Helicobacter pylori infection causes gastric cancer? A review of the epidemiological, meta-analytic, and experimental evidence

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Abstract
Since the discovery of Campylobacter-like organisms Helicobacter pylori (H pylori) more than two decades ago the possibility of a relationship with gastric cancer has been postulated, tested and supposedly proven. There have been numerous human studies of various designs from many countries around the world. Several meta-analyses have been published and more recently a small number of experimental animal studies were reported looking at the association between H pylori infection and gastric cancer. Over the years, the human epidemiological studies have produced conflicting results; the meta-analyses have as one would expect produced similar pooled estimates; while the early experimental animal studies require replication. The exact mechanisms by which H pylori might cause gastric cancer are still under investigation and remain to be elucidated.

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INTRODUCTION
"They (Helicobacter pylori) may have a part to play in other poorly understood gastritis associated diseases (ie, peptic ulcer and gastric cancer)."

The suggestion of a link between Helicobacter pylori (H pylori) infection and gastric cancer was first proposed by co-discoverer Marshall in 1983.[1] It is of interest that at that time the majority of physicians and scientists around the world did not even believe that there was a link between H pylori and gastritis.[2,3]. Just over a decade later in 1994, the International Agency for Research on Cancer (IARC) classified H pylori as a definite class I carcinogen,[3] despite some conflicting results.[4,5]. No experimental studies had been conducted at that time and the epidemiological studies that had been done produced mixed results. Almost all of the studies did not take into consideration other important potential confounders or sources of interaction (eg, salt intake, diet, alcohol consumption, and smoking). A number of additional studies have also failed to detect an association even in high risk populations[7,8] which has led some to question whether there is a causal link.[9]. However, these epidemiological observations appear to be directly supported by early data from animal models on cancer development following H pylori infection[10].

This review addresses some of the controversies in the expanding literature supporting a positive association for H pylori infection leading to gastric cancer. This review will not address the relationship between H pylori and mucosa-associated lymphoid tissue (MALT) lymphoma. An excellent review on this topic has recently been published[11]. Specifically, this review aims to assess the epidemiological evidence based on Bradford Hill's criteria of causality[12] and summarize the meta-analytic evidence for the association between H pylori and gastric cancer.

MATERIALS AND METHODS
The search strategy involved the major computer databases, including Medline, PubMed, EMBASE and Current Contents (January 1983 to February 2006). The search methodology involved using combinations of the following keywords: H pylori, Campylobacter pylori, Campylobacter pyloridis, gastric cancer, gastric carcinoma, stomach cancer, meta-analysis, systematic review, gastric adenocarcinoma, experimental, animal studies, systematic review. Additional manual searches were made using the reference lists from the selected articles to retrieve other papers relevant to the topic. No language restriction was placed on any of the literature searches.

RESULTS
The IARC-WHO report
In 1994, The International Agency for Research on Cancer (IARC) published a report based on a meeting of experts between 7-14 June of that year in Lyon, France[16]. In terms of a link between \textit{H pylori} and gastric cancer, the conclusions reached in this report stated that there was sufficient evidence for carcinogenicity among humans and inadequate evidence for carcinogenicity in animals, with an overall evaluation classifying \textit{H pylori} as a group 1 definite carcinogen. Sufficient evidence relating carcinogenicity in humans as stated in the report is: “Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between exposure to the agent, mixture or exposure circumstance and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence.” Inadequate evidence relating carcinogenicity in animals as stated in the report is: “Inadequate evidence of carcinogenicity: The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available.”

In the overall evaluation a Group 1 carcinogen as stated in the report is: “Group 1 - The agent (mixture) is carcinogenic to humans: The exposure circumstance entails exposures that are carcinogenic to humans: This category is used when there is sufficient evidence of carcinogenicity in humans. Exceptionally, an agent (mixture) may be placed in this category when evidence in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent (mixture) acts through a relevant mechanism of carcinogenicity.” The findings of the IARC were four years before the published experimental animal data or meta-analysis of the human epidemiological studies[9,10,13,17,18]. So why was \textit{H pylori} given such a classification? Would another classification have been more appropriate and if so, which one?

The overall IARC evaluation options (Group 1, Group 2A, Group 2B, Group 3, Group 4) appear to assume that there are usually experimental animal data but may not be sufficient human data to support that an agent is carcinogenic to humans. However, in the case of \textit{H pylori} and gastric cancer the opposite is actually true. There were human studies, but at that point in time (1994) there were no actual animal or experimental data. From a cause and effect point of view, one would think that animal data would be essential to link an agent with causing carcinogenic effects, but this does not occur with \textit{H pylori}. Of all the agents assessed in the IARC monograph, only \textit{H pylori} with inadequate animal evidence but ‘sufficient human evidence’ was classified as a class 1 definite carcinogen (Table 1). All the other agents except for \textit{H pylori} and \textit{Opisthorchis felineus} had at least a limited amount of animal data on which an overall evaluation regarding their carcinogenicity to humans was based. Therefore, based on the data available in 1994 regarding \textit{H pylori} and gastric cancer, it might appear that the IARC prematurely classified \textit{H pylori} as a definite class 1 carcinogen.

This is because the available epidemiological evidence was insufficient in quality (confounders not adequately assessed) and quantity to establish causal link and there were no experimental animal studies at that time.

**Epidemiological data**

In 1965, Bradford Hill (1897-1991) published his seminal paper titled “The Environment and Disease: Association or Causation?”[12]. This paper was initially written to assess causal links between sickness and injury related to work. Bradford Hill’s criteria will be used to assess the possibility of a causal association between \textit{H pylori} and gastric cancer[16].

**Consistency:** The association is consistent when results are replicated in studies in different settings using different methods. The human epidemiological studies have produced mixed results with approximately 50% finding a positive association between \textit{H pylori} infection and gastric cancer and 50% reporting a negative relationship[13,17,18]. This variation also exists within countries and between countries[13,17,18]. The majority of studies reported were case-control in design with a smaller number of cohort (usually nested case-control) studies which also provided mixed results[13,17,18].

**Strength:** This is defined by the size of the risk as measured by appropriate statistical tests. The strength of the relationship between \textit{H pylori} and gastric cancer varies quite considerably. Negative studies have produced results as low as (OR: 0.54, 95% CI: 0.24-1.19)[19], and positive studies as high as (OR: 13.3, 95% CI: 5.30-35.60)[20]. The average strength of the relationship as determined by meta-analysis produces an effect size (odds ratio) of approximately 2.00[13,17,18].

**Specificity:** This is established when a single putative cause produces a specific effect. \textit{H pylori} is predominantly found in the stomach and is associated with gastritis, peptic ulcer disease, and gastric cancer; however, it is linked with

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**Table 1** IARC evaluation of schistosomes, liver flukes and \textit{H pylori}

| Agent (infection with) | Degree of evidence of carcinogenicity | Overall evaluation |
|------------------------|--------------------------------------|--------------------|
|                        | Human | Animal  |                      |
| Schistosoma haematobium | Sufficient | Limited | Definite carcinogen |
| Schistosoma japonicum  | Limited | Limited | Possible carcinogen  |
| Schistosoma mansoni     | Inadequate | Limited | Not classifiable     |
| Opisthorchis viverrini  | Sufficient | Limited | Definite carcinogen  |
| Opisthorchis felineus   | Inadequate | Inadequate | Not classifiable |
| Clonorchis sinensis     | Limited | Limited | Probable carcinogen  |
| Helicobacter pylori     | Sufficient | Inadequate | Definite carcinogen |

1 No data available. 2 Other relevant data taken into account in making overall evaluation.
numerous extra-gastric conditions including foetal intrauterine growth restrictions\[20\], glaucoma\[21\], Raynaud’s phenomenon\[22\], gallstones\[23\], primary headache\[24\], diabetes\[25\], ischemic heart disease\[26\], Sjögren’s syndrome\[27\], Schönlein-Henoch purpura\[28\], autoimmune thyroiditis\[29\], chronic bronchitis\[30\], Parkinson’s disease\[31\], non-arterial optic ischemic neuropathy\[32\], chronic idiopathic urticaria\[33\], rosacea\[34\], alopecia areata\[35\], sideropenic anemia\[36\], growth retardation\[37\], late menarche\[38\], hepatic encephalopathy\[39\], and stroke\[40\]. Thus, currently H pylori is not associated with a single specific condition or disease within or outside the human stomach\[41-46\]. It must be remembered that none of these conditions are causally linked with H pylori.

**Dose-response relationship:** An increasing level of exposure (in amount and/or time) increases the risk. It is well known that infection with H pylori involves an inflammatory process occurring over many years\[47-51\], thus, the risk of gastric cancer may correlate with the duration of infection with H pylori. Therefore, those individuals who are infected during childhood have a longer time to develop mutations compared to those who acquire infection during adulthood. It has been suggested that a child’s stomach might be physiologically different from an adult’s stomach, because children have less acute inflammation and an increased number of lymphoid follicles than adults\[52\]. However, the amount of organisms living in a human’s stomach has never been correlated with pathology.

**Temporal relationship:** Exposure always precedes the outcome. This is the only absolutely essential criterion. Current epidemiological evidence suggests that infection is usually acquired during childhood and is attributed to a cohort effect\[53-57\]. A recent study showed that age of acquisition after one year of age is not the most important factor related to the differences in incidence rates of gastric cancer in adulthood\[58\]. However, studies have also shown that re-infection with H pylori is also possible, even though it may occur infrequently\[59,60\].

**Biological plausibility:** The association agrees with currently accepted understanding of pathobiological processes. This criterion should be applied with caution. The prospect that cancer might be spread via an infectious mechanism has been considered for centuries\[61,62\]. Moreover, over the last decade there has been an exponential increase in the scientific knowledge related to infectious agents associated with cancer\[63-65\]. There are a large number of infectious agents associated with cancers including Epstein-Barr virus (EBV), human papillomaviruses (HPVs), hepatitis B or C virus, human herpesvirus type 8 (HHV-8), Salmonella typhi, paratyphi, Schistosoma hematobium, polyoma viruses\[66-68\]. Over the last decade there has certainly been an enormous increase in the amount of data on association between H pylori and gastric cancer, with numerous studies and hypothetical mechanisms explored\[69-77\]. However, while it is definitely plausible that H pylori could cause gastric cancer, at present the exact mechanism remains unknown.

**Coherence:** The association should be compatible with existing theory and knowledge. Epidemiologically, at times, there are clear signs of a relationship between H pylori and gastric cancer, for example, studies that reported a high prevalence of H pylori among a population with a high rate of gastric cancer (e.g., Japan)\[78-80\]. Conversely, there are times when a high prevalence of H pylori correlated with the low rate of gastric cancer (e.g., Africa)\[79,80\]. However, one African study reported that there was no difference in prevalence of H pylori infection among gastric cancer cases and non-ulcer dyspepsia controls\[81\]. The fact that only approximately 1% of those infected with H pylori actually go on to develop gastric cancer suggests a lack of coherence. Of course there are exceptions; in Changle, China, up to 20% of H pylori infected individuals developed gastric cancer. Should not all those infected with H pylori eventually develop gastric cancer? Indeed, if 50% of the world is infected then this equates to 30 million cases of gastric cancer, which is a gigantic number of potentially preventable malignancies. The latest epidemiological data from GLOBOCAN 2002 (data reported 2-5 years earlier) reported that there were 933 937 incident cases and 700 349 deaths due to gastric cancer in that year (Table 2)\[79\]. Histopathologically, there is a paradox where H pylori organisms are not found in the stomachs of gastric cancer cases, which may explain the lower antibody response among these patients\[82-84\]. These are arguments against coherence for the causal relationship between H pylori and gastric cancer.

**Experiment:** The condition can be altered by an appropriate experimental regimen. This is possibly the most important support for a causal relationship. Thus,
the strongest proof for a link between *H pylori* and gastric cancer would be established only if controlled trials demonstrate that elimination or prevention of *H pylori* infection prevents malignancy. An animal study has documented that among Mongolian gerbils treated with *N*-methyl-*N*-nitrosourea (MNU) and infected with *H pylori* where 2 of the 6 groups underwent eradication of *H pylori* infection at 21 weeks, after 50 weeks they showed a decrease in the number of gastric cancers developed[86].

Recently, a human prospective randomized, placebo-controlled prevention trial compared patients who received eradication therapy for *H pylori* (n = 817) and those taking placebo (n = 813) and at follow-up (7.5 years) determined the incidence of gastric cancer between the groups[96]. However, there was no significant difference in gastric cancer incidence between those who received eradication therapy and placebo (P = 0.33). This study was criticised for being stopped early, as it was believed that if the study had continued for a few more years it might have yielded more conclusive results[87]. Kamada et al[98] conducted a prospective non-randomized follow-up study of 1787 patients who underwent *H pylori* eradication therapy and were followed up after 9 years. Gastric cancer occurred in 20 patients (1.1%), while early gastric cancer consisted of 5.7% (6/105) after endoscopic resection. This study concluded that even after successful eradication therapy for *H pylori* endoscopic assessment should be undertaken for occult early gastric cancer or severe mucosal atrophy. Moreover, studies trying to determine if gastric atrophy is a reversible process have produced conflicting results[89]. Thus, endoscopic screening in high risk populations still remains appropriate[99,100]. It should be remembered that epidemiological evidence by itself is insufficient to establish causality, but it does provide strong circumstantial evidence.

**Meta-analysis**

At present, five meta-analyses have been published assessing the relationship between *H pylori* and gastric cancer[15,17,18,92,93], and one that focuses specifically on the CagA cytotoxin, will be discussed separately[89]. An additional earlier combined-analysis[95] which contained only three early (all published in 1991) prospective studies produced a pooled odds ratio of 3.80 (95% CI: 2.30-6.20). This paper will not be discussed in this review due to the lack of information regarding this particular combined-analysis. These meta-analyses vary in several different ways: (1) the number of studies included in the analysis; (2) the types of studies included; (3) whether the studies were peer-reviewed or in abstract form; (4) published language of the studies; (5) databases used; (6) the search terms used; (7) method of *H pylori* diagnosis; (8) statistical analyses used; (9) statistical heterogeneity; (10) if quality assessment was undertaken; (11) determination of publication bias; (12) how to deal with duplicate studies; and (13) the number of reviewers involved in data extraction. Of the five meta-analyses that assessed the association between *H pylori* and gastric cancer the number of studies included in each of the meta-analyses varies mostly due to study design. The number of studies included ranged between 11-44. Moreover, the number of studies used in the statistical analysis is exactly the same as the number of studies included except for one meta-analysis where the analysis was undertaken based on 10 out of the 44 studies (Table 3)[98]. Three of the meta-analyses combined both case-control and cohort studies[15,17,18], whereas, two meta-analyses contained only case-control studies[15,17].

Two meta-analyses placed no language restrictions on the publications included[15,17,18], one incorporated only English language publications[15] while another only used those published in Chinese[93]. The types and number of databases used differed with the majority using only one database[11,13,20], and one meta-analysis using five databases[97]. Only three meta-analyses incorporated manual searches of reference lists[93,17,94], one searched conference proceedings[95], and two contacted investigators[17,18]. The meta-analyses also used assorted search terms varying in number between 3-5. Three meta-analyses only used studies that determined *H pylori* status by serology[15,18,93] while one used a combination of serology and histology[93] and one did not state the method of *H pylori* determination[97]. Statistical methods also differed with four of the meta-analyses using a combination of a fixed and random-effects procedure. The pooled estimates from these five meta-analyses ranged between 1.92-2.56 (mean 2.28) with confidence intervals ranging between 1.35-3.55. Quality assessment was only undertaken in two of the meta-analyses[15,17], with only one using quality scores[17]. In addition, publication bias was only determined in one of the meta-analyses[15]. Duplicate studies were removed in two of the meta-analyses[15,17] and not stated in the other meta-analyses. The number of assessors also differed between the meta-analyses ranging between one and three and two studies having an unknown number of assessors.

The additional meta-analysis, focused on the relationship between cagA seropositivity and gastric cancer[94]. Previous studies have reported a higher prevalence of cagA-positive strains among populations with a high incidence of gastric cancer[94]. This meta-analysis included 16 case-control studies, and there were no language restrictions used on the literature search which included the databases of Medline and PubMed that only assessed publications between the years 1990-2003. The study produced a pooled odds ratio of 2.28 with a confidence interval ranging between 1.71-3.05. However, there was significant heterogeneity among the studies included in this analysis. A quality assessment was undertaken but did not involve producing a score for each particular study included in the meta-analysis. The authors did assess publication bias, while duplicate studies were removed and three authors conducted the literature searches. One meta-analysis[95] found that younger subjects were at lower risk (OR 0.77, 95% CI: 0.68-0.89) of developing gastric carcinoma if infected with *H pylori*, which is supported by the epidemiological data. However, another meta-analysis[96] showed that the odds ratios decreased significantly with increasing age (9.29, 3.43-34.04 aged 20-29 years; 1.05, 0.73-1.52 aged ≥ 70 years). The reason for this difference may be due to the staging of
gastric cancer and the difficulty in diagnosing *H. pylori* infection in the advanced stages where the normal gastric mucosa has been destroyed.

All these meta-analyses showed that *H. pylori* infection is associated with approximately a two-fold increased risk of developing gastric cancer (Figure 1). The strength and consistency of these meta-analyses in terms of a lack of heterogeneity (as only one meta-analysis reported heterogeneity) suggests that these observations are reliable. One of the possible reasons for this heterogeneity might be the variation in study design as both case-control and cohort studies were included.

### Animal experimental data

In order to assess a causal relationship experimentally between *H. pylori* and the formation of gastric cancer a systematic approach similar to that applied in epidemiological studies is essential. Historically, Henle-Koch postulates (1877 and 1882) have been used to determine causal relationships, however, these postulates were revised in 1976 by Evans (Evans 1976). This review will only use Henle-Koch postulates to assess this relationship. These were developed in 1877 by Jacob Henle and subsequently revised in 1882 by Robert Koch. The postulates from Last are: The agent must be shown to be present in every case of the disease by isolation in pure culture. As mentioned previously, not all animals or humans infected with *H. pylori* go on to develop gastric cancer. At present 50% of the animal studies have used carcinogens in combination with *H. pylori* infection and the remainder have only used the organism in an attempt to induce gastric cancer.

The agent must not be found in cases of other disease. *H. pylori* is associated with other gastrointestinal diseases (chronic gastritis, gastric ulcer, duodenal ulcer, and gastric MALToma) and also a large number of extra-gastric diseases. Currently, *H. pylori* is not associated with a single specific condition or disease within or outside the gastrointestinal tract.

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### Table 3 Summary of all meta-analyses looking at the association between *H. pylori* and gastric cancer

| Study Factors | Huang et al 1998(14) | Danesh 1999(19) | Eslick et al 1999(18) | Xue et al 2001(94) | HCCG 2003(95) | Huang et al 2003(96) |
|---------------|---------------------|----------------|----------------------|-------------------|----------------|---------------------|
| Journal       | Gastroenterology    | Aliment Pharm Ther | Am J Gastroenterol | World J Gastroenterol | Gut | Gastroenterology |
| Number of studies | 19                 | 44              | 42                   | 11                | 12            | 16                  |
| Cohort studies | 5                  | 10              | 8                    | 0                 | 0             | 0                   |
| Case-control studies | 14                | 34              | 34                   | 11                | 12            | 16                  |
| Peer-reviewed papers | 18               | 37              | 42                   | †                | 12            | 12                  |
| Abstracts     | 1                  | 7               | 0                    | †                | 0             | 4                   |
| Non-English language studies | English only | No restrictions | No restrictions | Chinese only | † | No restrictions |
| Searching method(s) | MEDLINE, Conference proceedings (1994-1996), manual searches | MEDLINE, Reference lists, hand searching | MEDLINE, Current contents, CINAHL, CANCER CD, Biological abstracts, manual searches, contact investigators | Chinese Biomedical database (CBM) | MEDLINE, contact investigators | MEDLINE, PubMed, contact investigators |
| Search terms used | Campylobacter pylori, stomach neoplasms, Helicobacter pylori | Campylobacter pylori, gastric adenocarcinoma, gastric cancer, Stomach cancer, Helicobacter pylori | Campylobacter pyloridis, Campylobacter pylori, gastric carcinoma, gastric cancer, Helicobacter pylori | Helicobacter pylori, gastric carcinoma, gastric cancer, precancerous lesion of stomach | † | Helicobacter pylori, meta-analysis, stomach neoplasms |
| Time period   | 1983-1996          | 1983-1998       | 1983-March 1999      | 1995-2001         | 1985-1999     | 1990-2003         |
| *H. pylori* status | Serology only       | Serology only   | Serology & histology | †               | Serology      | Serology          |
| Statistical analysis | Random-effects M-H or D&L | Inverse-variance weighted log risk odds | Random-effects D&L | Fixed-effects D&L | Logistic regression | Random-effects D&L |
| Number of studies in analysis | 19                 | 10              | 42                   | 11                | 12            | 16                  |
| Pooled odds ratio (OR) | 1.92               | 2.5             | 2.04                 | 2.56              | 2.36          | 2.28               |
| 95% confidence interval (CI) | 1.32-2.78          | 1.90-3.40       | 1.69-2.45            | 1.85-3.55         | 1.98-2.81     | 1.71-3.05          |
| Overall (*P*-value) heterogeneity | 0.2                | > 0.05          | 0.001                | > 0.05           | 0.09          | < 0.001            |
| Quality assessment | Yes                | No              | Yes                  | No               | No            | Yes               |
| Assessment of publication bias | No                 | No              | Yes                  | No               | Yes           | Yes               |
| Duplicate studies | Removed            | †               | Removed              | †                | †             | Removed           |
| Number of reviewers | Two                | One             | Two                  | †                | †             | Three             |

† Not stated. D&L: DerSimonian & Laird. M-H: Mantel-Haenszel.
the human stomach. However, it must be highlighted that none of these disease conditions have as yet been definitively causally linked with *H pylori* infection.

Once isolated, the agent must be capable of reproducing the disease in experimental animals. Marshall’s classic back-to-back publications which were published in 1985 in the *Medical Journal of Australia* where the authors aimed to fulfill Koch’s postulates[91,101]. These publications described the now famous experiment where Dr Marshall ingested a 10 mL suspension of approximately 10⁹ colony forming units of *H pylori* which had been isolated from a patient with gastritis (then referred to as *pyloric Campylobacter*). Over the course of the next ten days, the subject developed symptoms (increased abdominal peristalsis, epigastric fullness, vomiting, headache, soft faeces, and halitosis). A gastroscopy was performed and biopsies taken for both light and electron microscopy, which revealed gastritis and spiral organisms (*pyloric Campylobacter*). These organisms were cultured and freeze-dried. The authors were able to fulfill Koch’s postulates in humans for gastritis[91,102]. However, it is not possible to complete Koch’s postulates for gastric cancer in humans. It was not until 1998 when the first report by Watanabe et al.[103] of *H pylori* leading to gastric carcinogenesis that animal models could be assessed in terms of Koch’s postulates. It has been suggested that these postulates have been fulfilled for *H pylori* and gastric cancer[103], however, no studies to date have specifically undertaken or successfully proven Koch’s postulates using animal models. It appears that these statements are not based on the strict adherence to these postulates of causation, but rather that ‘sometimes’ *H pylori* is associated with gastric cancer.

The agent must be recovered from the experimental disease produced. It is not always possible to isolate *H pylori* organisms from gastric cancer tissue whether this be from humans or animals[104]. This is due to the histopathological changes that occur which decrease the ability of *H pylori* to adhere to the stomach and thus over time leads to a decreased antibody response[91,101,106].

## CONCLUSION

Currently, the epidemiological data are conflicting on the relationship between *H pylori* and gastric cancer. The independent meta-analyses provide an overall consensus that *H pylori* infection is associated with an increased risk (approximately a two-fold increased risk) of developing gastric cancer even though 50% of the studies have produced negative findings. However, there is still a lack of ‘cause and effect’ evidence concerning this relationship, which requires further animal and epidemiological studies to determine the possible carcinogenic mechanisms by which *H pylori* might cause gastric cancer. One of the major problems in determining a true causal association with *H pylori* and a disease is related to its high world-wide prevalence making associations with many conditions possible. Only strict adherence to Bradford Hill’s criteria, Henle-Koch’s and/or Evans’ postulates ensures that cause-and-effect relationships are correctly identified. Prevention studies in the form of *H pylori* eradication randomised placebo controlled trials among gastric cancer patients are currently being conducted.

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