

Helicobacter pylori Infection and Risk of Gastric Cancer in Korea: A Quantitative Systematic Review

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Objectives: In the context of the global decrease in mortality due to gastric cancer, previous studies have reported that the effect of chronic *Helicobacter pylori* (*H. pylori*) infection on the incidence of gastric cancer varies among regions. This systematic review was conducted to investigate *H. pylori* as a risk factor for gastric cancer in Korea, where the incidence of gastric cancer is among the highest in the world.

Methods: A search strategy was established to identify articles published in Korean as well as in English. Ultimately, we included observational studies conducted among Korean patients that designed with an age-matched and sex-matched control group that reported the odds ratio associated with *H. pylori*. Gastric cancer cases were subdivided into overall (OGC), cardia (CGC), non-cardia (NGC), early (EGC), advanced, intestinal (IGC), and diffuse forms of gastric cancer. Summary odds ratios (SORs) with 95% confidence intervals (CIs) were calculated in the meta-analysis using a random-effect model.

Results: Eleven case-control studies were ultimately selected. *H. pylori* was associated with an SOR of 1.81 (95% CI, 1.29 to 2.54) for OGC. Additionally, statistically significant risks were observed for CGC, NGC, EGC, and IGC.

Conclusions: Chronic *H. pylori* infection was found to raise the risk of gastric cancer among Koreans, with the highest risk observed for CGC and EGC (SOR=2.88 for both). Follow-up clinical epidemiologic studies are needed to assess the effects of current treatments aimed at eradicating *H. pylori* infections.

Key words: Stomach neoplasms, *Helicobacter pylori*, Risk factors, Meta-analysis, Korea

INTRODUCTION

Gastric cancer is responsible for 8% of global cancer cases [1]. However, the global death rate due to gastric cancer has

decreased over the past decades [2-4], which has been explained as resulting from changes in dietary habits and the decreased prevalence of chronic *Helicobacter pylori* (*H. pylori*) infections [1,5-7]. The incidence and mortality rates of gastric cancer have also decreased in Korea, where its incidence has been found to be among the highest worldwide [4,8]. This trend has likewise been explained by a decrease in the prevalence of *H. pylori* [2,9].

Since *H. pylori* was first described in scientific circles in 1984 [10], it has been recognized as the most significant risk factor for the incidence of gastric cancer [4,11-13]. The relative risk ratio of *H. pylori* for gastric cancer was reported to be approximately six in epidemiologic studies performed in the early

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2000s [14,15]. However, a systematic review of studies published through June 2009 found that *H. pylori* infection was associated with a 3.02 times higher risk of non-cardia gastric cancer (NGC) in areas with a high incidence of gastric cancer, which is approximately 50% of the risk reported in earlier studies, whereas no statistically significant association was found between *H. pylori* infection and cardia gastric cancer (CGC) [16].

However, only three studies published in English [17-19] were considered in the selection process of the systematic review conducted by Cavaleiro-Pinto et al. [16], and none were published in Korean. Hence, it was necessary to conduct a quantitative systematic review with a search period extending until December 2015 that included articles published in Korean. Thus, the purpose of this study was to conduct a systematic review to investigate the effect of *H. pylori* infection on the incidence of gastric cancer among Koreans.

METHODS

Search Strategy and Study Selection

We searched for previous studies on *H. pylori* infection as a risk factor for gastric cancer among Koreans. The search formula was [(gastric OR stomach) AND (cancer OR neoplasms) AND (Helicobacter OR pylori) AND (Korea OR Korean)]. In addition to PubMed, we used the KoreaMed, the Korean Medical Database (KMBase), the Korean Studies Information Service System (KISS), and the Research Information Sharing Service (RISS4U). In addition to the publications that were retrieved, the cited articles were separately added to the selection list.

After removing duplicates from the lists, laboratory studies, studies with different hypotheses, reviews, and systematic reviews were eliminated. Studies including the same gastric cancer patients in specific cohorts or medical institutions with overlapping time periods were considered to be duplicates and were eliminated, while we selected the study that included the greatest number of gastric cancer patients selected as representative of a given set of patients. Thus, the final selection criteria for our meta-analysis were as follows: (1) an article must have been an analytical epidemiology study on gastric cancer among Koreans; (2) information was provided about the risk associated with *H. pylori*; (3) if it was a case-control study, the control group was selected through age-matching and sex-matching.

The eligibility of each abstract or full-text article was as-

sessed independently in a standardized manner by two reviewers. Disagreements between reviewers were resolved by consensus.

Information Extraction

The odds ratios (ORs) for gastric cancer incidence associated with *H. pylori* infection and the 95% confidence intervals (CIs) were extracted. The standard error of the logarithm of the OR was calculated by applying the formula $[\ln(OR_{upper}) - \ln(OR_{lower})] / 3.92$ based on the 95% CI [20]. The ORs specified for each study were divided into two types: frequency-matched (FORs), which were calculated based on frequencies after sex-matching and age-matching, and adjusted (AORs), which were adjusted for other covariates after the matching process.

Information related to how *H. pylori* infections were determined and the types of gastric cancer types assessed was extracted. The cases were divided into early gastric cancer (EGC) and advanced gastric cancer (AGC) depending on the degree of gastric cancer progression, and when that information was not available, cases were categorized as overall gastric cancer (OGC). Cases were categorized as CGC and NGC according to the region of incidence. Cases were also categorized according to their histopathology as diffuse-type (DGC), intestinal-type (IGC), and mixed-type (MGC). Cases were classified according to the measurement method of *H. pylori* infection, depending on whether an enzyme-linked immunosorbent assay for immunoglobulin G antibodies within the serum was used or *Campylobacter*-like organism tissue staining using urease.

Statistical Analysis

Heterogeneity was defined as a Higgins' I^2 value $> 50\%$ [21]. A meta-analysis was conducted using a random effect model to calculate the summary odds ratio (SORs) and 95% CIs. Egger's test for small-study effects was used when applicable [22]. Subgroup analyses were conducted for gastric cancer type, *H. pylori* measurement method, and OR type. A p -value < 0.05 was considered to indicate statistical significance, and Stata/SE version 14.0 (StataCorp., College Station, TX, USA) was used for meta-analysis and forest plot.

RESULTS

Final Selection of Related Articles

A list of 4239 articles was retrieved from our electronic search of KoreaMed, KMBase, KISS, RISS4U, and PubMed. Fifty-

Table 1. Articles selected and excluded due to including the same gastric cancer cases

Sources	Reference number	
	Selected	Excluded
Korean Multi-Center Cancer Cohort	23	19, 24-28
Seoul Bundang Hospital	29	30-35
National Cancer Center Hospital	36	37, 38
Hallym/Hanyang University Hospital	39	40, 41

seven additional articles were identified by a manual search of the references. When duplicates were eliminated from the combined list, 1082 abstracts remained. Based on a review of the study titles and abstracts, 381 laboratory studies, 528 studies with different hypotheses, and 117 expert or systematic reviews were eliminated. Once the full texts were obtained, we reviewed 56 articles. Subsequently, we eliminated 10 papers in which the control group was selected without age-matching and sex-matching, 19 papers without information necessary for the meta-analysis, and 16 papers drawing on duplicate patient groups. Ultimately, 11 case-control studies were selected for the meta-analysis (Table 1, Figure 1).

Results of the Meta-analysis

Table 2 presents the information extracted from the 11 articles, categorized according to the area of incidence, clinical stage, and histological pattern [17,23,29,36,39,42-47]. OGC-related information was obtained from eight articles [17,23,29,36,39,44-46], while four articles contained information on EGC [36,42,43,47], Only one article discussed MGC [36], and MGC was therefore eliminated from the following meta-analysis.

Figures 2 and 3 show forest plots for each gastric cancer type. In the eight OGC articles, *H. pylori* infection was observed to increase the risk of gastric cancer by 1.81 times (95% CI, 1.29 to 2.54; $I^2=84.4\%$). The CGC and EGC articles showed the highest SORs (SOR=2.88 in both), which was a statistically significant finding.

OGC, NGC, DGC, IGC, and EGC showed I-squared values >75%, and Egger's test was thus performed. All *p*-values for publication bias were confirmed to be >0.10, indicating that no small-scale study effects were present (not shown).

Table 3 illustrates the results of subgroup analyses conducted on articles that reported AORs and detected *H. pylori* infections using serum antibodies. Our findings remained statistically significant for OGC, CGC, and NGC, whereas statistical significance was lost for EGC and DGC in this sub-analysis.

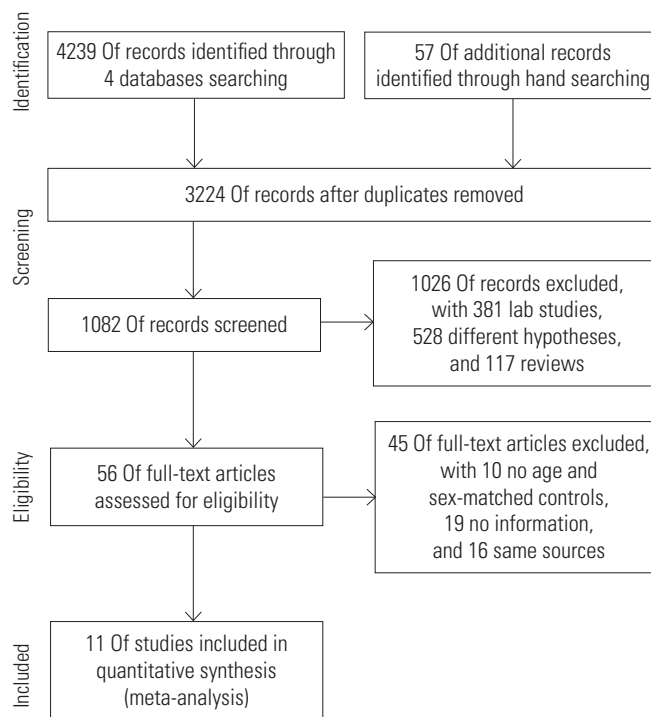


Figure 1. Systematic review flow chart.

DISCUSSION

Chronic *H. pylori* infection was confirmed to be a major risk factor for gastric cancer among Koreans, as it was associated with an SOR of 1.81 (95% CI, 1.29 to 2.54). Furthermore, for CGC and NGC, the SOR was found to be 2.88 (95% CI, 2.15 to 3.87) and 2.37 (95% CI, 1.32 to 4.26), respectively, confirming that the area of the incidence of cancer was not significantly affected by *H. pylori*. These SORs are similar to the results reported in the meta-analysis conducted by Cavaleiro-Pinto et al. [16] on high-risk populations. For CGC, the carcinogenic mechanism was confirmed to be distinctly different in the Far East and the West [2,48,49]. While Hansen et al. [49] reported that NGC was less common and CGC was more common in the West, this pattern has not been observed among Koreans [50], although additional studies are needed in the future.

Furthermore, IGC has become less common and DGC has become more common in the West [2]. This pattern has not been found among Koreans [50], although IGC has been found to increase with age [51]. The present study showed that *H. pylori* infection significantly raised the risk of IGC (SOR, 1.88; 95% CI, 1.01 to 3.47), but not the risk of DGC (SOR, 1.58; 95% CI, 0.63 to 3.95). Although proposals have been made re-

Table 2. Summary table of information extracted from the selected case-control studies

First author (year of publication) [Ref]	Inclusion period	Type of cancer	No. of cases /controls	Test for <i>H. pylori</i>	Type of OR	OR	95% CI
Kim (1997) [17]	1994	O	160/160	U&H	F	1.39	0.89, 2.17
		C	12/12		F	1.43	0.27, 7.52
		N	148/148		F	1.39	0.88, 2.20
		D	63/63		F	1.40	0.68, 2.87
		I	97/97		F	1.39	0.79, 2.45
Kim (2000) [42]	Nov 1996 to Jul 1998	E	79/33	IgGAb	F	0.88	0.42, 1.83
		A	208/33		F	0.72	0.32, 1.64
Chang (2002) [39]	May 1997 to Oct 1998	O	136/136	IgGAb	J	1.82	1.10, 3.00
Lee (2003) [43]	Mar 1999 to Sep 1999	E	69/199	IgGAb	J	5.30	1.70, 16.5
Kim (2005) [44]	Aug 1997 to Jul 1998	O	295/295	IgGAb	J	1.71	1.13, 2.58
Gwack (2006) [23]	1993-2002	O	100/400	IgGAb	J	0.96	0.68, 1.36
Cho (2010) [36]	Jun 2003 to Apr 2007	O	2819/562	IgGAb	J	3.13	2.46, 3.97
		E	1244/562		J	3.01	2.27, 4.01
		A	1575/562		J	2.94	2.24, 3.85
		C	216/562		J	2.98	2.16, 4.02
		N	2603/562		J	3.17	2.48, 4.04
		I	1349/562		J	3.00	2.24, 3.93
		D	974/562		J	3.15	2.45, 4.05
		M	102/562		J	2.56	1.82, 3.58
Chung (2012) [45]	Jan 2004 to Oct 2010	O	277/1108	IgGAb	J	1.16	0.77, 1.76
		I			J	1.31	0.62, 2.86
		D			J	0.81	0.45, 1.45
Kim (2012) [29]	Jun 2003 to Feb 2011	O	829/279	IgGAb	F	2.49	1.78, 3.49
		C	60/270		J	2.62	0.90, 7.65
		N	769/270		J	3.06	1.90, 4.93
Gong (2014) [46]	Apr 2000 to Dec 2010	O	327/327	IgGAb	J	2.93	1.88, 4.59
Woo (2014) [47]	Apr 2011 to May 2014	E	334/334	U&H	F	4.93	3.42, 7.10

Ref, reference number; OR, odds ratio; CI, confidence interval; A, advanced; C, cardia; D, diffuse; E, early; I, intestinal; M, mixed; N, non-cardia; O, overall; IgGAb, immunoglobulin G antibody test; U&H, rapid urease test and histological evaluation; F, frequency matching; J, adjusted for covariates.

Table 3. Subgroup analysis of SORs and 95% CIs according to the test for *H. pylori*, and the type of OR

	ELISA		Adjusted OR	
	No. of articles	SOR (95% CI)	No. of articles	SOR (95% CI)
OGC	7	1.88 (1.30, 2.72)	6	1.79 (1.15, 2.77)
EGC	3	2.31 (0.93, 5.75)	2	3.11 (2.36, 4.10)
CGC	2	2.95 (2.19, 3.98)	2	2.95 (2.19, 3.98)
NGC	2	3.16 (2.50, 4.00)	2	3.16 (2.50, 4.00)
DGC	2	1.64 (0.43, 6.20)	2	1.64 (0.43, 6.20)

SOR, summary odds ratio; CI, confidence interval; OR, odds ratio; ELISA, enzyme-linked immunosorbent assay; O, overall; GC, gastric cancer; E, early; C, cardia; N, non-cardia; D, diffuse.

garding how *H. pylori* leads to gastric cancer, such as atopic gastritis or intestinal metaplasia [52,53], additional studies are needed among Koreans to elucidate this mechanism.

A statistically significant SOR of *H. pylori* for gastric cancer was found for EGC (SOR, 2.88; 95% CI, 1.55 to 5.38), but not for AGC (SOR, 1.54; 95% CI, 0.39 to 6.08). These findings should be interpreted with caution because only two studies evaluated AGC.

The present systematic review had some limitations. First, all 11 articles were case-control studies. The case group in the study of Gwack et al. [23] was unlike the others in that the data source was a cohort, but the study design incorporated a control group within the cohort (a nested case-control study). Moreover, the other studies had a significant risk of uncon-

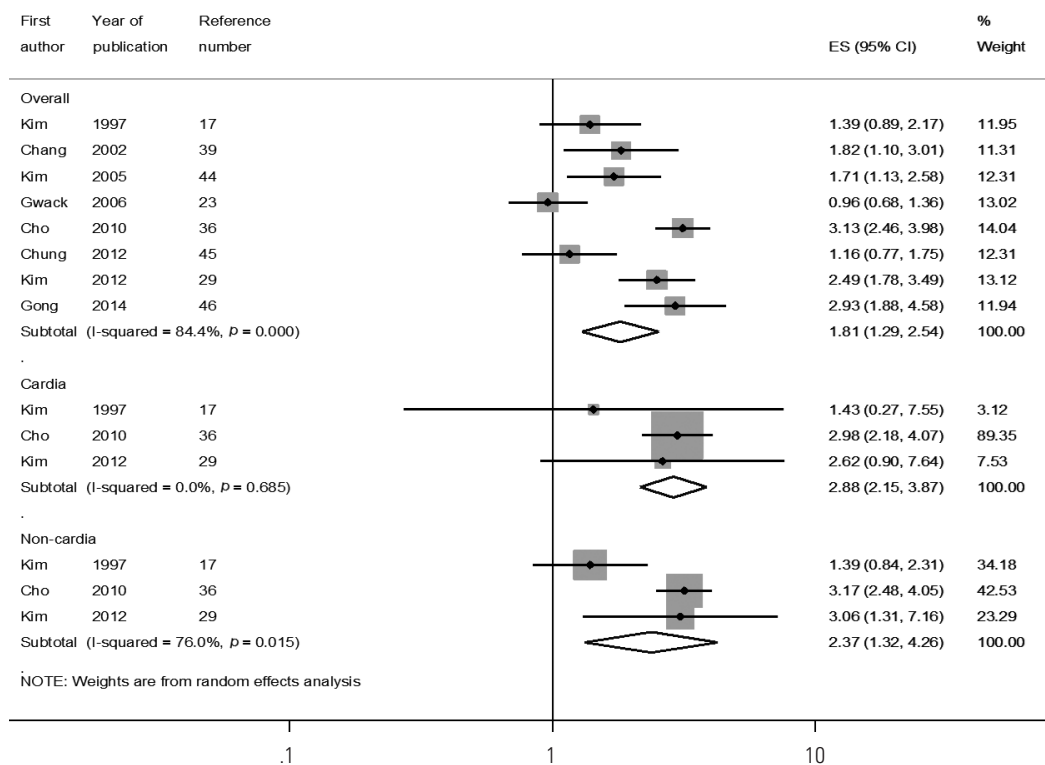


Figure 2. Summary effect size (ES) of *Helicobacter pylori* infection on overall, cardia, and non-cardia gastric cancer in Korean.

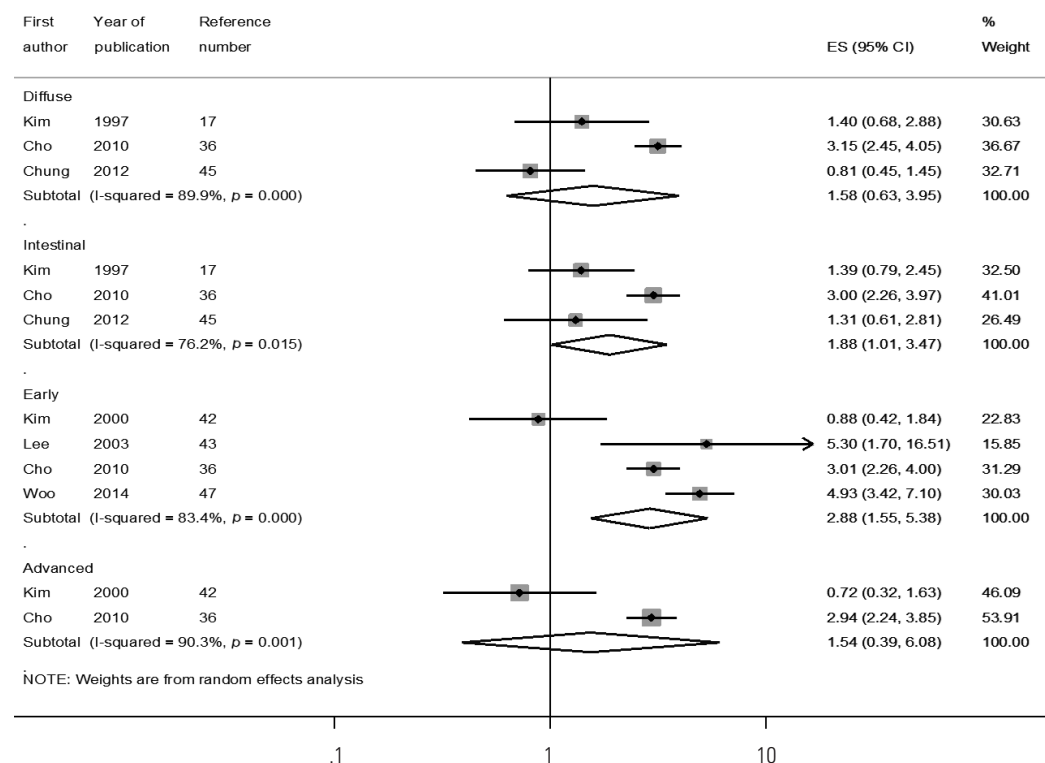


Figure 3. Summary effect size (ES) of *Helicobacter pylori* infection on diffuse type, intestinal type, early, and advanced gastric cancer in Korean.

trolled biases in that they were all hospital-based case-control studies with outpatient subjects [54]. The *H. pylori* infection rate may be different in the general public, which could cause problems regarding the inferences drawn in those studies [55]. Considering this limitation, subgroup analyses were carried out of studies reporting FORs and AORs. Additionally, only two articles addressed AGC and one article addressed MGC, and only Gwack et al. [23] obtained information on cytotoxin-associated antigen and vacuolating cytotoxin, which are known to be the virulence factors of *H. pylori* that mediate carcinogenesis [11,57]. Additional studies are required to address these limitations.

CONCLUSION

Chronic *H. pylori* infection was found to increase the risk of gastric cancer by 1.81 times in Koreans, with the highest risk observed for CGC and EGC (SOR = 2.88 for both). Clinical epidemiologic studies are needed on the effects of treatments intended to eradicate *H. pylori* [58], and such a study is currently being conducted on patients with *H. pylori* with the goal of gastric cancer prevention.

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CONFLICT OF INTEREST

The authors have no conflicts of interest associated with the material presented in this paper.

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