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REVIEW

The Korean Perspective of Helicobacter pylori Infection: Lessons from Japan Policy to Prevent Gastric Cancer

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The guideline of the Korean College of *Helicobacter* and Upper Gastrointestinal Research group for *Helicobacter pylori* infection was first produced in 1998. Definite indication for *H. pylori* eradication is early gastric cancer in addition to the previous indications of peptic ulcer (PUD) including scar lesion and marginal zone B cell lymphoma (MALT type). Though treatment regimen was similar, Japan government declared the inclusion of *H. pylori* eradication in patients with *H. pylori*-associated chronic gastritis, suggesting the treatment guideline is quite different between Korea and Japan from February 21, 2013. The prime rationale of Japanese extended treatment guideline for *H. pylori* infection was based on the drastic intention to prevent gastric cancer according to their beliefs that *H. pylori* eradication can decrease gastric cancer incidence as well as mortality. In this review, the discrepancy in treatment guideline between Korea and Japan will be explained. **(J Cancer Prev 2013;18:107-112)**

Key Words: Helicobacter pylori, Inflammation, Gastric cancer, Chemoprevention, siTRP

INTRODUCTION

The principle of "innocent until proven guilty" isaccepted in the legal field of society, but in the field of infectious diseases, the principle of "guilty until proven innocent" applies, a part of Koch's definition of infection. In case of *Helicobacter pylori* infection, despite of International Agency for Research on Cancer (IARC)'s definition that *H. pylori* is class I, definite, carcinogen for gastric cancer, the principle "the eradication of *H. pylori* can decrease or prevent gastric cancer" remains obscure and under debates.[1] Though proactive preventive measures are adopted for cancers that are suspected to be caused by infection, for instances, hepatitis B and C virus, human papilloma virus, and some other parasite or protozoa for the prevention of hepatocellular carcinoma, cervical or esophageal cancer, bladder cancer, *etc*, and thereby resulting in a reduction of cancer related deaths, obscure debates still exist between *H. pylori* infection and the prevention of gastric cancer. Based on enormous medical costs that the cost of gastric cancer treatment in Japan has been reported currentlyaround 300 billion yen per year and will exceed 500 billion yen annually if measures are not taken for a decade or so, the Japanese government decided to eradicate *H. pylori* in patients with gastritis, indication not permitted in Korea yet, from February 21, 2013.[2-4] These facts cast the homework "should we follow up Japanese decision or collect more evidences for Korean population?" to our Korean College of Helicobacter and Upper gastrointestinal Research and the Korean Society of

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cancer Prevention. We can't just observe Japanese government belief that potentially, it might be possible to eliminate gastric cancer-related deaths from Japan around the middle of this century, but the problems might be either the shortage of Korean government effort or insufficient evidences to persuade government policy maker sue to lack of convincing clinical evidence. In this review, the Korean perspective of *H. pylori* infection as well as Japanese efforts will be described in this background.

LINK BETWEEN *H. PYLORI* INFECTION AND GASTRIC CANCER; OUTCOMES FROM CLINIC

Gastric cancer is the second most common cause of cancer deaths worldwide. Until the early 20th century, Europe and the United States suffered a high incidence of gastric cancer, of course, very high incidence as well as mortality in Asian including Japan, Korea, China, and Russia, but with the changes in life style such as improved sanitation and the widespread adoption of refrigeration for food preservation, the incidence of gastriccancer rapidly decreased coincidently. However, in spite of the drastic advancement of health care system and endoscopic screening in Japan and Korea, still gastric cancer threatened population and notorious statistics showing 20-50 mortality per 100,000 populations is put forwarded.[5] Besides of *H. pylori* infection, dietary factors such as excessive intake of salt or nitrates and hidden hereditary factors are still hurdle to be solved. Among these risks ranked, the proportion of *H. pylori* infection is still high supported with definition that in 1994, *H. pylori* was classified as a definite carcinogen by the IARC of the World Health Organization.[1] Since that time, many clinical studies have been conducted to examine how eradication of *H. pylori* might contribute to the prevention of gastric cancer, but the results was proven to be ambiguous, half of trials supported the eradication to achieve the gastric cancer prevention, but the remains negative outcome. These discrepancies might be explained as arelatively low incidence of gastric cancer, the relatively short duration of available studies, the lack of risk stratification, differences in eradication times, and differences in observation periods.[6,7] Among these trials, in 2008, a multicenter clinical study was conducted in Japan to examine the incidence of new gastric cancer afterendoscopic submucosaldissection or mucosal resection (ESD or EMR) in high-risk patients with earlygastric cancer who were randomly allocated to eradication of *H. pylori* group by Fukase *et al*.[8] The study concluded that *H. pylori* eradication resulted in a reduction in the incidence of new gastric cancers by approximately one-third, thus demonstrating the efficacy of *H. pylori* eradication in reducing the incidence of gastric cancer. Though eradication could not completely prevent metachronous gastric carcinogenesis, but statistically eradication provide clear benefit to prevent secondary gastric cancer. Along with the evidence that Uemura *et al*'s NEJM paper[9] that *H. pylori* infection is associated with gastric carcinogenesis in Japan, these Lancet paper stimulated government policy maker to conclude that *H. pylori* infection played an important role in the development of Japanese gastric cancer and that *H. pylori* eradication could prevent or reduce the incidence of gastric cancer, releasing a new strategy to eliminate gastric cancer through eliminating *H. pylori* in patients with gastritis in Japan at February 21, 2013.[4] The new strategy could be one that combined primary prevention by *H. pylori* eradication with secondary prevention using surveillance of high-risk patients.

In Japan, *H. pylori* infection was approved as an official disease name in the 2003 edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). *H. pylori* infection itself is soon expected to be accepted by the Japanese national health scheme as a disease entity. According to the Guidelines for the Management of *Helicobacter pylori* Infection in Japan: 2009 Revised Edition of the Japanese Society of Helicobacter Research (JSHR), *H. pylori* eradication has, based on strong evidence, been strongly recommended as level A (minds recommendation grades) for all *H. pylori* infections. In the guidelines, the level of evidence for each recommendation was classified from Level I to Level VI. For example, peptic ulcer, ITP, atrophic gastritis, and FD were categorized as Level I. In contrast, early gastric cancer post-endoscopic treatment, gastric hyperplastic polyp, and reflux esophagitis were categorized as Level II (supported by at least one randomized controlled clinical trial),

while gastric MALT lymphoma, iron-deficiency anemia, and chronic urticaria were categorized as Level III.[10]

In Korea, eradication should be considered in subjects younger than 40 years who have a family history of gastric cancer and in subjects with long-term medications that might lead to bleeding (anti-platelet agents) or atrophy (proton pump inhibitors) as well as peptic ulcer diseases, MALT lymphoma, and NSAID administration Beyond these currently accepted indications, including various upper gastrointestinal disorders and extra-gastric diseases, a significant amount of new information regarding *H. pylori* eradication is emerging. Certain types of acute gastritis, such as nodular gastritis, hypertrophic gastritis, Ménétrier's disease, hemorrhagic gastritis, and granulomatous gastritis are reversible after *H. pylori* eradication.[11] Further, for chronic gastritis, closed-type atrophic gastritis and complete-type intestinal metaplasia appear to be more reversible after *H. pylori* eradication than open-type atrophic gastritis and incomplete-type intestinal metaplasia. Emerging evidence indicates that *H. pylori* eradication could be an effective treatment for some extragastric diseases that are unresponsive to conventional therapy.[12] Future indications for *H. pylori* eradication should focus more on reversible lesions before preneoplastic conditions develop, but not now in Korea.

Additionally, functional dyspepsia is the most common reason for patients to experience chronic epigastric pain or discomfort of which causes are quite multifactorial. However, *H. pylori* infection is one likely candidate. Since *H. pylori* infection clearly results in chronic mucosal inflammation in the stomach and duodenum, which might lead to abnormalities in gastroduodenal motility and sensitivity.[13] Chronic gastritis might affect a variety of endocrine functions of the stomach including the production of the gastrointestinal hormones and neurotransmitters somatostatin, gastrin and ghrelin. However, more evidences should be accumulated more to eradicate *H. pylori* in order to improve functional dyspepsia. This evidence has led to alterations in most of the major guidelines throughout the world, which now recommend *H. pylori* eradication in patients with functional dyspepsia if they test positive for this bacterium. With the accumulated proof from gastric cancer prevention through *H. pylori* eradication, more high level of proof will be set for functional dyspepsia since eradication of *H. pylori* was commenced in *H. pylori*-associated chronic gastritis, mostly presenting with symptoms of functional dyspepsia.

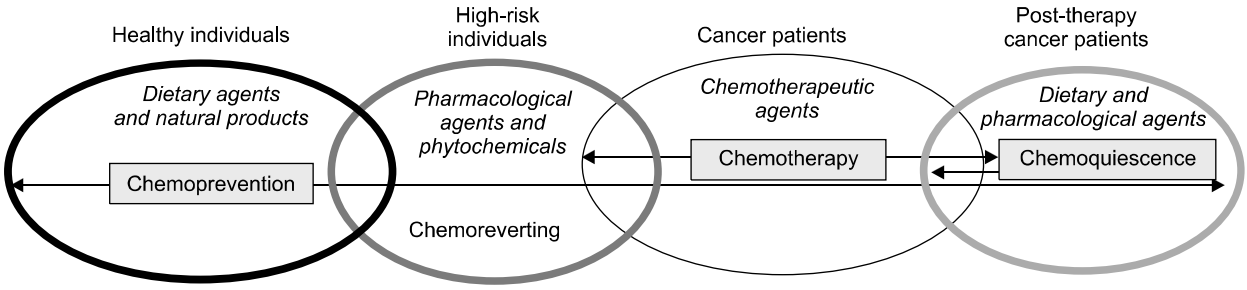
LINK BETWEEN *H. PYLORI* INFECTION AND GASTRIC CANCER; OUTCOMES FROM BENCH

H. pylori is a gram-negative, flagellated bacterium that expresses catalase and urease, enzymes which help neutralize host responses and enable intragastric colonization, these facts led to the development of accurate diagnostic tests, including the rapid urease test (RUT) and the urea breath test (UBT), very essential and core diagnostic modality in clinic exceeding direct bacterial cultures for diagnosis. Additionally stool antigen test has emerged as an informative, non-invasive means in pediatric or ICU patients. The modern discovery of *H. pylori* may have been delayed by Palmer's declaration in 1954 that there were no microorganisms in the human stomach, stomach as desert to pathogen under the belief that microorganisms were believed to be unable to survive in the acidic gastric environment. In 1983, Marshall and Warren successfully cultures unidentified microorganism in stomach and proved pathogen responsible for gastritis by ingesting cultured specimen.[14] Novel prize in medicine was given to them at 2005. Our department has published data that *H. pylori* infection was insufficient to develop gastric cancer in wild-type animal, whereas *H. pylori* infection led to gastric tumors in genetically defective animals.[15] On additional experiment, we have identified that *H. pylori* infection might be promoter for gastric carcinogenesis, gastric cancer developed in salt drinking mice followed with *H. pylori* infection, MNNG initiated-, *H. pylori*-infected mice.[16] Also we are using animal model that *H. pylori* infection followed with high salt containing water drinking developed in either wild-type or IL-10 KO/TGF-type II receptor KO mice signifying that *H. pylori* infection contributed to gastric carcinogenesis, but combined with additional risk factor. Clear findings were that since gastric epithelium changes during the progression from inflammation to cancer, with evidence of disruption of normal

epithelial cell differentiation and recruitment of inflammatory cells, *H. pylori* infection was pivotally and critically associated with the changes of tumor microenvironment as well as critical mutagenic activities. Therefore, detouring the unpleasant journey from chronic strophic gastritis to gastric cancer might yield cancer prevention through either removal of etiologic microbes or detouring the mutagenic path (Fig. 1).

KOREAN PERSPECTIVE ON THE PREVENTION OF GASTRIC CANCER RELEVANT TO *H. PYLORI* INFECTION

Early diagnostic strategies might be the best proven way of gastric cancer prevention, available program in either Korea and Japan as public health interventions in gastric cancer, but the mortality rates of 20-40/100,000 still rendered gastric cancer troublesome malignancy. *H. pylori* infection, smoking, and salt are strong independent risk factors for gastric cancer besides of individual genetic risk condition. Fresh fruits, vegetables and certain micronutrients such as selenium, vitamin C reduce the risk, but foods that can inhibit *H. pylori* viability, colonization and infection may reduce cancer risk, for which Korean red ginseng, licorice special extracts, S-allyl cysteine from garlic, some probiotics, and even Korean gimchi cuisine were proven to very effectively impose anti-bacterial activities, exert anti-mutagenic actions as well as rejuvenating activities. Though these findings should be proved to be "evidence based medicine", great deals might be the adoption of generalized policy to "eliminate bug to achieve gastric cancer prevention" or siTRP (short-term intervention to eliminate premalignancy (Fig. 2 and Table 1), execution, part of which was already approved in Japan this year that eradicate *H. pylori* in patients with *H. pylori*-associated chronic gastritis. As member of the Korean Society of Cancer Prevention and the Korean College of Upper Gastrointestinal Disease and *Helicobacter* Research, cautious step should be put forwarded to generalize policy that *H. pylori* eradication to prevent gastric cancer in Korea, but our group want to extend more the supplementation of efficacious phytoceuticals or phytonutrients to catch both rabbits of higher eradication rate and efficacious prevention of gastric cancer based on our accomplishments that merely eradication yielded lower than eradications accompanied with the attenuation of bug associated gastric inflammations through certain periods of phytoceuticals or phytochemicals, presumptively Korean red ginseng (2-3 g for additional 10 weeks after eradication regimen), probiotics based on evidence higher eradication rates, fewer side effects of triple regimen, and higher levels of anti-inflammatory cytokines, special



Chemoprevention (Hong WK & Sporn MB, Science 1996)
Chemointerception/delay (Hong WK, 2012 AACR)
Detouring carcinogenesis (Hahm KB, CCR 2005)
Chemoquiscence (Peng X, 2010)

Fig. 1. Type of cancer prevention. Chemoprevention using chemicals or nutrient to prevent malignancy was extended meaning of chemo-delay. Our research teams applied the concept "detouring carcinogenesis", well exemplified in *H. pylori*-associated gastric carcinogenesis. Another recent concept of cancer prevention might be chemoquiescence to eliminate the resistant factors of chemoresistance. Since *H. pylori* took long journey to gastric cancer after chronic infection, detouring might offer either best outcome or royal road to tackle carcinogenesis pathway.

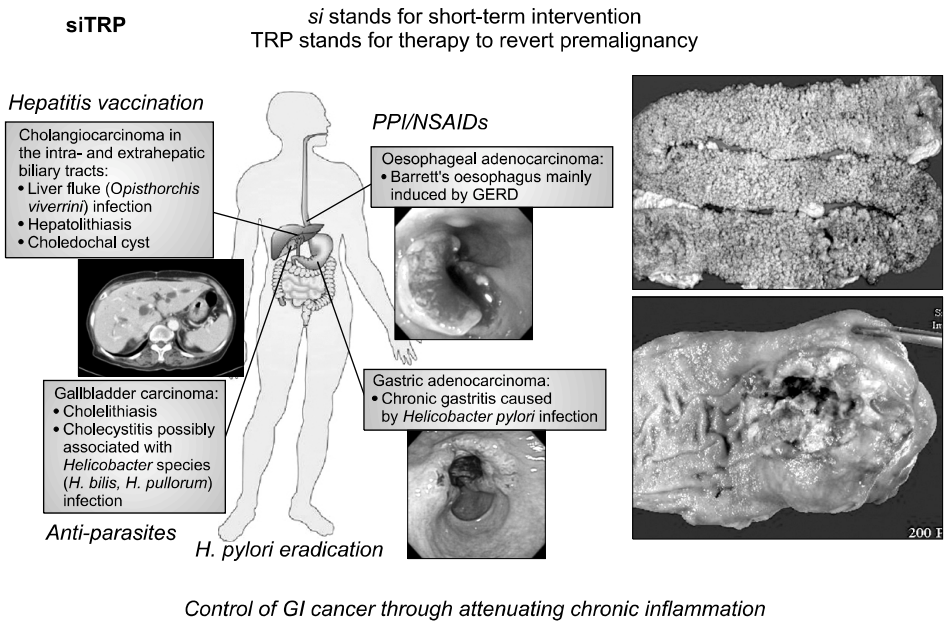


Fig. 2. siTRP strategy to revert premalignancy. Chronic *H. pylori* infection led to chronic atrophic gastritis and intestinal metaplasia, a premalignant lesion progressing to cancer. Through intense intervention with short-term intervention, CAG can be reverted into lower levels of malignant potential or non-malignant lesions. As much as *H. pylori* eradication, efforts to revert premalignancy might offer the hope of gastric cancer prevention. Several trials incorporating phytoceuticals, phytochemicals, stem cells or conditioned media, and some chemicals are under progress.

Table 1. Potential agents for siTRP strategy for *H. pylori*-induced gastric cancer

Agents	Functions
Korean red ginseng (KRG)	Increase eradication rate or rejuvenate atrophic gastritis
Chloroquine (CQ)	Remove cancer stem cells
S-allyl cysteine (SAC)	Regulate *H. pylori*-induced inflammation
CHA stem cell (mesenchymal)	Restore atrophied gastric mucosa relevant to *H. pylori* infection

licorice extracts achieving lower mutagenic actions as well as high rejuvenating activities of *H. pylori*-associated chronic atrophic gastritis, n-3 polyunsaturated fatty acids (so called, omega-3 PUFA) through inhibiting bacterial adhesion and colonization, anti-inflammatory actions, higher regenerative activities, and lowered mutagenic outcomes, and S-allyl cysteine (SAC) from garlic as demethylating agent globally regulating *H. pylori*-inflammatory activities.[17-22] Common concerted mechanisms might be some rescue from antibiotics resistance. Conclusively, natural phytochemicals possessing potential antioxidant and/or anti-inflammatory and anti-carcinogenic activities, which are exerted by regulating or targeting specific molecules against gastric cancer might potentiate the efficacy of *H. pylori* removal to achieve gastric cancer prevention.[23] Currently we are waiting the results from anticipating role of stem cells to rejuvenate *H. pylori*-atrophic gastritis, on-going study. Korean perspective regarding *H. pylori* eradication and gastric cancer prevention will be enriched with a couple of year because clear limitation of current strategy of endoscopic surveillance was shown in Korea. Recent cancer statistics from United States[24] showed that a total of 1,660,290 new cancer cases and 580,350 cancer deaths are projected to occur in the US in 2013. During the most recent 5 years for which there are data (2005-2009), delay-adjusted cancer incidence rates declined slightly in men (by 0.6% per year) and were stable in women, while cancer death rates decreased by 1.8% per year in men and by 1.5% per year in women. Interestingly, death rates continue to decline for all 4 major cancer sites (lung, colorectum, breast, and prostate) and over the past 10 years of data (2000-2009), the largest annual declines in death rates were for chronic myeloid leukemia (8.4%), cancers of the stomach (3.1%) and colorectum (3.0%), and non-Hodgkin lymphoma (3.0%). The reduction in overall cancer death rates since 1990 in men and 1991 in women translates to the avoidance of approximately 1.18 million deaths from cancer, with 152,900 of these deaths averted

in 2009 alone. Though small decline witnessed in gastric cancer mortality from this statistics, Japan government is also awaiting remarkable decline in gastric cancer incidence as well as mortality from the commencement of *H. pylori* eradication in patients with chronic gastritis. Our Korean government should pay attention in this Japanese effort to prevent gastric cancer through extending treatment guideline of *H. pylori* infection in spite of ambiguous debates.

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