April 2006 week 1); EMBASE (Dialog 1974 to 1979; SilverPlatter 1980 to April 2006 week 1), Biological Abstracts (SilverPlatter 1969 to April 2006) and Science Citation Index-Expanded (Web of Science 1974 to April 2006). We used the search terms *Helicobacter pylori* and (gastric or stomach) and (cancer$ or neoplasm$) and (systematic review$ or meta-anal$), and searched for articles in all languages and limited the search to humans. The Science Citation Index-Expanded was used to identify articles that cite the relevant studies. The relevant studies were also keyed into PubMed and the Related Articles feature used. We selected for review all those articles which from their abstract or title appeared to be relevant, and obtained full-text versions if the abstract or title to assess them fully. We then reviewed all the relevant articles in full text.

MeSH terms (non-mesh indicated by .mp) used in three separate searches:

- *Helicobacter pylori* AND dyspepsia OR dysphagia.mp OR duodenal ulcer OR stomach ulcer OR gastritis OR deglutition disorders
- *Helicobacter pylori* AND antibodies OR Enzyme-Linked Immunosorbent Assay OR elisa.mp OR breath tests OR serology OR serum OR feces OR stool.mp OR saliva OR pepsinogen A or pepsinogen.mp OR endoscopy
- *Heliocobacter pylori* AND cost-benefit analysis OR cost-effective.mp OR sensitivity and specificity OR predictive value of tests OR mass screening.

We included RCTs, cohort, and case-control studies, interrupted time series, systematic reviews and meta-analyses, and excluded non-systematic reviews.

Evaluation of the Level of Evidence: We used the rating system of the American Family Physician: Level A (randomised controlled trial/meta-analysis; Level B (other evidence); and C (consensus/expert opinion).[9]

RESULTS

The search terms *Helicobacter pylori* AND cancer AND meta-analysis OR systematic review identified 3 studies in DARE, 3 in the Cochrane Database of Systematic Reviews, 63 in EMBASE, 45 in MEDLINE and 21 in Biological Abstract/BIOSIS Previews. Of these, 31 studies provided data on the relationship between *Helicobacter pylori* and stomach cancer, and 54 were excluded, as on closer inspection they did not provide data. It is difficult to estimate bias in the included compared to the excluded studies as most did not cite whether they received funds from a pharmaceutical company or not.

THE RELATIONSHIP OF H. PYLORI INFECTION AND GASTRIC CANCER

H. pylori increases the odds ratio of gastric cancer in various studies by 2.1 to 16.7. The longer the individual has *H. pylori* the higher the risk of developing gastric cancer.[8]

H. pylori is associated with the development of both types of gastric adenocarcinoma (intestinal type and diffuse type).[8] The stages of development of intestinal type gastric adenocarcinoma are better understood, and consist of the transition from

normal mucosa through chronic superficial gastritis, atrophic gastritis, intestinal metaplasia and dysplasia to adenocarcinoma.[8] The WHO[10] has classified *H. pylori* as a class I carcinogen for gastric cancer.

Danesh reviewed 34 retrospective sero-epidemiological studies of the association of *H. pylori* and gastric cancer and retained 25 for analysis but concluded that the controls were of uncertain validity (Level A Evidence: systematic review).[11] The ten case-control studies nested within prospective studies had about 800 participants and the risk ratio of *H. pylori* sero-positivity for gastric cancer was 2.5 (95% CI = 1.9 to 3.4); all the ten studies adjusted for age and gender but only some adjusted for smoking history, diet or social class.

Uemura followed 1,526 patients with duodenal or gastric ulcers, gastric hyperplastic polyps or non-ulcer dyspepsia for an average of 7.8 years; 1,246 were *H. pylori* positive (Level B Evidence: prospective cohort study). [12] In the infected group 36 (2.9%) developed gastric cancer (23 intestinal-type and 13 diffuse-type) and none in the 253 in the *H. pylori* group treated with antibiotics and followed up for an average of 4.8 years, or in the non-infected group. The average age of diagnosis was 53 years in the gastric ulcer and 63 in the non-ulcer dyspepsia group.

Watabe[2] performed the first large population-based study and followed 6,983 of the 9,293 participants in a health appraisal programme for 4.7 years with an average of 5.1 endoscopic examinations, and 43 developed gastric cancers during this period. He found that the group of 443 with "atrophic" levels of pepsinogen and who were negative for *H. pylori* antibodies had an annual incidence of gastric cancer of 0.6%; the group of 3,324 with normal pepsinogen levels and who were negative for *H. pylori* antibodies had an annual incidence of 0.04%; the group of 2,134 with normal pepsinogen and who were positive for *H. pylori* antibodies a rate of 0.06%; and the group of 1,082 with "atrophic" levels of pepsinogen and who were positive for *H. pylori* antibodies a rate of 0.36%.

H. pylori is also related to gastric carcinoma in animals. One third of Mongolian gerbils infected with *H. pylori* developed gastric carcinoma over a two-year period (Level C Evidence: expert review).[13-14]

However, on average only three per cent of those who carry *H. pylori* develop gastric carcinoma.[8] For specific individuals who carry *H. pylori* the risk of gastric carcinoma is increased by at least four factors (the genetic sequences of the *H. pylori* strains; patient polymorphisms that express higher levels of the cytokine IL-1β; the expression of higher levels of (TNF)-α; and if the individual has major histocompatibility complex genotypes that are upregulated by *H. pylori* and affect how the epithelium responds to the inflammation caused by *H. pylori*).

The individual may carry strains of *H. pylori*, which, due to mutations, substitutions, deletions and insertions have gene sequences that are more carcinogenic and these can also be transmitted between strains. The gene sequences cag (which allows bacterial proteins to enter host epithelial cells), vacA, and babA2 (which permits adhesion of bacteria to the cell surface) are associated with an increased risk of gastric cancer (Level B evidence: genome sequence studies),[8,15,16] and strains that possess all three genes have the highest risk.[8]

The risk of gastric cancer is also increased if the individual has polymorphisms that result in the expression of higher than average levels of the cytokine IL-1β (Level B Evidence: study of interleukin polymorphisms).[17] IL-1β is the most powerful suppressor of gastric acid secretion and causes marked inflammation. Administration of recombinant IL-1β receptor antagonists to Mongolian gerbils normalises their gastric acid levels (Level B Evidence: cohort study).[18] Specifically, carriers of the IL-1 1B-511T and IL-1RN*2 homozygotes have an increased risk of developing gastric cancer (Level B Evidence: study of interleukin receptors).[19]

The risk is also increased if *H. pylori* proteins increase levels of the (TNF)-α factor, which suppresses gastric acid production and increases gastric inflammation (Level B Evidence: interleukin studies).[20-22]

Other pathways by which *H. pylori* induces cancers at the cellular level include the release of nitric oxide synthase, nitric oxide, and superoxide anion radicals; apopotosis; and the conversion of N-nitrosamines to nitrites.[8]

A systematic review identified eight case-control studies and one cohort study of the relationship between aspirin and gastric cancer and three reviewers independently assessed study quality. The meta-analysis concluded that NSAID use is associated with a significant reduction in the risk of non-cardia gastric cancer (OR = 0.72; 95%CI = 0.58 to 0.89) but not of cancer at the cardia (OR = 0.80; 95% CI = 0.53 to 1.20). The prospective cohort study followed 635,031 individuals for six years and found that the relative risk of gastric cancer for aspirin users was RR = 0.64 (95%CI = 0.51 to 0.80) compared to the non-users. The hypothesized relationship between

NSAID use and gastric cancer is that the cycloxygenase 2 gene Cox-2 is overexpressed in gastric cancers, and that NSAIDs inhibit the production of both Cox-1 and Cox-2 (Level A Evidence: systematic review).[23]

There is no evidence that nutritional supplements prevent gastric cancer. Malila gave alpha-tocopherol or beta-carotene to middle aged smokers in Finland and found no effect on gastric cancer rates (Level A Evidence: randomised controlled trial).[24] Bjelakovic in a Cochrane systematic review found no benefit of beta-carotene, vitamins A, C or E, or selenium (Level A Evidence: systematic review).[25]

DOES TREATING H. PYLORI REDUCE THE RISK OF GASTRIC CANCER?

Ley in Chiapas, Mexico, an area with both high *H. pylori* and gastric cancer rates, enrolled 1,344 healthy volunteers to participate in a trial of treating *H. pylori* (Level A Evidence: randomised controlled trial);[26] 1,178 (87%) gave a blood sample; 468 (40%) were found to be both cag positive and have gastrin levels ≥25µg/ml; and 316 (67% of 468) were randomised to receive either omeprazole, amoxicillin and clarithromycin or placebo. The power computation assumed a background 10% regression rate of inflammation, and found that 240 patients would be needed to identify a 3-fold difference in response rates between the study arms with 97% power and significance level of 5%, assuming 10% dropouts. Ninety-three per cent of the patients in the experimental arm took more than 90% of their prescribed pills. The biopsies were read independently by two pathologists blinded to the treatment arm and the time when the endoscopy was performed. The correlations between the pathologists on the weighted index of seven biopsy scores were $\rho = 0.71$ at baseline, $\rho = 0.81$ at 6 weeks, $\rho = .088$ at one year and the correlation between the changes seen at six weeks and one year was $r = 0.44$. The analysis was by intention-to-treat. The cure rate for *H. pylori* in the experimental group at one year was 76%, and the weighted index of biopsies improved compared to placebo ($p = .03$). Problems in this study were the less than optimal agreement between the pathologists and the cure rate of 76%.

Wong randomised 1,630 patients in Fujian Province, China, with *H. pylori* to receive either two weeks of omeprazole, amoxicillin and clavulanate, and metronidazole, or placebo and followed them for an average of 7.5 years (Level A Evidence: randomised controlled trial).[27] Eighteen patients developed gastric cancer, with no differences between the *H. pylori* treated and untreated groups, but in the group with no pre-cancerous lesions at baseline no patient developed gastric cancer compared with six in the placebo group ($p = .02$).

Correa showed that patients in Columbia who received treatment for *H. pylori* had an odds ratio of regression of gastric metaplasia of 3.1 (95% CI = 1.0 to 9.3) and regression of gastric atrophy of 8.7 (95% CI = 2.7 to 28.2) (Level A Evidence: randomised controlled trial).[28]

Leung randomised 587 patients in Shandong province, China, with *H. pylori* to receive either a week of omeprazole, amoxicillin and clarithromycin or placebo and followed them for five years (Level A Evidence: randomised controlled trial);[29] 75% of those treated were clear of *H. pylori* at five years. Persistent *H. pylori* infection (OR = 2.13; 95% CI = 1.41 to 3.24; age > 45 years (OR = 1.92; 95% CI = 1.18 to 3.11); alcohol use (OR = 1.67; 95% CI = 1.07 to 2.62); and drinking water from a well (OR = 1.74; 95% CI = 1.13 to 2.67) were independent risk factors for progression of intestinal metaplasia. Ten patients (2.3%) developed gastric cancer, with six in the control and four in the experimental group, but as all ten died it is likely they were all in advanced stages. The highest risk of progression to gastric cancer was in those > 45 years with persistent *H. pylori*, and duodenal ulcer patients had a low risk of progression of intestinal metaplasia (OR = 0.23; 95% CI = 0.09 to 0.58).

Uemura found that patients with early gastric cancer who received therapy to eradicate *H. pylori* had significantly reduced rates of atrophic gastritis and recurrence of gastric cancer (Level B Evidence: prospective cohort study).[30]

In a study of 115 patients with gastric MALT lymphomas, 86% were positive for *H. pylori* and of these 73% showed tumour regression after antibiotic therapy (Level B Evidence: prospective cohort study).[31]

CONCLUSIONS

Gastric cancer is preceded by a long latency period before it invades the muscularis propria. Infection with *H. pylori* is a primary cause of the precancerous cascade from gastritis to dysplasia, and eradicating *H. pylori* by antibiotic therapy results in a modest retardation of the cancerous process.[4]

Most trials have been in adults in a rather advanced stage of gastric atrophy and intestinal metaplasia, in whom *H. pylori* had been present for

several decades. The research to date reviewed above suggests that the best strategy is twofold. Firstly, focus on high risk individuals with known risk factors of *H. pylori* exposure, "atrophic" pepsinogen levels, and known pre-cancerous gastric histopathology, treat them for *H. pylori* and screen them endoscopically for the development of early gastric cancers which can be ideally resected endoscsopically. Secondly, screen younger individuals (< 45 years) at risk for *H. pylori* who have not been exposed to *H. pylori* for as long and treat them.[32]

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RESUMO

O objectivo da presente revisão é avaliar se existe uma relação entre a infecção por* Helicobacter pylori *e cancro gástrico.

Pesquisámos o* Cochrane Central Register of Controlled Trials*, o* Cochrane Database of Systematic Reviews *e o* NHS Database of Abstracts of Reviews of Effectiveness; MEDLINE; EMBASE; SilverPlatter, Biological Abstracts and Science Citation Index-Expanded. *Usámos os termos de pesquisa* Helicobacter pylori *e (gastric or stomach) and (cancer$ or neoplasm$) e (systematic review$ or meta-anal$), e pesquisámos artigos de todas as línguas limitando a pesquisa a humanos.

Avaliação do Nível de Evidência: usámos o sistema de classificação da revista* American Family Physician*: Nível A (ensaios clínicos aleatorizados/meta-análises). Nível B (outras fontes de evidência). Nível C (consensos/opinião de peritos).

O* H. Pylori *aumenta a OR para cancro de estômago em vários estudos. O* H. Pylori *está associado ao desenvolvimento de ambos os tipos de adenocarcinoma gástrico. Em média, apenas três por cento dos portadores de* H. Pylori *desenvolvem carcinoma gástrico. O risco de cancro de estômago está igualmente aumentado se o indivíduo tem polimorfismos que resultam numa expressão maior do que os níveis médios da citocina IL-1β. Não existe evidência que os suplementos nutricionais previnam o cancro gástrico.

O cancro gástrico é precedido por um longo período de latência. A infecção por* H. pylori *é uma causa primária da cascata pré-cancerosa da gastrite à displasia e a erradicação do* H. pylori *por terapêutica antibiótica resulta num atraso moderado do processo canceroso. A investigação apresentada revista até hoje sugere que a melhor estratégia é, primeiro, incidir nos indivíduos de alto risco com factores de risco conhecidos de exposição ao* H. pylori *e rastreá-los endoscopicamente para o desenvolvimento de cancros gástricos iniciais que podem ser ressecados endoscopicamente; seguidamente, rastrear indivíduos mais novos (< 45 anos) em risco para* H. pylori *que não foram expostos ao* H. pylori *por um período tão longo e tratá-los.

Palavras-chave: *Helicobacter Pylori; Dispepsia; Úlcera Duodenal; Úlcera Gástrica; Gastrite; Perturbações da Deglutição; Anticorpos; Testes Respiratórios; Serologia; Soro; Fezes; Saliva; Pepsinogénio A; Endoscopia; Análise Custo-Benefício; Sensibilidade e Especificidade; Valor Preditivo; Rastreio Sistemático; Meta-Análise; Revisão Sistemática.*