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Review article

Helicobacter pylori and gastric cancer

Hidekazu Suzuki, Eisuke Iwasaki, and Toshifumi Hibi

Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

Abstract
***Helicobacter pylori* is now well known as an important pathogen related to the development of gastric cancer. However, some clinicians still doubt the causal association of *H. pylori* with the development of gastric cancer. To summarize the recent clinical data on the link between *H. pylori* and gastric cancer, we reviewed related articles published over the past 3 years, after the award of the Nobel Prize for Physiology or Medicine to Drs. J.R. Warren and B.J. Marshall for the first culture and isolation of *H. pylori* and the investigation of their relevance to peptic ulcer disease. This updated summary of the relationship between *H. pylori* and gastric cancer highlights the strong link between the organism and the development of gastric cancer, and suggests eradication of this bacterial infection as a possible prophylactic measure against the development of this lethal malignancy. At present, clinicians and researchers in the field emphasize the strong need for *H. pylori* eradication from the human stomach.**

Key words Gastric cancer · *Helicobacter pylori* · Eradication · Randomized controlled trial · Gene polymorphism · Food factor

Introduction

In December 2005, Dr. J.R. Warren and Dr. B.J. Marshall were awarded the Nobel Prize for Physiology or Medicine [1]. At that time, although they received the award for their work on the culture and isolation of *Helicobacter pylori* and their recognition of the potent etiological relation of this organism to gastritis and peptic ulcer disease [2], the possible relation of *H. pylori* to the development of gastric cancer had not yet been fully evaluated [1, 3]. However, in the period before their Nobel Prize award in 2005, outstanding findings about the relationship between *H. pylori* and gastric cancer had been reported. In 1994, the International Agency for Research on Cancer and the World Health Organization (WHO) classified *H. pylori* as a definite (group I) carcinogen [4], based upon epidemiological data using serum anti-*H. pylori* IgG [5–7]. Subsequently, large-scale prospective clinical studies clearly showed the causal relationship between *H. pylori* and gastric cancer development [8–11]. Uemura et al. [8] prospectively studied 1526 *H. pylori*-positive and 280 *H. pylori*–negative subjects for an average of 7.8 years and showed that gastric cancers developed in 36 (2.4%) of the infected and none of the uninfected patients. On the other hand, a large-scale randomized prospective comparative study in China, carried out by Wong et al. [10], investigating 1630 *H. pylori*-positive subjects (817 receiving and 813 not receiving *H. pylori* eradication) for 7 years showed no significant difference in gastric cancer development between the two treatment arms ($P = 0.33$) [10]. However, because their definition of preneoplastic lesions included so-called "early gastric cancer" in the category of dysplasia, Wong et al. [10] counted only advanced gastric cancer cases as the gastric cancer group, suggesting a difficulty in making direct comparisons with other studies. According to a meta-analysis by Huang et al. [12], *H. pylori* infection was associated with gastric cancer, but there was little information on early gastric cancer at that time. In terms of the recurrence of early gastric cancer after endoscopic mucosal resection, Uemura et al. [13], in 1997, showed significantly less frequent recurrence in patients with *H. pylori* eradication. In the present article we review the clinical data confirming the link between *H. pylori* infection and gastric cancer published after the award of the Nobel Prize mentioned above (2006–2008).

Methods employed for literature review (Fig. 1)

A literature search was performed in PubMed using the key words [*Helicobacter pylori*] and [gastric cancer]

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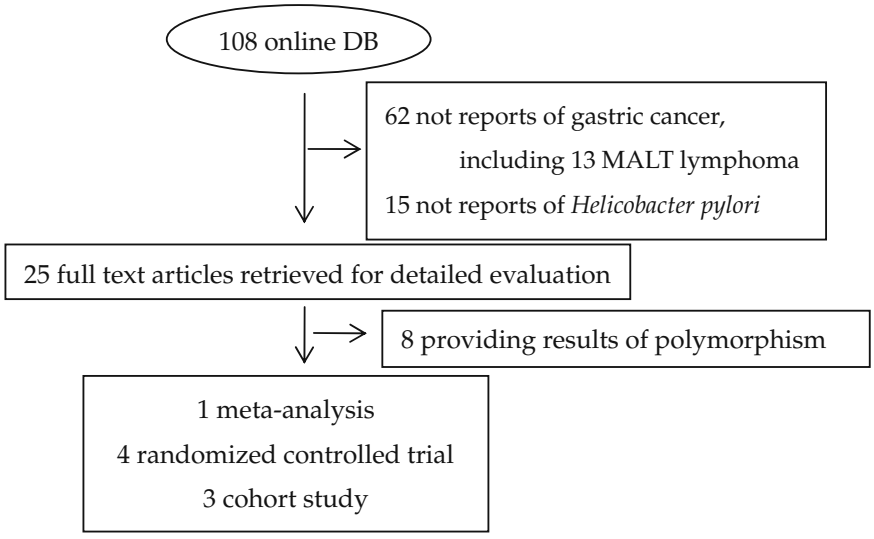

Fig. 1. Literature selection flow. *DB*, database; *MALT*, mucosa-associated lymphoid tissue

and the list was limited to studies added to PubMed or published over the past 3 years (2006–2008), to human studies, meta-analyses, practice guidelines, randomized controlled trials, clinical trials (phase I, II, III, IV), comparative studies, systematic reviews, and to studies including subjects older than 19 years. After compiling a list of the 108 studies included, 83 publications not directly involving the link between *H. pylori* and the development of gastric cancer were excluded. The remaining 25 studies were finally systematically reviewed.

Results of the literature review (Fig. 1)

Of the 25 clinical studies dealing with the relationship between *H. pylori* infection and the development of gastric cancer, 4 were randomized controlled trials (RCTs) [14–17], 1 was a meta-analysis [18], 3 were cohort studies [19–21], 9 were case-control studies [22–30], and 8 examined gene polymorphisms related to the link between *H. pylori* and gastric cancer [26, 31–37]. Two European studies [38, 39] showed a relationship between dietary factors and *H. pylori*-associated gastric cancer development.

Randomized controlled trials (RCTs; Table 1)

You et al. [14] conducted an RCT to examine the effects of one-time *H. pylori* treatment and long-term intake of vitamin or garlic supplements in reducing the prevalence of advanced precancerous gastric lesions. In their study, most of the adults (age, 35–64 years) in 13 randomly selected villages underwent baseline endoscopies in 1994. Then, in 1995, 3365 eligible subjects were randomly assigned to one of three interventions or a placebo group: amoxicillin + omeprazole for 2 weeks in 1995; vitamin C, vitamin E, and selenium for 7.3 years; aged garlic extract and steam-distilled garlic oil for 7.3 years. The *H. pylori* eradication treatment resulted in a statistically significant decrease in the combined prevalence of severe chronic atrophic gastritis, intestinal metaplasia (IM), dysplasia, and gastric cancer, as evaluated in 1999 (odds ration [OR], 0.77) and 2003 (OR 0.60), and had favorable effects on the average histopathologic severity and progression/regression of precancerous gastric lesions, as evaluated in 2003 [14]. Fewer subjects receiving *H. pylori* eradication therapy (1.7%) than the number receiving placebo (2.4%) developed gastric cancer (adjusted $P = 0.14$) [14]. No statistically significant favorable effects were noted for garlic or vitamin supplementation [14].

In a recent multicenter, open-label, RCT conducted in Japan on 544 patients with early gastric cancer [15] who were either newly diagnosed and scheduled for endoscopic treatment or were under post-resection follow up after endoscopic treatment, the patients were randomly assigned to receive *H. pylori* eradication therapy ($n = 272$) or no eradication ($n = 272$); at the time of the 3-year follow-up examination, metachronous gastric cancer was found to have developed in 9 patients in the eradication group and 24 patients in the control group [15]. In the full intention-to-treat (ITT) population, which included all patients irrespective of the length of follow up, the OR for the development of metachronous gastric cancer was 0.353 (95% confidential interval [CI], 0.161–0.775; $P = 0.009$); in the modified ITT population, which included patients with at least one post-randomization assessment of the tumor status and adjustment for loss to follow up, the hazard ratio (HR) for the development of metachronous gastric cancer was 0.339 (95% CI, 0.157–0.729; $P = 0.003$) [15]. Based on the results of this study [15], the Japanese Society for *Helicobacter* Research (JSHR) revised their

Table 1. Randomized controlled trials

Author	Year	*n*	Subjects	Randomization	Endpoint	RR (95% CI)	Period
You et al. [14]	2006	3365	Chinese population	Eradication	AG+IM+dysplasia+GC	0.60 (0.47–0.75)	7.3 Years
				Control	Dysplasia+GC	NS	
Fukase et al. [15]	2008	544	Patients with post-endoscopic resection of early GC	Eradication	Diagnosis of new GC	0.353 (0.161–0.775)	3.0 Years
				Control			
Kim et al. [16]	2008	1790	Outpatients	Eradication	Diagnosis of new GC	NS	9.4 Years
				Control			
				— Subanalysis IM (+) vs IM (–)		10.9 Times	
Ji et al. [17]	2006	48	Patients with hyperplasic polyps	Eradication	Disappearance of polyps	68.2%	6.5 Months
				Control		0.0%	

n, number of patients; GC, gastric cancer; AG, atrophic gastritis; IM, intestinal metaplasia; NS, not significant

guideline for physicians on the diagnosis and treatment of *H. pylori* infection in routine medical practice in 2008.

In a Korean study conducted on 1790 subjects [16], gastric cancer was found to occur 10.9 times more frequently in the presence of IM than in its absence, suggesting that for effective prevention of gastric cancer [16], *H. pylori* eradication therapy must be administered before the development of IM. IM lesions frequently show high expression levels of cyclooxygenase-2 (COX-2). According to a double-blind, randomized, placebo-controlled trial conducted by Leung et al. [40], on subjects with confirmed IM ($n = 213$) who were randomized to receive either rofecoxib or placebo, there was no evidence to suggest that treatment with rofecoxib for 2 years resulted in the regression of gastric IM [40].

One study focused on the efficacy of *H. pylori* eradication therapy for preventing the development of gastric hyperplastic polyps [17]. Forty-eight patients with hyperplastic gastric polyps infected with *H. pylori* were randomly assigned to an eradication group and a control group which received only the gastroprotective agent, teprenone [17]. While the polyps disappeared by 1–12 months after the treatment in 69% of the patients in the eradication group and *H. pylori* infection was eradicated in 86% of the patients, no change in the polyp or *H. pylori* status was observed in any of the patients in the control group by 12 months after the start of the study [17].

The efficacy of *H. pylori* eradication against the development of gastric cancer in the remnant stomach after gastrectomy has not been adequately assessed. A total of 138 patients with distal gastric cancer and *H. pylori* infection were randomized to receive *H. pylori* eradication therapy either preoperatively (preop) or postoperatively (postop) [41]. According to ITT analysis, the *H. pylori* eradication rate was 84.6% (95% CI, 73.5–92.4) in the preop group and 83.1% (95% CI, 71.7–91.2) in the postop group ($P = 0.99$), suggesting that the effect of *H. pylori* eradication was not significantly different between the group administered the treatment postoperatively and the group administered the treatment preoperatively [41].

To identify the molecular changes in the gastric mucosa following *H. pylori* eradication, Tsai et al. [42] used cDNA microarrays to analyze 54 gastric biopsies obtained in a randomized, placebo-controlled trial of *H. pylori* therapy. The results of the analysis revealed that, while in the eradication group, 30 genes could be identified whose expression levels had changed significantly from the baseline to 1 year after the treatment [42], 55 genes whose expression levels had changed significantly during the 1-year period (32 up- and 23 downregulated) could be identified in the placebo group [42]. Five

genes, involved in cell-to-cell adhesion and lining (*TACSTD1* and *MUC13*), cell cycle/differentiation (*S100A10*), and lipid metabolism and transport (*FABP1* and *MTP*) were downregulated in the eradication group but upregulated in the placebo group during the same 1-year period [42].

Nonrandomized cohort studies (Table 2)

Take et al. [19] reported a prospective cohort study conducted to determine the risk of development of gastric cancer in patients with peptic ulcer diseases; the severity of gastric atrophy was evaluated in this study. Among the 1131 patients followed up for up to 9.5 years, the risk of development of gastric cancer was decreased significantly after *H. pylori* eradication. In addition, the development of gastric cancer was related to the severity of the baseline gastric mucosal atrophy. Analysis with a Cox's proportional hazards model identified persistence of infection (HR, 3.35; 95% CI, 1.00–11.22) as significant factors for the development of gastric cancer [19].

Takenaka et al. [20] conducted a retrospective cohort study to determine the cancer-preventive effect of *H. pylori* eradication (n = 1807) and reported that 6 of 1519 (0.39%) patients in whom *H. pylori* infection was eradicated and 5 of 288 (1.74%) subjects in whom the infection was persistent developed gastric cancer. Kaplan-Meier analysis also indicated a significantly lower incidence of gastric cancer in the group with eradication of *H. pylori* infection than in the group with persistent infection (OR, 0.20; 95% CI, 0.061–0.66) [20].

Case-control studies (Table 3)

Plummer et al. [25] reported, based on the results of examination of gastric biopsy specimens obtained from 2145 participants, that the OR for gastric dysplasia was 15.5 in individuals infected with *cagA*-positive *H. pylori* as compared with that in uninfected individuals and the OR was 0.90 in individuals infected with *cagA*-negative *H. pylori* as compared with that in uninfected individuals. Gwack et al. [22] conducted a nested case-control study of 100 patients with gastric cancer and 400 control subjects to examine the risk of gastric cancer in relation to the virulence factors of *H. pylori* in a Korean cohort. They showed that CagA seropositivity was significantly associated with a higher risk of gastric cancer among *H. pylori*-infected subjects (OR, 3.57; 95% CI, 1.05–12.14) [22].

H. pylori infection, atrophic gastritis, and dietary and lifestyle factors were evaluated as risk factors in a large nested case-control study in the European Prospective Investigation into Cancer and Nutrition trial carried out in nine countries (EPIC-EURGAST study), in 233 patients diagnosed as having gastric cancer after enrolment and 910 control subjects [24]. In a conditional logistic regression analysis conducted with adjustment for education, smoking, body weight, and total consumption of vegetables, fruits, and red and preserved meat, *H. pylori* seropositivity was associated with an increased risk of gastric cancer. The OR associated with severe chronic atrophic gastritis was 3.3 (95% CI, 2.2–5.2). According to site, the risk of noncardia gastric cancer associated with CagA seropositivity was increased further (OR, 6.5; 95% CI, 3.3–12.6); on the other hand, severe chronic atrophic gastritis was associated with a tenfold increase in the risk of gastric cancer of the cardia (OR, 11.0; 95% CI, 3.0–40.9). The causal relationship between infection with *H. pylori* CagA+ strains and gastric cancer in these European populations, even after dietary habits were taken into account, was limited to distal gastric cancer, while a low serum pepsinogen level was strongly associated with gastric cancer of the cardia, thus suggesting a divergent risk pattern for cancer at these two sites [24].

Only a few papers have been published on *H. pylori* infection in gastric cancer patients younger than 40

Table 2. Nonrandomized cohort studies

Author	Year	*n*	Subjects	Study arms	Endpoint	Efficacy (95% CI)	Period
Takenaka et al. [20]	2007	1807	Patients under eradication therapy	Retrospective cohort Eradication 1519 Persistent infection 288	GC	OR 0.20 (0.061–0.66)	39.0 Months 34.6 Months
Ogura et al. [21]	2008	708	Patients diagnosed with *H. pylori* infection	Retrospective cohort Eradication 404 Persistent 304	GC	HR 0.335 (0.114–0.985)	3.1 Years
Take et al. [19]	2007	1131	Patients with peptic ulcer	Prospective cohort Eradication 953 Persistent infection 178	GC	HR Eradication 1.0 Persistent 3.9 (1.2–12.9) Atrophy 3.3 (1.3–8.6)	46.8 Months

n, number of patients; GC, gastric cancer

Table 3. Case–control studies

Author	Year	Subjects (*n*)	Risk factor	OR (95% CI)	Period (years)
Gwack et al. [22]	2006	GC 100 Control 400	CagA(+) vs (–)	3.74 (1.10–12.73)	9
Hansen et al. [23]	2007	Cardia GC 44 Noncardia GC 129 Control 3	Hp infection PG(+)	4.75 (2.59–8.81) 4.47 (2.71–7.37)	11.9
Palli et al. [24]	2007	GC 233 — Noncardia GC 127 — Cardia GC 54 — Mixed GC 4 — Undetermined GC 44 Control 910	Hp IgG (+) vs (–) CagA Ab(+) vs (–) AG (+) vs (–)	2.6 (1.7–3.9) 6.5 (3.3–12.6) for noncardia GC 0.8 (0.4–1.9) for cardia GC 2.4 (1.3–4.5) for noncardia GC 11.0 (3.0–40.9) for cardia GC	6.1
Plummer et al. [25]	2007	All subjects 2145 Dysplasia 120 Control 91	CagA (+) vs uninfected	15.5 (6.42–37.2)	3.5
Masuda et al. [26]	2007	GC (<40) 31 Control 120	Hp infection	13.69 (5.11–36.71)	5
Sasazuki et al. [27]	2006	GC 511 Control 511	Hp IgG(–) PG (–) Hp IgG(–) PG (+) Hp IgG(+) PG (–) Hp IgG(+) PG (+) Hp IgG(+) vs (–) PG(+) vs (–)	1.0 (2.0–12.1) 4.9 (4.5–14.0) 4.2 (2.2–8.0) 10.1 (5.6–18.2) 11.4 (4.4–29.2) 3.2 (1.5–7.0)	5
Sawaya et al. [28]	2008	GC 17 AG 13	P53DINP1 mRNA expression	GC < AG ($P < 0.05$)	Not described
Tatemichi et al. [29]	2008	GC 350 Control 350		Differentiated / Undifferentiated	15
			Hp IgG negative	1.0 / 1.0	
			Hp IgG low	5.9 (3.0–11.6) / 6.4 (2.1–19.6)	
			Hp IgG middle	4.4 (2.2–8.5) / 5.9 (1.9–18.5)	
			Hp IgG high	3.2 (1.6–6.4) / 7.8 (2.4–24.9)	
Watanabe et al. [30]	2006	GC 53 Hp(+) NUD 122	DQB1*0401	2.83 (1.44–5.55)	Not described

n, number of patients; GC, gastric cancer; AG, atrophic gastritis; PG, pepsinogen; NUD, nonulcer dyspepsia; Hp, *H. pylori*

years of age. Masuda et al. [26] reported that the prevalence of *H. pylori* infection was higher in patients with gastric cancer than in patients with a normal endoscopic study or those with chronic gastritis, especially among subjects younger than 40 years old (OR, 13.7). Gastric cancer in patients younger than 40 years is closely associated with *H. pylori* infection.

Meta-analysis

Wang et al. [18] reported the results of a meta-analysis of 87 relevant studies, including 19 case-control studies, conducted to estimate the prevalence of *H. pylori* infection in early gastric cancer. The prevalence of *H. pylori* infection was significantly higher in patients with early gastric cancer than in the noncancer controls (OR, 3.38; 95% CI, 2.15–5.33). The prevalence of *H. pylori* infection among patients with early gastric cancer was significantly higher than that among patients with advanced gastric cancer (OR, 2.13; 95% CI, 1.75–2.59) and the prevalence of the infection was 16-fold higher in patients with differentiated-type early gastric cancer than in those with undifferentiated-type early gastric cancer (OR, 16.53; 95% CI, 2.64–103.43). They concluded that the prevalence of *H. pylori* infection was significantly higher in patients with early gastric cancer as compared with that in noncancer controls or patients with advanced gastric cancer, which suggests a causal relationship between *H. pylori* infection and early gastric cancer [18].

Polymorphisms and H. pylori*-associated gastric cancer (Table 4)*

The interplay between bacterial factors and host gene polymorphisms may explain why gastric cancer occurs in only a small fraction of *H. pylori*-infected cohorts. Polymorphisms of the interleukin-1 beta gene (*IL-1B*) and interleukin-1 receptor antagonist gene (*IL-1RN*) have been shown to be associated with an increased risk of gastric atrophy and cancer, especially in *H. pylori*-infected subjects. In an Omani Arab population, while *IL-1RN* polymorphism was found to be associated with an increased risk of gastric cancer, consistent with previous reports [43], the *IL-1B -31* polymorphism was not associated with increased gastric cancer risk [31], sup-

Table 4. Genetic polymorphisms associated with the development of gastric cancer

Authors	Year	Country	Patients (*n*)	Polymorphism associated with enhanced risk	Odds ratio (95% CI)
Al-Moundhri et al. [31]	2006	Oman	GC 118 Control 245	IL-1RN -2018*2 IL-1RN -2018*2 Hp(+) IL-1B -31, -511, and +3954	2.2 (1.0–3.3) 3.5 (1.0–11.9) NS
García-González et al. [50]	2007	Spain	GC 404 Control 404	IL-1B, IL-1RN, IL-12p40, LTA,IL-10, IL-4, TGF-B1	NS
Hou et al. [33]	2007	Poland	GC 305 Control 427	TNFA -308 G/A TNFA -308 A/A IFNGR2 Ex7-128 T/C IFNGR2 Ex7-128 C/C	1.4 (1.0–2.0) 2.5 (1.3–4.9) 1.5 (1.0–2.3) 1.7 (1.1–2.7)
Kubben et al. [34]	2006	Netherlands	GC 79 Control 169	MMP-7 MMP-2, -8, -9 TIMP-1, -2	0.50 (0.28–0.87) NS
Masuda et al. [26]	2007	Japan	GC (<40) 31 (60–70) 231 (80 <) 38	P4502E1 (CYP2E1)	NS
Prasad et al. [35]	2008	India	GC 62 Control 241	PPARγ G carrier PPARγ G carrier Hp(+)	2.14 (1.11–4.10) 3.05 (1.20–7.81)
Seno et al. [36]	2007	Japan	GC 100 NUD 93	IL-4- 984 and 2983 AA/GA IL-1RN- 1102 and 6110 CG/GA (>66 years) IL-1alpha, IL-1beta, IL-4R, IL-8, IL-10, IL-12, TNF-alpha, INF-beta, IFN-gamma	0.3 (0.1–0.9) 0.2 (0.1–0.7) NS
Shirai et al. [37]	2006	Japan	GC 181 Control 482	IL-8-251 T/T for MSH IL-8-251, IL-1B-511, IL-1RN, TNFA-857	5.2 (1.5–18.0) NS

n, number of patients; NS, not significant; GC, gastric cancer; NUD, nonulcer dyspepsia; Hp, *Helicobacter pylori*

porting the notion of ethnic differences in the effect of *IL-1B* polymorphism on gastric carcinogenesis. According to a study by Zabaleta et al. [44], the presence of the *IL1B+3954T* allele was a risk marker for multifocal atrophic gastritis in the population studied. Seno et al. [36] reported, based on a study of 207 single-nucleotide polymorphisms (SNPs), that polymorphisms of the *IL-4* and *IL-1RN* genes were negatively associated with the risk of development of gastric cancer associated with *H. pylori* infection.

On the other hand, the *IL-8 -251 T/T* genotype was associated with a significantly increased risk of high-frequency microsatellite instability (MSI-H) gastric cancer compared with that of low-frequency MSI (MSI-L) or MSI-stable gastric cancers and noncancer controls [37]. The *MPO -463G/G* genotype, which is associated with increased myeloperoxidase (MPO) expression and antral IM, has been reported to be a risk factor for gastric cancer arising from the antrum [45].

In relation to the association of gastric cancer with polymorphisms of genes responsible for Th1-cell-mediated immune responses, Hou et al. [33] concluded, from a population-based study of 305 gastric cancer cases and 427 age- and sex-matched controls in Poland, that two Th1-related polymorphisms (TNFα -308 A > G and IFNγR2 Ex7–128 C > T) may be associated with an increased risk of gastric cancer.

Matrix metalloproteinase (MMP)-related SNPs, especially MMP-7(-181A > G) and TIMP-2(303C > T), might be helpful in identifying gastric cancer patients with a poor clinical outcome [34]. The *TGFB1 T+869C* gene polymorphism was shown to be involved in susceptibility to duodenal ulcer, but not in that to gastric cancer [32]. While 8-hydroxy-2′-deoxyguanosine (8-oxo-dG) levels in the gastric mucosa were increased in carriers of *H. pylori*, the levels were significantly higher in a small subset of subjects having a homozygous variant allele of the 8-oxoguanosine-glycosylase 1 (*OGG1*) gene, which codes for the enzyme removing 8-oxo-dG from DNA [46]. The Pro12Ala PPARγ polymorphism has also been shown to be associated with the development of gastric cancer, and is a potential marker of genetic susceptibility to gastric cancer with *H. pylori* infection [35].

E-Cadherin is an adhesion molecule thought to be involved in the development of gastric cancer. Germline mutations in the E-Cadherin gene (*CDH1*) have been identified in hereditary diffuse gastric cancer, and a promoter polymorphism at position -160 C/A of *CDH1* has been shown to influence the risk of gastric cancer in some studies [47, 48]. However, Jenab et al. [49] reported that none of the *CDH1* polymorphisms or haplotypes analyzed were associated with gastric cancer risk.

Furthermore, according to a report by Garcia-Gonzalez et al. [50], at least in some white populations examined in Spain, the contribution of the cytokine gene polymorphisms evaluated (*IL-1B*, *IL-1RN*, *IL-12p40*, *LTA*, *IL-10*, *IL-4*, and *TGF-B1*) to gastric cancer susceptibility may be less relevant than previously reported. Furthermore, although gastric cancer in

patients younger than 40 years of age was shown to be closely associated with *H. pylori* infection, it was not associated with genetic polymorphism of *P4502E1* (*CYP2E1*) [26].

Dietary factors

Food factors seem to have a very important influence on the risk of development of gastric cancer. According to the EPIC-EURGAST study conducted by Gonzalez et al. [38], while there seemed to be no evidence of any association between fresh fruit intake and gastric cancer risk, a negative association was possible between total vegetable (calibrated HR, 0.66; 95% CI, 0.35–1.22 per 100-g increase) and onion/garlic intake (calibrated HR, 0.70; 95% CI, 0.38–1.29 per 10-g increase) and the risk of development of intestinal-type gastric cancer. They also reported that the risk of noncardia gastric cancer was statistically significantly associated with the total intake of meat (calibrated HR per 100-g/day increase, 3.52; 95% CI, 1.96 to 6.34), red meat (calibrated HR per 50-g/day increase, 1.73; 95% CI, 1.03 to 2.88), and processed meat (calibrated HR per 50-g/day increase, 2.45; 95% CI, 1.43 to 4.21), and they noted that this association between the risk of noncardia gastric cancer and total meat intake was especially pronounced in *H. pylori*-infected subjects (OR per 100-g/day increase, 5.32; 95% CI, 2.10 to 13.4) [39].

Japanese guideline on the diagnosis and treatment of *H. pylori* infection

According to the previous guideline for physicians on the diagnosis and treatment of *H. pylori* infection in routine medical practice published by the Japanese Society for *Helicobacter* Research (JSHR) [51], *H. pylori* eradication therapy was recommended in patients with low-grade duodenal ulcer. Although eradication therapy was also recommended for patients with low-grade gastric mucosa-associated lymphoid tissue (MALT) lymphomas, it was suggested that this be undertaken only at specialist institutions. Furthermore, the significance of *H. pylori* eradication therapy after endoscopic mucosal resection or gastrectomy for gastric cancer was still under evaluation, as was that in patients with hyperplastic polyps, chronic atrophic gastritis, or nonulcer dyspepsia. However, according to the recently updated guideline by the JSHR, *H. pylori* eradication is recommended at recommendation level A; i.e., based on strong scientific evidence, for all patients with *H. pylori* infection. A previous nonrandomized study [13] and recent open-label RCT [15] showed that *H. pylori* eradication after endoscopic resection for early gastric cancer could prevent the development of metachronous gastric cancer.

As for the *H. pylori* eradication treatment, triple therapy, consisting of amoxicillin (AMX) and clarithromycin (CLR), along with a proton pump inhibitor (PPI), was officially authorized in the year 2000 as the first-line regimen for *H. pylori* eradication in Japan. Then, in 2007, the combination of metronidazole (MNZ), AMX, and a PPI was approved as a second-line regimen. Although the *H. pylori* eradication rate following first-line treatment was around 90% in 2000 [52], it has declined in recent years to less than 80%. Such eradication failure has been attributed mainly to the development of antibiotic resistance to CLR [53] (primary resistance rate, 9.1% [54]; secondary resistance rate, 79.2% in Japan). Under such circumstances, the regimen for *H. pylori* eradication was switched to the second-line regimen consisting of AMX, MNZ, and a PPI [55, 56]. Even after treatment with the second-line regimen, a large-scale multicenter study in the Tokyo Metropolitan area showed that eradication failure was still observed in approximately 10% of patients [57], suggesting an increasing demand for the development of third-line regimens.

In 2009, the JSHR has just established a board certification system for doctors treating *H. pylori* infection; the JSHR aims to standardize the diagnostic and therapeutic medical skills required to eradicate this bacterium in Japan.

Summary

In summary, the association between *H. pylori* and the development of gastric cancer is now more clearly established than before. As announced by the JSHR recently, *H. pylori* eradication should be undertaken in all subjects who are infected, based on all the accumulated scientific evidence. For this purpose, standard effective *H. pylori* eradication protocols, including third-line regimens, should be urgently developed. Rokkas et al. [58] reported that, by adopting the first- and second-line regimens proposed by the Maastricht III consensus and a levofloxacin (LEV)-based regimen as the third-line regimen, high cumulative eradication rates, of 89.6 % (ITT) and 98.1% (per protocol; PP), were achieved. Quinolones are one of the most suitable candidate categories for a third-line regimen [58, 59], even though a high resistance rate to gatifloxacin (43%) was reported in *H. pylori* isolated from patients with first- and/or second-line eradication failure [53]. Recently, a new generation of quinolones (e.g., sitafloxacin and garenoxacin) has been developed; in-vitro, these have been shown to overcome the resistance of *H. pylori* strains that have resistance-determining *gyrA*

mutations, and these quinolones are expected to be tested clinically [60]. Another possible candidate component for a third-line eradication regimen is rifabutin [61], which has very low resistance rates at present in Japan, although there remains the problem of cross-resistance to rifampicin [62]. The efficacy of the above-mentioned candidate agents should be carefully evaluated in well-designed clinical trials.

In conclusion, we emphasize that, even after eradication of *H. pylori* has been achieved in patients with high-risk gastric mucosa (frequently seen in older subjects with severe gastric atrophy), endoscopic surveillance for gastric cancer should not be omitted in such high risk patients.

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