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Review article

Epidemiology of *Helicobacter pylori* and gastric cancer

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Abstract

Findings in epidemiological studies of the relationship between *Helicobacter pylori* and gastric cancer have been inconsistent: many studies have yielded a positive relationship, whereas several studies have shown no relationship. The inconsistency arises because of the occurrence of seroreversion during the period between the time that *H. pylori* exerts a carcinogenic effect and the time of blood sampling. When this seroreversion is taken into account, there is an epidemiologically positive association between *H. pylori* status and the risk for gastric cancer. In addition to the epidemiological evidence, experimental studies using Mongolian gerbils have shown that *H. pylori* infection elevates the risk for gastric cancer. It is concluded that *H. pylori* is a causal factor for gastric cancer. In the creation of preventive strategies against gastric cancer by the eradication of *H. pylori*, determination of the time at which *H. pylori* plays a role as a carcinogen is important. Three hypotheses have been proposed in regard to this timing: that *H. pylori* infection in childhood or the teenage years acts as a factor that produces precancerous lesions with irreversible damage in the gastric mucosa, that in adulthood it acts as an initiator, and also in adulthood, that it acts as a promoter. As these hypotheses are not mutually exclusive, the extent to which each hypothesis plays a part in explaining gastric carcinogenesis should be evaluated. Only a small proportion of subjects infected with *H. pylori* have gastric cancer during their lifetime. Interleukin-1 polymorphism, a host factor, and CagA, a virulence factor of *H. pylori*, are suspected to be risk factors for gastric cancer in subjects with *H. pylori* infection. Dietary factors, especially vitamin C, and patterns of precancerous lesions also seem to influence the relationship between *H. pylori* and gastric cancer. *H. pylori* seems to reduce the risk for esophageal and for some gastric cardia adenocarcinomas. This finding, as well as determination of the time at which *H. pylori* exerts this preventive effect, should be considered in the creation of preventive strategies against gastric cancer that target the eradication of *H. pylori.*

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Introduction

Helicobacter pylori is a gram negative bacillus that lives in the mucus of the human stomach. *H. pylori*, which was discovered in 1982 [1], produces carbon dioxide and ammonia from urea by the action of urease [2]. The ammonia elevates the pH of the mucus so that this bacillus can live there.

In this review article, studies of the relationship between *H. pylori* and gastric cancer to date are reviewed, and differences in the relationship depending on histopathological type (diffuse/intestinal), stage (early/advanced), the location of the cancer (cardia/noncardia), and CagA status are discussed. Problems in the creation of a preventive strategy against gastric cancer by the eradication of *H. pylori* are also discussed.

Epidemiology of *Helicobacter pylori*

Helicobacter pylori usually continues to live in the stomach once infection has occurred [3]. In Japan, prevalence of *H. pylori* increases with age [4]. It is believed that most *H. pylori* infection occurs in childhood [5,6]. Acquisition of *H. pylori* is related to sanitary conditions, such as living conditions [7–9], water supply, and sewerage [10,11]. The age-dependent prevalence of *H. pylori* in Japan may be a result of the gradual progress in sanitary conditions that has taken place in Japan since 1950. Even in adulthood, a family history of stomach diseases and sibship size showed an association with the prevalence of *H. pylori* [6]. The prevalence of *H. pylori* is also related to periods spent in nursery school [9]. Child-to-child infection may be the main infection route of *H. pylori*. In regard to world distribution, the pre-

Table 1. Prospective studies evaluating the relationship between *Helicobacter pylori* and gastric cancer

Authors	Place	Age, in years (mean)	Follow-up (years)	Odds ratio (95% CI)	Seroprevalence	
					Patients	Control
Forman et al. [22]	England	41–63 (54)	6.0	2.8 (1.0–8.0)	69%	47%
Nomura et al. [23]	Hawaii, USA	46–65 (59)	13.0	6.0 (2.1–17.3)	94%	76%
Parsonnet et al. [24]	California, USA	(54)	14.2	3.6 (1.8–7.3)	84%	61%
Webb et al. [25]	Shanghai, China	48–69 (61)	2.4	0.9 (0.6–1.5)	54%	56%
Lin et al. [26]	Taiwan	(63)	3.0	1.6 (0.7–2.6)	69%	59%
Watanabe et al. [27]	Kyoto, Japan		3.2	3.4 (1.2–9.9)	91%	76%
Aromaa et al. (IgA) [28]	Finland	(62)	13.0	2.5 (1.1–5.6)	89%	76%

CI, Confidence interval

Table 2. Case-control studies evaluating the relationship between *Helicobacter pylori* and gastric cancer

Authors	Place	Age, in years (mean)	Odds ratio (95% CI)	Seroprevalence	
				Patients	Control
Hasson et al. [29]	Sweden	≦79 (67)	2.6 (1.4–5.0)	80%	61%
Asaka et al. [30]	Hokkaido, Japan	(60)	2.6 (1.5–4.3)	88%	75%
Kikuchi et al. [31]	Tokyo, Japan	20–39 (34)	13.3 (5.3–35.6)	89%	39%
Kikuchi et al. [32]	Tokyo, Japan	20–69		(See Table 3)	
Rudi et al. [33]	Germany	26–83 (60)	1.4 (0.8–2.4)	59%	51%
Fukuda et al. [34]	Tokyo, Japan	23–83 (57)	1.0 (0.7–1.5)	76%	74%

valence of *H. pylori* is low in Western and Northern Europe and North America and high in Asia and Eastern Europe [12].

Rod and coccoid forms of *H. pylori* have been seen in dental plaque [13]. In an experimental study, volunteers with *H. pylori* infection were given a cathartic and an emetic. *H. pylori* was cultured from all vomitus samples, 38% of air samples during vomiting, 19% of saliva samples before emesis, 56% of saliva samples after emesis, no normal stools, and 22% of induced stools [14]. In attempts to show that feco-oral infection is the main infection route of *H. pylori*, the association between *H. pylori* status and presence antibody for hepatitis A virus, the infection route of which is known to be feco-oral, has been investigated, but results have been controversial [15,16]. In Japan, no association was observed between *H. pylori* status and hepatitis A virus antibody [17], although this does not necessarily deny feco-oral infection. Oral-oral, that is, gastro-oral, infection is suspected, rather than feco-oral infection [18].

Causal relationship between *H. pylori* and gastric cancer

Initially, the relationship between *H. pylori* and gastric cancer was investigated epidemiologically, with most of the studies being serological. Ecological studies showed that the prevalence of *H. pylori* was positively related to gastric cancer mortality [12,19]. In Japan, the prevalence of *H. pylori* differs among areas and is related to gastric cancer mortality [20,21]. The association between gastric cancer and *H. pylori* was shown by prospective studies [22–28] in which odds ratios were 0.9 to 6.0 (Table 1). Several case-control studies were also carried out. The results of the studies were not consistent (Table 2) [29–34]. Some of them showed a positive association, but some studies found no association, or nonsignificant results. A few cohort studies have shown no association between gastric cancer and *H. pylori*. Thus, to date the findings of the epidemiological studies have been inconsistent. Seroconversion and seroreversion (negative-to-positive and positive-to-negative changes in serology, respectively) in accordance with the stages of progression of gastric cancer can explain the inconsistencies.

Seroconversion and seroreversion

Most epidemiological studies that evaluated the relationship between *H. pylori* and gastric cancer determined *H. pylori* status serologically. In case-control studies, it is possible that seroconversion and seroreversion occurred during the incubation period, i.e., during the period between the time at which *H. pylori* exerts a carcinogenic effect and the time of diagnosis of cancer [32]. New infections can occur in both cases and control subjects during the incubation period, bringing about seroconversion in the subjects. Gastric mucosa with severe atrophy with intestinal metaplasia is less pleasant

for *H. pylori* to live in, and the bacillus sometimes disappears from the mucosa [35]. While seroreversion could occur in control subjects because of advanced atrophy, it is expected to be much more rare than in gastric cancer patients. *H. pylori* causes mucosal atrophy and intestinal metaplasia [36], and the seroprevalence of *H. pylori* was often higher in gastric cancer patients than in control subjects. Seroreversion does occur in healthy older subjects [37,38]. As atrophy of the gastric mucosa progresses with time, its effect appears to be greater in older subjects [39].

Early and advanced gastric cancers

A few studies, most of which are Japanese, have compared the effect of *H. pylori* in early and advanced gastric cancers. *H. pylori* showed a stronger relationship with early cancer than with advanced cancer [30–32]. Many other studies, including cohort studies, have not mentioned the stage of progression of gastric cancer.

Seroreversion may occur as a result of the natural progression of gastric cancer rendering the gastric mucosa inhospitable to *H. pylori* [39], or through weakening of the immune reaction [40]. It takes from 6 months to 7 years for early cancer to progress to advanced cancer [41]. The incubation period of *H. pylori* infection is longer in advanced cancer patients than in early cancer patients, and this may cause more frequent seroreversion [42,43] in advanced cancer patients. These mechanisms are consistent with the weaker relationship between advanced gastric cancer and *H. pylori*. When age is considered, the weaker relationship of *H. pylori* with advanced cancer is observed more frequently among those aged over 50 years [32].

Intestinal type and diffuse type

Intestinal type gastric cancer, which is more differentiated than diffuse type cancer, is usually associated with atrophy of the gastric mucosa [44] and is thought to develop in mucosa with atrophy. Diffuse type cancer often develops in mucosa without atrophy. *H. pylori* is known to cause atrophic gastritis. Therefore, it was believed, at first, that *H. pylori* elevated the risk of intestinal type cancer, but not the risk of diffuse type cancer. A few microscopic studies yielded a closer association of *H. pylori* with intestinal type cancer [45,46].

However, many serological studies have shown that both diffuse type and intestinal type cancers are related to *H. pylori* status [23,24,29,31,47]. There appears to be little difference in the seroprevalence of *H. pylori* between the two types of cancers, even after adjusting for age [32]. In terms of a relationship to *H. pylori*, no difference seems to exist between diffuse type and intestinal type cancers. The results of the microscopic studies may have reflected the characteristic that diffuse type cancer is less hospitable to *H. pylori* than intestinal type [48], and *H. pylori* was less frequently observed in diffuse type cancer tissue.

Explanation for the inconsistencies among the epidemiological studies

We consider that seroconversion and seroreversion, especially the latter, may account for the inconsistencies among epidemiological studies that have assessed the relationship between *H. pylori* and gastric cancer. In most countries, except for Japan, screening programs for gastric cancer have not been put into practice [49]. In countries other than Japan, gastric cancer patients are more likely to have advanced disease. Actually, most epidemiological studies to date, with a few exceptions [30–32], have not mentioned the stage of progression in their case subjects. Case-control studies that show lack of a relationship between *H. pylori* and gastric cancer would be expected to have examined mainly older subjects and subjects with advanced cancer [32], so that seroreversion would have occurred during the incubation period. Even in prospective studies, if the observation period [25,26] is short, it is possible that the tumor in the stomach may have existed at the baseline point of the study and that seroreversion may have occurred before the baseline point at which blood sampling was performed. Thus, the inconsistencies among the findings of the epidemiological studies may be the result of seroreversion, and it is concluded that there is a consistent relationship between *H. pylori* and gastric cancer.

Causal relationship

As discussed above, epidemiological studies have shown a relationship between *H. pylori* and gastric cancer. Five points, that is, strength of association, temporality between the cause and the disease, consistent findings among epidemiological studies, specificity, and biological plausibility of the relationship, should be checked for the determination of a causal relationship [50]. A strong relationship between *H. pylori* and gastric cancer, that is, a high odds ratio, has been observed [24,31]. Temporality is confirmed by cohort studies. Temporality is reinforced by the finding that time after the blood sampling (baseline) was positively related to the strength of the relationship [24]. Consistency exists, as mentioned above (i.e., the inconsistent epidemiological findings have been explained). Specificity may be confirmed by noting the high seroprevalence in gastric cancer patients (Tables 1, 2). Lack of biological plausibility, however, used to be a drawback when a causal relationship between *H. pylori* and gastric cancer was considered.

Recently, an animal model of gastric carcinogenesis was established, using the Mongolian gerbil. A study showed that long-term *H. pylori* infection alone caused stomach cancer in the Mongolian gerbil [51], although other studies of the same design have not succeeded in causing stomach cancer. Several studies have shown that *H. pylori* infection markedly increases [52,53], and eradication of *H. pylori* markedly reduces, gastric cancer in the Mongolian gerbil [54]. Thus, it has been established that *H. pylori* plays a part in gastric carcinogenesis.

Preventive strategy against gastric cancer by the eradication of *H. pylori*

Prevention of gastric cancer by the eradication of *H. pylori* is possible, if *H. pylori* is a causal risk factor. When an effective prevention strategy is considered, determination of the critical timeframe (critical time) during which *H. pylori* produces its carcinogenic effect is important, because the eradication of *H. pylori* after this time would have no preventive effect on the incidence of gastric cancer. Although cancer prevention trials focusing on the eradication of *H. pylori* have already been started, the critical time has not yet been identified. To identify the critical time and the mechanism by which a risk factor operates, it is important to elucidate the relationship between the length of exposure and the magnitude of the effect. As the length of exposure is associated with age, the effect of age on the strength of the relationship provides useful information.

Effect of age on the relationship between H. pylori *and gastric cancer*

In the younger Japanese population (those under 40 years of age), a high odds ratio, of 13.3, was shown for the relationship between *H. pylori* and gastric cancer [31]. A meta-analysis reported that the relationship between *H. pylori* and gastric cancer was stronger in a younger population [47]. In subjects from a defined ethnic group from a single region of Japan, a case-control study gave similar results (Table 3) [32]; in that study, the level of *H. pylori* antibody was measured in the sera of 787 patients with gastric cancer and 1007 control subjects, aged 20 to 69 years, stratified into several 10-year age classes. No studies to date have reported a stronger relationship in an older population. Thus, the relationship between *H. pylori* and gastric cancer is generally weaker in an older population.

However, the weaker relationship in older populations could be the result of seroreversion in older patients. In order to control for the effect of seroreversion owing to atrophy or cancer, a separate analysis that focused on early diffuse-type cancer was conducted. In early diffuse-type cancer, the odds ratios did not depend on age, but they did depend on age in all other gastric cancers [32]. The weaker relationship in the older population may be a superficial phenomenon because of seroreversion in older patients with gastric cancer. The relationship between *H. pylori* and gastric cancer may not depend on age.

Table 3. Odds ratios of association of *Helicobacter pylori* and gastric cancer in patients stratified by age

Age (years)	Control *n* (positive %)	Case *n* (positive %)	Odds ratio (95% CI)
20–29	201 (28.4)	4 (75.0)	7.58 (0.68–infinity)
30–39	202 (43.1)	36 (88.9)	10.58 (3.40–36.70)
40–49	199 (54.3)	156 (91.3)	8.85 (4.62–17.21)
50–59	203 (71.4)	262 (90.5)	3.79 (2.21–6.54)
60–69	202 (81.2)	329 (88.4)	1.77 (1.06–2.98)

From [32]

Exposure to H. pylori *and risk of gastric cancer*

In developed countries, infection with *H. pylori* mainly occurs before 20 years of age, and infection after 20 years of age is relatively rare [8,38]. Thus, older subjects infected with *H. pylori* are likely to have been exposed to the bacillus for a longer period of time. On the other hand, the relationship between *H. pylori* and gastric cancer does not change with age, although it is superficially stronger in younger subjects. Long exposure does not seem to increase the magnitude of *H. pylori* influence on gastric carcinogenesis.

This relationship is markedly different from that between smoking and lung cancer. Studies of the relationship between smoking and lung cancer have shown that the relative risk or odds ratio increases with age; that is, the longer the exposure to smoking, the greater the magnitude of its effect on the incidence of lung cancer [55,56]. Hypotheses to explain the mechanisms of and critical time for *H. pylori* in gastric carcinogenesis have to be consistent with the finding that long exposure does not increase the magnitude of its influence.

Hypotheses for the relationship between length of exposure to H. pylori *and magnitude of its influence*

Three hypotheses have been proposed to explain the noncumulative effect of *H. pylori* [32]. The first hypothesis is that, during childhood or the teenage years, *H. pylori* damages the gastric mucosa in such a manner that the damage, which may be a kind of precancerous lesion, remains into adulthood. The second hypothesis is that *H. pylori* has an initiator effect on carcinogenesis, as does a small dose of radiation. The third hypothesis is

that *H. pylori* acts as a promoter, reducing the threshold for carcinogenesis.

According to the first hypothesis, continuous infection with *H. pylori* during childhood or the teenage years may irreversibly harm the gastric mucosa. In this case, the critical time is childhood or the teenage years. Eradication should be conducted in childhood or early in the teenage years, because eradication after the irreversible harm has been produced does not prevent carcinogenesis at all. This hypothesis is supported by an American study of Japanese-Americans, in which those suspected of childhood infection with *H. pylori* had a higher risk of gastric cancer [57]. If the diagnosis of the irreversible harm so hypothesized becomes possible, the risk for gastric cancer of each subject could be evaluated much more precisely.

According to the second hypothesis, *H. pylori* may increase the risk of carcinogenesis while the infection continues, but the effects are not cumulative, and may be important in adulthood. Inflammation provoked by *H. pylori* may damage the DNA of the mucosal cells. Thus, any period of continuous infection could be the critical time, and, in the presence of other factors, especially promoters, the infection may cause carcinogenesis. If this is so, then eradication should be conducted early in adulthood, or before that, because eradication after the initiation of carcinogenesis has no preventive effect.

According to the third hypothesis, *H. pylori* may promote gastric carcinogenesis while the infection continues, and the effect of *H. pylori* may be completed during a short period. Inflammation provoked by *H. pylori* accelarates the turnover of mucosal cells, which may promote carcinogenesis. Any period of continuous infection could be the critical time, and the promoter effects of *H. pylori* may be important in adulthood when most initiation is expected to occur. This hypothesis is supported by a Japanese study in which the eradication of *H. pylori* prevented the subsequent development of gastric cancer after endoscopic resection [58]. A recent experimental study, using Mongolian gerbils, has suggested that *H. pylori* may exert a promoter effect in gastric carcinogenesis [53]. If this is so, then *H. pylori* eradication at any time may reduce the risk of gastric cancer.

These hypotheses are not mutually exclusive; that is, two or three of these hypotheses could be true. Whether or not each hypothesis is true should be confirmed, and the extent to which each hypothesis plays a part in explaining gastric carcinogenesis should be evaluated.

Other factors involved in the relationship between *H. pylori* and gastric cancer

Only a small proportion of subjects with *H. pylori* infection harbor clinical gastric cancer during their lifetimes, whereas other subjects do not, although they are infected with *H. pylori*. Factors other than *H. pylori* infection seem to determine whether subjects with *H. pylori* harbor gastric cancer during their lifetimes. Among factors involved with *H. pylori* infection, a host factor and a factor related to the virulence of *H. pylori* have attracted attention. The former is an interleukin–1 polymorphism, which is related to the severity of inflammation in the stomach when *H. pylori* infection occurs. The latter is the cytotoxin-associated antigen, CagA, produced by some strains of *H. pylori.*

In addition to these factors, the distribution of gastritis provoked by *H. pylori*, as well as dietary factors, have been confirmed to influence the relationship between *H. pylori* and gastric cancer.

Interleukin-1β (IL-1β) polymorphism

H. pylori increases IL-1β production, which amplifies the inflammatory response to *H. pylori* infection [59,60] and inhibits gastric acid secretion [61]. The excess production of IL-1β depends on the presence of an IL-1β polymorphism. *H. pylori*-positive individuals who had haplotypes that upregulated IL-1β production, such as *IL1*-β-511T/31C and *IL-1RN**2, showed an increased risk for gastric cancer [62,63]. In other words, the effect of *H. pylori* infection on the risk for gastric cancer depends on the severity of inflammation, which is determined by genetic factors. These findings may be one explanation for the findings that only a small proportion of *H. pylori* infections cause gastric cancer. In the near future, it is to be hoped that the precise effect of *IL1*-β-31 haplotypes on the risk of gastric cancer will be established.

CagA and gastric cancer

H. pylori strains are divided into two groups; strains with and without a *cag* pathogenicity island. Strains with the *cag* pathogenicity island produce CagA, a cytotoxin-associated antigen [64], and have stronger virulence than strains without a *cag* pathogenicity islands [65,66]. When *H. pylori* infection occurs, with a strain that produces CagA, CagA antibody is produced in the serum [67] and can be measured with an immunoassay [68].

Several serological studies have assessed the relationship between gastric cancer and CagA-positive or -negative strains of *H. pylori*. Two studies conducted in the United States have shown that a CagA-positive strain was more strongly related to intestinal type gastric cancer than a CagA-negative strain, while CagA was not associated with a risk for diffuse type gastric cancer [69,70]. A Japanese study showed a positive relationship between CagA and gastric cancer; in that study, the control subjects were those who underwent gastric endoscopy. In a young Japanese population (those

under 40 years of age), CagA was not related to diffuse type gastric cancer, and it showed an odds ratio of 1.0 for intestinal type cancer, although the sample size was too small for a definitive conclusion [71]. In China, no difference in seroprevalence for antibody against CagA antigen was observed between gastric cancer patients and asymptomatic subjects [72]. A Brazilian study, in which the *cag*A gene was detected by polymerase chain reaction, showed that *cag*A-positive strains of *H. pylori* entailed a stronger risk for both intestinal and diffuse types of gastric cancer than *cag*A-negative strains [73]. Thus, results regarding the effect of CagA on the risk for gastric cancer have been controversial. A recent study has revealed that CagA protein is inserted into the host cell by *H. pylori* [74]; the biological effect of CagA is attracting the attention of many researchers. Further epidemiological studies are needed to determine conclusively whether the CagA status of *H. pylori* strains is related to the risk for gastric cancer.

Chronic gastritis and intestinal metaplasia provoked by H. pylori *and risk of gastric cancer*

Chronic gastritis and intestinal metaplasia are thought to be precancerous lesions [75,76]. Gastritis provoked by *H. pylori* is also related to the risk for gastric cancer [77]. Recent case-control and cohort studies have shown that individuals with chronic gastritis in the corpus, including pangastritis, have a higher risk for gastric cancer than those with antrum-predominant gastritis [78–80], and those with intestinal metaplasia have an even higher risk [79,80].

Dietary factors and gastric cancer

It is well-known that the intake of fresh vegetables reduces the risk for gastric cancer, and vitamin C (ascorbic acid) is thought to be the major preventive factor [81–88]. Beta-carotene is also thought to be a preventive factor. The eradication of *H. pylori* improves the secretion of vitamin C into gastric juice [89]; that is, *H. pylori* reduces this secretion. *H. pylori* also reduces the systemic availability of dietary vitamin C [90]. From results of a retrospective study, it was inferred that a daily intake of fresh fruits and vegetables prevented the transition from gastritis to intestinal metaplasia, while smoking accelerated [91]. An intervention study has shown that the eradication of *H. pylori*, and supplements of vitamin C and beta-carotene brought about the regression of cancer precursor lesions [92]. A cohort study has revealed that individuals with a low level of serum vitamin C have a higher risk for gastric cancer, although serum beta-carotene concentration was not related to the risk [93]. Thus, although no direct proof has been obtained yet, the studies to date strongly indicate the preventive effect of vitamin C against carcinogenesis in the stomach associated with *H. pylori* infection. On the other hand, the effect of beta-carotene in this regard seems to be unclear.

Negative relationship between *H. pylori* and gastric cardia or esophageal adenocarcinoma

Several studies have shown that *H. pylori*, especially CagA-positive strains, exert a protective effect against gastric cardia and esophageal adenocarcinoma [94,95], although a few contradictory results have been obtained [96]. Inflammation provoked by *H. pylori* inhibits gastric secretion, and prevents gastroesophageal reflux disease (GERD) [97,98]. GERD creates lesions in the esophageal mucosa known as Barrett's esophagus. Barrett's esophagus is positively related to, and is thought to be, a precancerous lesion of esophageal adenocarcinoma [99].

There is a remarkable difference between the United States and Japan in the incidence of esophageal adenocarcinoma. In the United States, adenocarcinoma accounts for not less than 50% of esophageal cancers [100], while in Japan it accounts for, at most, 3%. Therefore, because of this low incidence, no Japanese study has yet assessed the relationship between *H. pylori* status and esophageal adenocarcinoma. In studies showing a negative relationship between *H. pylori* status and esophageal adenocarcinoma, the areas from which the population were drawn had a low prevalence of *H. pylori*. In Japan, the prevalence of *H. pylori* is still high among those aged over 50 years, who are at considerable risk for esophageal cancer. Those with genetic or lifestyle factors that would cause esophageal adenocarcinoma without *H. pylori* infection may not have the disease during their lifetime because they have *H. pylori* infection. In the future, esophageal adenocarcinoma is expected to increase in the Japanese population, because the prevalence of *H. pylori* is decreasing. In the United States, both esophageal and gastric cardia adenocarcinoma increased from 1975 to 1995 [100,101].

Results of studies in Japan have contradicted the findings of a negative relationship between gastric cardia cancer and *H. pylori* infection reported in the United States. Our study, in subjects under 40 years of age, has shown that proximal cancer, the main lesion of which is within the proximal third of the stomach, is positively related to *H. pylori* infection, although the odds ratio for proximal cancer was smaller than that for distal cancer [31,71]. Calculations with data from another study, in which the subjects were aged 20–69 [32], has given similar results. An explanation for the controversial results is that two types of cancers appear in the proximal region of the stomach; one positively related

to, and the other negatively related to, *H. pylori* infection. The former type may be prevalent in areas with a high prevalence of *H. pylori* infection, while the latter type may be prevalent in areas with a low prevalence of *H. pylori* infection. As mentioned above, Barrett's esophagus is frequent in individuals without *H. pylori* infection and is thought to be a precancerous lesion of esophageal adenocarcinoma or cardia cancer. In subjects without Barrett's esophagus, another type of intestinal metaplasia is observed around the cardia [102]. This may be a precancerous lesion of gastric cancer that is positively related to *H. pylori* infection. In accordance with the decrease in *H. pylori* prevalence in Japan, the type of cardia cancer with a positive relationship to *H. pylori* infection may decrease, and the type with a negative relationship to *H. pylori* infection may increase, so that cardia cancer in Japan will show a negative relationship to *H. pylori* infection.

Could an increase in esophageal adenocarcinoma be a drawback in the employment of a preventive strategy against gastric cancer that involves the eradication of H. pylori*?*

An increase in esophageal adenocarcinoma is expected if the prevalence of *H. pylori* decreases. The eradication of *H. pylori* may therefore elevate the risk for esophageal adenocarcinoma, and an anticipated increase in esophageal adenocarcinoma could be a drawback in the employment of preventive strategies against gastric cancer involving the eradication of *H. pylori*.

In Table 4, esophageal and gastric cancer mortality in Japan, the United States, and the United Kingdom is shown [103]. Japan shows a higher gastric cancer mortality than these two other countries. The United Kingdom shows a higher esophageal cancer mortality than Japan, but the difference is small compared with that in gastric cancer mortality. Esophageal cancer mortality in the United States is lower than that in Japan. It is expected that the eradication of *H. pylori* will cause both a decrease in gastric cancer and an increase in esophageal adenocarcinoma, and, in terms of numbers, the former is much larger than the latter. Thus, judging from this comparison of mortality among these countries, eradication of *H. pylori* may have the effect of decreasing the total number of cancer patients.

Table 4. Esophageal and gastric cancer[a] mortality

	Stomach		Esophagus	
Japan	Male 34.5	Female 15.2	Male 7.0	Female 1.0
USA	Male 5.1	Female 2.3	Male 4.7	Female 1.1
UK	Male 12.4	Female 5.1	Male 7.8	Female 3.2

[a] 1988–1992, mortality per 100000 person-years, age-adjusted (From [103])

However, the critical time of *H. pylori* in gastric carcinogenesis is still unclear. It has been argued that *H. pylori* eradication often causes gastroesophageal reflux, so that the eradication predisposes to the development of Barrett's esophagus; however, the precise time period during which *H. pylori* exerts its inhibitory effect on esophageal carcinogenesis is not clear. If the critical time of *H. pylori* in gastric carcinogenesis were in early childhood and if *H. pylori* exerted its inhibitory effect on esophageal cancer even in adulthood, eradication in adulthood would elevate the risk for esophageal cancer without showing any decrease in the risk for gastric cancer. In the creation of preventive strategies against gastric cancer, these problems are very important, and they should be solved by well-designed clinical trials.

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