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- 총 설 -

Helicobacter pylori and Gastric Carcinogenesis

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Ever since the World Health Organization classified *Helicobacter pylori* as a class I carcinogen, a variety of discussions over the actual role of *H. pylori* infection in gastric carcinogenesis has existed. Although a majority of researches support the positive correlation between *H. pylori* infection and the development of gastric cancer, many aspects of this association are yet uncertain, and some data even suggest that there may be no correlation between *H. pylori* infection and gastric carcinogenesis. However, there are proofs indicating these reports underestimated the prevalence of *H. pylori* infection and therefore, the association of the infection and gastric adenocarcinoma. In this report, I reviewed the epidemiology of *H. pylori* and gastric cancer, evidence supporting and against the positive correlation of the infection and the disease, and the possible pathological role *H. pylori* infection may have in gastric carcinogenesis referring particular to published literature. As a conclusion, despite a few reports of a possible negative or no relationship between gastric cancer and *H. pylori* infection, I was able to find that *H. pylori* infection did have a pathological role in the development of gastric cancer.

Key words – *Helicobacter pylori*, gastric carcinogenesis, pathology

Introduction

In most of the developed countries, having socioeconomic and hygienic environments drastically improved, the prevalence of gastric cancer has been significantly declined for the past few decades. However, in Korea, the lethal disease still remains as the second most common cause of cancer death after lung cancer. According to the statistics of the Korean ministry of health and welfare, 7,183 Korean males (29.4/100,000) and 3,807 Korean females (15.7/100,000) died of gastric cancer in year 2005 [71].

Recent reports propose that infection with a bacterium, namely *Helicobacter pylori* is a crucial environmental factor in gastric carcinogenesis. *H. pylori* is a gram-negative rod known to induce gastritis and peptic ulcer disease. *H. pylori* inhabits in a neutral-pH niche between the gastric epithelium and the mucus layer of the stomach. *H. pylori* does not invade tissues and has not been observed remote from gastric epithelium. *H. pylori* produces great amount of urease, degrading urea into ammonia. This ammonia protects the bacterium from the extremely acidic surrounding environment. Prevalence of infection increases with age and low socioeconomic condition. Various studies conducted in Korea suggest that more than 80% of Korean adults (age > 25) are infected with *H. pylori* and more than 50% of Korean minors (age>10) are infected. *H. pylori* infection cannot be removed without sophisticated antibiotic therapy [98].

Well before the *H. pylori* was classified, the stomach was known to experience a sequence of histopathologic modifications before the final development of cancer. These 'pre-cancerous' stages are, chronologically given, superficial gastritis, atrophic gastritis, intestinal metaplasia, dysplasia, and neoplasm. For *H. pylori* infection is the distinct causal factor in superficial gastritis, *H. pylori* was suspected to participate in gastric carcinogenesis. A variety of studies including ecologic studies, case-control studies, and nested case-control studies within large cohort populations provide rigid supports for this pathologic association. The crosses of studies suggest reliable evidence that gastric cancer prevails in areas of high *H. pylori* infection rates that *H. pylori* infection is more usual in patients than in controls, and that *H. pylori* infection comes before the development of gastric cancer. In many statistical studies, the infection seems to raise the likelihood of carcinogenesis between three fold and six fold. From accumulated data, it was calculated that roughly 40-60% of gastric cancer would

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not have been developed without the infection of *H. pylori* [130].

Several reports though suggest that *H. pylori* is not the sole factor for gastric carcinogenesis. The researchers propose that age and the infected site within the stomach are quite important conditions that determine the breakout of cancer development. Furthermore, in many cases, *H. pylori* infection alone is not enough to trigger the carcinogenesis unless combined with other environmental factors as dietary salt or nitrates.

Roughly one-third of cancers are now assumed to be attributable, at least in part, to infective factors as schistosomes, *Clonorchis sinensis*, papillomavirus, hepatitis viruses, or Epstein-Barr virus. *H. pylori* is the first bacterium among these pathogens to be linked to carcinoma. There are reliable mechanisms for *H. pylori*-related gastric carcinogenesis confirmed by curative antibiotics trials against the bacterium.

Pathogenesis of *H. pylori* infection

H. pylori infection epidemiology

H. pylori infection is nearly always gained in childhood [6]. The infection commonly lasts for life unless treated. The rate of new infection among grownups is not quite significant with rates of infection <1% per year [22]. The methodology of *H. pylori* infection transmission is not yet clearly known but person to person transmission is likely to be the route [8].

The primary risk factor for gaining *H. pylori* infection is low social and economic circumstance during childhood [82]. Hence, the prevalence of infection can be >80% in children<10 years old of developing countries. In developed countries, while the total prevalence of *H. pylori* infection in children is <10%, up to 50% of children in poor social and economic environments hold *H. pylori* infection [29].

The prevalence of *H. pylori* infection in developed countries vary from 10% in children to 60% in older generations. But the increasing prevalence of *H. pylori* infection with age is considered to be attributable to a cohort effect. Most adults gained *H. pylori* infection frequently in childhood as social and economic conditions in their countries were worse then than those are now [6].

Virulence of *H. pylori*

Firm-based *H. pylori* virulence factors are essential for colonization in various *in vivo* models. These factors include the existence of flagella and urease activity. According to a report [42], two isogenic *H. pylori* mutants have been demonstrated defective in colonization of mouse stomach. One of the mutants lacked fumarate reductase and the other super oxidase dismutase. Super oxidase dismutase seems crucial for the proliferation and survival of *H. pylori* under oxidative stress because of *H. pylori*'s microaerophilic growth requirements and increased levels of reactive oxygen species in infected hosts. Fumarate reductase is the central enzyme in fumarate respiration caused by anaerobic growth of bacteria. In *H. pylori*, fumarate reductase seems to be constantly expressed under microaerobic conditions. Moreover, it is not crucial for *H. pylori*'s survival *in vitro*. The fact that colonization of the murine stomach by *H. pylori* requires fumarate reductase might indicate that *H. pylori* employs an active anaerobic respiration with fumarate as the electron acceptor *in vivo*. Denaturation or inactivation of fumarate reductase could get rid of the energy source essential to *H. pylori* get into the mucus layer of the gastric epithelia. This insist is confirmed by experimnetal data proving the existence of a fumarate carrying system and a fumarate reductase-driven catabolism within *H. pylori*.

VacA, or *Helicobacter pylori* vacuolating toxin causes establishments of intracellular vacuoles in tissue culture cells. Published reports propose that strains of *H. pylori* that express more toxin cause more serious gastric disease in their hosts. Salama *et al.* [111] has started to cover the role played by vacA during the process of chronic *H. pylori* infection. Employing the SS1 *H. pylori* model in C57BL/6 mice, the group showed that isogenic mutants without any expression of vacA were not able to colonize mice. The infectious amount essential for a 50% infection rate for the vacA mutant was 1.6×10^8 bacteria, which was about 320-fold greater than the ID50 of wild-type *H. pylori* SS1, 5×10^5 bacteria. Likewise, in experiments employing both 1:1 and 90:10 ratios of mutant to wild-type *H. pylori*, the researchers could find only wild-types from infected hosts. The results of this report oppose the previous results with gnotobiotic piglets and gerbils, which provided data of vacA mutants which were able to colonize their hosts as efficiently as wild-types. Also, the manifestation of a impaired colonization in mixed competition experiments proposes a weak virulence phenotype. Quite possibly, vacA mutants behave differently in distinct hosts, or perhaps the

results indicate the fact that in normal animal experiments, high degrees of bacteria are administered in various doses. Further investigations are necessary on the mechanism involved in this unexpected discovery in mice. Nonetheless, using competition studies in the future might furnish a better method for *in vivo* testing of acknowledged virulence genes.

Odenbreit *et al.* [95] suggested a question asking if the existence of the cag pathogenicity island (PAI) in *H. pylori* was required in the capability of the bacteria to evade the phagocytic cells. The researchers distinctly established that the cag positive *H. pylori* employed the type IV secretion system to put *CagA* into various professional phagocytes. The *CagA*, which is promptly processed, produces a 35 - 45 kD, C-terminally tyrosine-phosphorylated protein fragment. *H. pylori* was effectively ingested by the distinct phagocytic cells, and an excision of the total PAI did not have any effect in the rate of insertion by these cells. Hence, the type IV secretion system is not involved either in active phagocytosis or prolonged survival of the bacteria in phagocytes.

Studies with explants of guinea pig gastric pit cells propose that cag PAI-positive *H. pylori* strains are possible causes of the inborn immune responses of the gastric mucosa. These strains of *H. pylori* activate the toll-like receptor 5 cascade and mitogen oxidase (MOX) in gastric pit cells [68]. The Mox1, a component of the nonphagocytic oxidases, possesses a superoxide-generating ability as that of macrophages. The superoxide from Mox1 and other oxygen intermediates is the primary cause of the initiation of inflammatory and immune responses and cell proliferation. The bioactive portion of the lipopolysaccharide (LPS) seems to be lipid A. A further investigation is needed on the genomic and molecular basis for the linkage between the cag PAI and the production of lipid A of *H. pylori*. Urease is likely to supply a protective effect to *H. pylori* through inhibiting the bactericidal activity of host-derived peroxynitrite generated by phagocytes. Urease, producing carbon dioxide and ammonia from urea, also generates carbon dioxide/bicarbonate. A group of *in vitro* studies distinctly demonstrated that the elimination of *H. pylori* by peroxynitrite was suppressed by adding 10 mmol urea to the substrate, and this bactericidal effect was nullified by adding 10 μM fluoranide, a specific urease suppressor. Addition of sodium bicarbonate also inhibited bactericidal activity of peroxynitrite, while adding ammonia did not [73].

Contrast to the various researches conducted on the cag PAI and the vacA of *H. pylori*, the hemolytic activity of *H. pylori* noted on unlysed blood agar plates has not been pursued as a potential virulenc factor. Investigation of the sophisticated sequencing of *H. pylori* strain 26695 displayed at least two different hemolysins, Hp 1086 and Hp1490, which had homology to pore-forming cytolysins (tlyAs) observed in other bacterial species. When the *tlyA* gene of Hp1806 *H. pylori* was cloned into a nonhemolytic *Escherichia coli*, it had hemolytic activity on blood agar. On the other hand, the *H. pylori* tlyA mutant had cut down hemolytic activity [81]. Significantly, the *H. pylori* tlyA mutant had reduced adhesive features in human gastric adenocarcinoma cells as well, and failed to colonize the gastric mucosa of CD mice. These results propose that the hemolysins of *H. pylori* have significance in the pathogenesis of *H. pylori*-related disease. The pathogenic potential of *H. pylori* is supported by the increased hemolytic activity under iron-limiting conditions. Segal *et al.* [113] stated that *H. pylori* hemolysin mutants could not bring about tyrosine phosphorylation of *CagA* in host cells but still, they could induce interukin (IL)-8 in gastric epithelia. Innocenti *et al.* [63] proposed that LPS of *H. pylori* caused a large production of CXC chemokinds (IL-8 and growth-related oncogenes) from sublimated human monocytes nearly to the same level as *E. coli* LPS, although 1,000 to 10,000 times higher concentrations of *H. pylori* LPS concentrations are demanded for activation of host spleen cells or macrophages. The consequences of this research also collide with the subtle effect *H. pylori* LPS has on causing production of proinflammatory cytokines.

H. pylori-dependent activation of host cell signaling - NF-κB, MAPK

Inside the gastric pits, *H. pylori* directly interacts with epithelial cells within the gastric mucosa. These interactions trigger the inflow of an inflammatory infiltrate of neutrophils, lymphocytes, plasma cells, and macrophages. Many groups have proved that *H. pylori* can directly interact with gastric epithelial cells *in vitro*, and that such interaction can raise the activation of signaling cascades inside the cells leading to transactivation of a plenty of transcription factors. The primary interaction guiding to activate intracellular signaling seems to be related to bacterial protein translocation. Most strains of *H. pylori* have a pathogenicity island that contains 31 genes required in a specialized type IV secretion machinery. Many groups have

shown that *H. pylori*-epithelial cell contact conducts to translocation of the *CagA* protein by a type IV secretion into host cells, and that *CagA* then is phosphorylated by host kinases. The importance of *CagA* translocation and phosphrylation is not fully studied but may be associated with cytoskeletal or host cell morphologic modifications [106]. However, it is likely that proteins other than *CagA* located in the *cag* locus are also translocated into host cells, and that these gene products activate the nuclear factor-kappaB (NF-κB) and mitogen-activated protein kinases (MAPKs) pathways.

NK-kB is composed of a family of inducible transcription factors that are one of the primary activators of the inflammatory and immune response, including apoptosis and cytokine/chemokine production. Raising the NF-κB pathway can induce numerous signals, including proinflammatory cytokines as interleukin-1 (IL1), tumor necrosis factor (TNF)-α, CD40 ligand, phorbol ester, and LPS. These signs all stimulate the IkB kinases (IKKs), IKKα and IKKβ, that phosphorylate inhibitory proteins recognized as IkB to result in their degradation by the proteosome. The degradation of IkB induces the translocation of NF-κB from the cytosol to the nucleus, where it induces the expression of a plenty of host cellular genes.

A few groups have proved that interaction of *H. pylori* and gastric epithelial cells activates NF-κB. Keats *et al.* [69] established that in *H. pylori* infections in AGS cells induced activation of NF-κB complied by IL-8 mRNA and protein increases. This innovating research also employed the method of immunostaining for activated p65 to demonstrate the existence of activated NF-κB in gastric epithelial cells of patients with *H. pylori* gastritis. This discovery was supported by a conducted research that also employed immunostaining for p65 to place activated NF-κB in the gastric mucosa of *H. pylori*-infected patients [64]. A study also proved that there was an increase in activated NF-κB in *H. pylori*-associated gastritis patients and correlation between the histologic scores of gastritis. A correlation between the degree of NF-κB staining and the level of IL-8 was also found. Eventually, nuclear NF-κB staining could be observed in vascular endothelial cells, macropahges and antral epithelial cells. Merely a slight immunoreactivity was noticed in T-lymphocytes, though the authors stated the possible limitation of their antibodies [64]. This report again presents the direct *in vivo* activation of NF-κB in numerous cell types in response to *H. pylori* infection NF-κB is able to activate multiple genes in the host immune and inflammatory response, including genes of at least 27 different receptors, cytokines and chemokines involved in immune recognition. The secretion of monocyte chemoattractant protein-1 from gastric epithelial cells is boosted by *H. pylori* infection, in addition to IL-8. Mori *et al.* [85] analyzed the mechanism by which *H. pylori* causes monocyte chemoattractant protein-1 production. The authors showed that *H. pylori*-dependent activation of the monocyte chemoattractant protein-1 promoter demands NF-κB activation. Transfection of kinase-deficient mutants of NF-κB inducing kinase (NIK) and IKKs distracted monocyte chemoattractant protein-1 promoter activation. Hence, activation of NF-κB by *H. pylori* occurs by the NIK-IKK signaling complex [85].

The mechanism of NF-κB activation by *H. pylori* was covered to a greater extent in two other researches. Whereas TNF-α is activated by TRAF2 in the classic pathways for NF-κB activation by TNF-α and IL-1, IL-1 is the molecule which activates NIK through a related molecule, TRAF6 [106]. Other researchers proved that NF-κB activation by *H. pylori* could be disturbed by kinase-deficient NIK, by a dominant negative mutant of TRAF2. The last consequences propose that the signaling pathway activated by *H. pylori* differs from those used for TNF-α And IL-1 [78]. A novel signaling molecule was discovered downstream of *H. pylori* [35]. The authors observed that p21-activated kinase (PAK) 1 was critical in the pathway leading to activation of NF-κB in *H. pylori* infection. *H. pylori* infection induced the association of PAK1 with NIK, leading to the phosphorylation of NIK. The energized NIK directed the activity of the IKKs to IkBα [35]. The potential involvement of the TRAFs was not covered in the report, even if the authors concluded that PAK1 was targeted by an *H. pylori* factor.

Many reports have confirmed that *H. pylori* infection of gastric epithelial cells also induces activation of the MAPK pathway. The activation of MAPK by *H. pylori* was probably initially proved by Naumann *et al.*, [91] and Keates *et al.* [70]. The correlation between the NF-κB signaling cascade and the MAPK pathway has been summed up in a review by Peek [106]. The transcription factor activating factor (AP)-1 is a crucial downstream target of the MAPK pathway, which plays a role along with NF-κB in the activation of IL-8 gene expression [106]. Hirata *et al.* [51] studied the regulation of the cyclin D1 gene by *H. pylori* in gas-

tric adenocarcinoma cells. AGS cell- *H. pylori* coculture led an increase in cyclin D1 transcription that could be inhibited by a MEK inhibitor, but not by NF-κB inhibitors. Therefore, though cyclin D1 is a renowned downstream target of both the NF-κB and the MAPKpathways, *H. pylori*-dependent activation of cyclin D1 is provoked by the MAPK pathway and not by NF-κB in AGS cells.

Apoptosis

NF-κB also plays a crucial role in the regulation of apoptosis. It is now apparent that inducing apoptosis in the gastric mucosa by *H. pylori* is an important start in the steps to gastric cancer and other gastric diseases. Apoptosis induction has been tightly linked to increases in cellular growth, and many researchers have proposed that increased cellular growth takes place as a reaction to increased apoptosis to maintain tissue homeostasis. The observation that *H. pylori* infection is related to increased apoptosis was first recognized in human patients by Moss *et al.* [87] Their discoveries were supported by many researchers. In animal models, increased apoptosis indirectly managed by *H. pylori* infection was observed initially in the *H. felis*-infected C57BL/6 mouse [134], and these discoveries were subsequently supported by others in the famous Mongolian gerbil model. *H. pylori* has also been observed to inhibit cell-cycle advance and lead to apoptosis in gastric epithelial cells *in vitro;* thus, questions could be derived about the significance of direct versus indirect consequences of *Helicobacter* in the apoptosis induction.

Helicobacter infection also induces a lot of primary and secondary consequences which could possibly activate the apoptotic cascade. *H. pylori* also produces cytotoxins such as VacA, popopolyasccharides, and urease inducing poisonous products as ammonia. *H. pylori* leads to an inflammatory response leading to increased reactive oxygen metabolites. Finally, *H. pylori* infection induces an inflammatory response and an upregulation of many Th1 cytokines such as TNF-α, IL-1, and interferon-γ. These cytokines are able to stimulate apoptotic pathways. Nonetheless, the primary pathway for apoptotic induction is the Fas/FasL system. Researches have demonstrated that *H. pylori* infection of the gastric mucosa induces an increased expression of Fas receptors in gastric epithelial cells. The influx of T-lymphocytes that make FasL induces Fas-FasL interactions and subsequently induces the spoptosis in gastric epithelial cells. A study conducted by Houghton *et al.* [55] has proved that the Fas-FasL pathway is crucial for the induction of both apoptosis and proliferation. Infection of a Fas Ag-deficient mice (B6.MRLFASlpr) in C57BL/6 background did not show any sign of increased apoptosis, atrophy , or proliferation whereas infection of wild-type C57BL/6 mice induces meaningful increases in apoptosis, proliferation, and Fas Ag expression. This report distinctly states the significance of the Fas pathway in the trigger of apoptosis.

Houghton *et al.* [55] have proposed that Fas Ag expression could be upregulated mainly by Th1 cytokines as TNF-α and interferon. Generally, type I or *CagA*- strains lead to a greater amount of inflammation response and tissue injury. Old studies at first proposed the somewhat surprising discoveries that *CagA*+ strain-infected patients displayed a lower apoptotic index than *CagA*-strain-infected patients. Still, a more recent study of a greater prospective was conducted by Moss *et al.* [88] This study suggested that the existence of *CagA*-positivity was related to increased apoptosis rather than decreased apoptosis. Additionally, this result indicated no clear relation between apoptosis and inflammation, but the type of inflammation and the levels of specific Th1 cytokines were not evaluated. Though the study employed distinct methods for assessing *cag* status and analyzed different patient population samples, it is certain that the relation of *CagA* to apoptosis need to be investigated further.

Several researchers have proposed a role for urease in the *H. pylori*-dependent apoptosis induction. A study found a potential novel role for urease in the apoptotis pathway. The class II major histocompatibility complex (MHC) was identified by Fan *et al.* [28] as a possible receptor for *H. pylori* and one that could also boost cellular apoptosis. They proposed that *H. pylori* ureases is the bacterial ligand for class II MHC and that it has a position in gastric mucosal colonization as an adhesion in the apoptotic induction. A separate group has reported that *H. pylori* urease has a part in gastric mucosal colonization through adherence to host mucin and LPSs in an acid-dependent manner [61]. Both studies indicate potential therapeutic mechanisms that could cut colonization and host tissue injury.

Lastly, though *H. pylori* infection in the short run induces increases in gastric epithelial cell apoptosis, over the

long term, the process of gastric cancer is believed to be related to a reduction in or resistance to apoptosis. Shirin *et al.* [117] studied the results of chronic *H. pylori* infection in AGS cells cultured *in vitro*. After long-term coculture of the cells with *H. pylori*, the investigators identified a subpopulation resistant to apoptosis and observed that the cells had lower levels of the protein p27kip1, a cell cycle controller. A decrease in p27kip1 also has been noticed in human patients with chronic *H. pylori* infection. The investigators proposed that downregulation of p27kip1 by *H. pylori* may be a possible mechanism of the induction to the development of apoptosis resistance and, ultimately, gastric cancer.

Gastric cancer

Morphology

Adenocarcinomas, or malignant tumor are the most common features of gastric cancer. About 97% of total gastric cancers are of this type. While the remaining 3% are lymphomas or leiomyosarcomas [56]. Primary gastric adenocarcinomas are classified by anatomic location as being either proximal in the cardia or distal, to the cardia. *H. pylori* infection has not been associated with proximal gastric carcinoma.

Gastric adenocarcinomas can be further classified according to the Lauren classification into 2 histologic types-intestinal and diffuse. Intestinal-type gastric cancer comprises of cohesively grouped neoplastic cells that form discrete polarized glandlike tubular structures with well-established lumina. These are mainly found in the prepyloric antrum [76]. Diffuse-type gastric cancer, in which cell cohesion is not present, primarily arises in the fundus and comprises of separately infiltrating neoplastic cells that thicken the stomach wall without building glandular structures or a distinct mass [76]. It should be understood that stomach neoplasms can be heterogeneous with both diffuse- and intestinal- type morphology, and also that some tumors do not fall into either category [56,76]. Intestinal-type tumors are more usual than diffuse-type tumors [76], particularly in locations with a high incidence of stomach cancer.

Epidemiology of gastric cancer

Until the 1940s, stomach cancer was the primary cause of cancer-related death in American males and the third leading cause following breast and cervical cancer in women [56]. From 1950, gastric cancer rate was progressively diminished in developed countries. The reason of this decrease is yet unexplained [56]. Between 1950 and 1980, gastric cancer-related death rate in the United States fell by 67% [56]. Nevertheless, the worldwide prevalence of gastric cancer is stepping up as the likelihood of gastric cancer development increases with human lifespan are elongated. Nowadays gastric cancer is the second most common cancer in men, after lung cancer [108]. Gastric cancer makes 12% of all cancers in men and 7.5% in women [100]. More than a million novel cases of gastric cancer emerge every year [101]. Gastric cancer rates vary substantially among distinct geographic regions. Age standardized rates in males are high (.35/100,000) in Korea, China, Japan and Columbia. They are low (.15/100,000) in North American whites, western European countries, Australia, and most African countries [93,99,101].

Traditionally, tumors located far from the cardia have contributed for the majority of gastric adenocarcinomas [38]. There has been an unexplained increase in adenocarcinoma of the gastric cardia and esophagus ever the last three decades in developed countries despite the decrease of the prevalence of distal gastric cancer [11]. It is not yet demonstrated that *H. pylori* infection and gastric carcinogenesis are closely related. Moreover, it is supposed that eradication of *H. pylori* may even result in the acidizing of stomach and hence boost the development of reflux esophagitis [75], which then increase the risk of developing esophageal adenocarcinoma.

The factors affecting gastric carcinogenesis are speculated to be multiple. They include both environmental and genetic risk factors. Gastric cancer is associated with social and economic status of a person [56]. Those from lower social or economic groups have double the risk of those from higher ones [56]. Cuisines with large amount of salt, nitrates, and canned foods may make people susceptible to gastric cancer. Diets low in fresh fruit and vegetables also heighten the risk of gastric cancer outbreak [33].

Several studies on migrated families demonstrated that early life environmental exposures are crucial in gastric carcinogenesis. First generation migrants have similar outbreak rate of gastric cancer and mortality rate to those in their original country [13,46]. A study on intracountry migration conducted in Columbia indicates the same result [16]. Second generation migrants, on the other hand, have

the same gastric cancer mortality rates as those of their adopted nation's [45,47]. In cases of intestinal-type gastric cancer, environmental factors are considered to be more important than they are in diffuse-type gastric cancer [56]. Intestinal-type gastric cancers are the more usual form in areas of high gastric cancer risk [38,76]. Furthermore, the decrease in the incidence of gastric cancer in developed countries can be attributed to a decreasing incidence of intestinal-type gastric cancer [38,89].

Conversely, genetic factors are believed to have an important role in the induction of diffuse-type gastric cancer. Diffuse-type has a similar incidence in males and females. Some suggest that diffuse-type gastric cancer is associated with blood type A. Diffuse-type gastric cancer is more easily observed in younger age groups [89].

Risk factors other than *H. pylori* infection

Through a broad range of epidemiological studies and animal modeling, several risk factors for gastric carcinogenesis have been confirmed. These include a diet high in salt and N-nitroso compounds or short of fresh fruits and vegetables [15,65,66,135], smoking and drinking [14], hereditary history [86], and precancerous gastric lesions as atrophy and intestinal metaplasia [20].

Dietary factors have long been known to have a crucial effect in gastric carcinogenesis [15,58,65,66,135] The association between certain diets and gastric cancer has been analyzed widely in human epidemiology researches, animal models, and human intervention trials [50]. The INTERSALT ecological research investigated the importance of consumption of dietary salt and nitrate, checked as 24-h urinary nitrate and sodium excretion, and gastric cancer mortality in 39 samples from 24 countries [65]. The research employed 9,059 subjects-5,756 for sodium and 3,303 for nitrate measurements, in whom the median sodium and nitrate levels of 24-h urine examples were assessed and standardized by gender and age. An ecological association-regression analysis for the 24 countries, in relation to the national gastric cancer mortality rates, was conducted and demonstrated a substantial association between urinary sodium levels and gastric cancer mortalty rates($r=0.70$ in men and $r=0.74$ in women, both $P < 0.001$). Researchers also found a notable correlation between urine nitrate levels and gastric cancer mortality rates ($r=0.63$, $P<0.001$ in men and $r=0.56$, $P<0.005$ in women). Further analysis found a substantial interaction between sodium and nitrate levels and gastric cancer mortality rates in both men and women (both $P<0.001$) [65].

A high consumption of fresh fruit and vegetables has been demonstrated to be effective to prevent gastric carcinogenesis in various case-control researches [18,41,66]. Chyou *et al.* [15] reported a meaningful dose-dependent inverse relationship between the quantity of daily vegetable consumption and the risk for gastric carcinogenesis. A study conducted in Italy has also established an inverse relationship between diet diversity and the risk of gastric cancer. That is, the greater variety of food consumed, the less the risk of gastric cancer [74].

H. pylori and gastric cancer

Evidence supporting positive association

Three possible long-term results for *H. pylori*-associated gastritis exist. The first is spontaneous resolution. This outcome takes place in very few cases [132]. The majority of patients experience persistence of a diffuse but predominantly antral gastritis. As many as 15% of patients with *H. pylori*-associated diffuse antral gastritis develop a duodenal ulcer [132].

The third possible result is the development of gastric atrophy, also named multifocal atrophic gastritis. This includes loss of gastric mucosal glands and therefore altered gastric secretion. These patients hence do not usually develop ulcer disease. The development of gastric atrophy was originally considered to be related to age. It is now likely that colonization with *H. pylori*, rather than increasing age, is the essential factor in gastric atrophy growth in susceptible individuals [72]. The causes for this process to gastric atrophy in some *H. pylori*-infected individuals are not yet specified. However, the development of gastric atrophy may be the first stage to the evolution of gastric cancer. Actually, Correa [19] suggested that gastric cancer evolved consequently from chronic gastritis to atrophic gastritis and intestinal metaplasia, and ultimately to dysplasia and carcinoma *in situ* even before the discovery of *H. pylori*.

Histopathological follow-up researches confirmed that a step-by-step progression from chronic gastritis to atrophic gastritis is possible [17,72,133]. Reports suggested an association between *H. pylori* infection and intestinal metaplasia [72,132]. There exist important methodological problems that are related to such studies for atrophy and intestinal

metaplasia are patchy and can hence easily be missed if only a few biopsies are collected.

The most powerful epidemiologic evidence associating *H. pylori* infection with gastric cancer is found in three nested case-control researches [31,94,104]. These researches employing stored serum proved that *H. pylori*-infected people are more probable to develop gastric cancer (Table 1). A combinatory speculation of these three researches concluded that the relative risk of cancer is 2.1 to 8.7 times greater in infected adults, compared to uninfected controls [32].

We can find a large amount of studies indicating that gastric cancer patients are more likely to have been infected with *H. pylori*- than matched controls free of gastric cancer (Table 1) [7,30,48,120]. Hansson *et al.* [48] have demonstrated that the likelihood of this association is higher for men with *H. pylori* as compared to women. It has been demonstrated that this association is stronger in younger generations with gastric cancer than in older people [84].

Case-control researches established on serologic proof of infection may underestimate the strength of association between *H. pylori* and gastric cancer [32] as *H. pylori* colonization of the gastric mucosa declines according to the development of gastric atrophy [67]. Crabtree *et al.* [21] demonstrated that 25% of patients with gastric cancer seronegative on enzyme-linked immunosorbent assay (ELISA) testing were positive on Western blotting, suggesting that ELISA testing can underestimate the prevalence of *H. pylori* infection. There are also difficulties with retrospective studies established on histologic evidence of *H. pylori* infection. *H. pylori* colonization does not take place in gastric tumor tissue [34]. Thus, reports based on the histologic diagnosis of infection employing tumor biopsies may also underestimate the actual rate of infection. The actual relative risk of gastric cancer in *H. pylori*-infected gastric cancer patients is therefore likely to be higher than proposed. The authors of a combinatory analysis of the three nested case-control researches propose that a roughly nine-fold relative risk of gastric cancer in infected adults might be a more accurate assumption [32].

In the last few decades there has existed a progressive decrease both in the incidence of gastric cancer and in the incidence of *H. pylori*-associated chronic gastritis in developed countries [121]. The diminishing prevalence of *H. pylori* infection is possibly the outcome of improving social and economic conditions. Sipponene [122] has proved that the prevalence rates of *H. pylori* gastritis for particular birth cohorts can determine the succeeding incidence rates of gastric cancer at specific ages.

Various groups have manifested a higher likelihood of *H. pylori* infection in intestinal-type gastric cancer, compared to diffuse-type gastric cancer [25,80,139]. Other groups have proved that a notable association between *H. pylori* and both intestinal- and diffuse-type cancers [4,115]. A study employing meta-analysis discovered that host genetic factors increase the likelihood of the development of gastric cancer.

Hereditary gastric cancer has been known for many

Table 1. Data that indicate a positive relation between *H. pylori* infection and gastric cancer (From Imrie *et al.*, Ref # 62)

Location	Yr. of Investigation	Study Type	Mean Follow-Up Period(Yrs)	Cases Total	Cases Infected(%)	Controls Total	Controls Infected	OR (CI 95%)
United Kingdom								
United States	1991	ncc	6	29	69	116	47	2.77 (1.04-7.97)
(California)	1991	ncc	14.2	109	84	109	61	3.6 (1.8-7.3)
United States	1991	ncc	13	109	94	109	76	6.0 (2.1-17.3)
(Hawaii)	1992	c	n/a	54	70	84	51	2.27 (1.0-5.0)
Finland	1993	c	n/a	112	80	103	61	2.6 (1.35-5.02)
Sweden	1994	c	n/a	51	92	102	70	5.1 (1.7-15.5)
China	1995	c	n/a	105	89	102	41	13.3 (5.3-35.6)
Japan	1996	c	n/a	50	72	50	43	3.27 (1.42-7.52)
Sweden	1997	ncc	3.2	45	91	225	76	3.38 (1.15-9.90)
Japan	1997	ncc	5.7	56	82	224	49	5.0 (2.2-11.5)
Sweden	1997	c	n/a	55	82	75	60	3.0 (1.69-5.33)
Japan	1997	c	n/a	215	92	215	40	16.7 (9.6-29.1)
Germany								

ncc indicates nested case-control study; c, case-control study; n/a, not applicable

years. Brenner *et al.* [12] demonstrated a high prevalence of *H. pylori* infection in the offspring of patients with gastric cancer than in the offspring of non-patients. Some suggest that if the study was restricted to noncardia gastric cancer rather than all types, the prevalence of *H. pylori* in the offspring of gastric cancer patients would have been even higher.

El-Omar *et al.* [24] have demonstrated that *H. pylori*-infected first degree relatives of gastric cancer patients tend to have higher rates of gastric atrophy than controls who do not have any familial gastric cancer history. The absence of DQA1*0102 allele is suggested to be a further host genetic factor. This allele could be a risk factor for *H. pylori*-associated atrophic gastritis and intestinal-type gastric cancer [5].

It has not been long since the first animal model was utilized to demonstrate a definite association between *Helicobacter* infection and gastric carcinoma. Nevertheless, Watanabe *et al.* [136] have demonstrated a relationship between *H. pylori* infection and gastric adenocarcinoma in Mongolian gerbils. The researchers also demonstrated the progression of chronic gastritis and intestinal metaplasia in *H. pylori*-infected gerbils. The neoplasm was shown to develop inside the areas of intestinal metaplasia [136]. *H. mustelae* is another member of the *Helicobacter* genus that infects ferrets. Fox *et al.* [36] have demonstrated that *H. mustelae*-infected ferrets with chronic gastritis may grow duodenal ulceration, and can develop multifocal atrophic gastritis. The investigators reported gastric adenocarcinoma emerging in two ferrets naturally infected with *H. mustelae* [37].

It is suggested that particular bacterial virulence factors may have a role in the progression of gastric cancer. *H. pylori* strains may be classified based on whether they possess the cytotoxin associated gene (*cag*). *Cag* is a marker for the existence of a pathogenicity island in the *H. pylori* genome. It may also be a marker for a more virulent type of *H. pylori*. Various researches have proposed that infection with *CagA* positive strains of *H. pylori* is associated with an increased risk of gastric cancer [10,103,109].

Evidence against the association

The strongest support against a positive relationship between *H. pylori* and gastric cancer is the discovery that locations with higher likelihood of *H. pylori* infection have a relatively lower prevalence of gastric cancer. The regions of China with high and low rate of *H. pylori* infection have similar prevalence of gastric cancer [57]. Also, cross-sectional studies in Italy [97], Costa Rica [118], and Japan [39] did not demonstrate a higher prevalence of infection among people in regions with a high prevalence of gastric cancer.

Countries in Africa have a high prevalence of *H. pylori* infection. In northern Nigeria [53] and the Gambia [126], half of the children who are 5 years old are seropositive for *H. pylori*. In Ethiopia [77], 60% of 4-year-olds are infected. However, the figured rates of gastric cancer are low in Africa [123]. These statistics suggest that there are at least other genetic or environmental risk factors which play a role in the gastric carcinogenesis. Some possible cofactors for the progression of gastric cancer as low vitamin C intake or a high salt intake might not be present in all populations.

Males and females almost always display the same prevalence of *H. pylori* infection [107], nevertheless, the prevalence of gastric cancer in males is statistically higher than in those of females. According to statistics, the ration of males to females among gastric cancer patients is 2.2:1 in patients < 60 years of age. This falls to 1.4:1 in those >60 years of age [56]. This statistics proposes that there must exist extra risk factors other than *H. pylori* in young men or some defensive factors in young women.

Two recent researches have failed to demonstrate an increased prevalence of gastric cancer in *H. pylori*-infected participants (Table 2) [137]. Still, the average intervals between serum collection and gastric cancer diagnosis were only 3.1 and 2.4 years. For *H. pylori* may disappear when gastric atrophy progresses, these statistics may have significantly underestimated the existence of *H. pylori* infection. Additional case-control studies that have not displayed a relationship between *H. pylori* infection and gastric cancer are included in Table 2 [2,9,27,40,110,128].

Eradication of *H. pylori* to prevent gastric cancer

No researches have studied specific mutational markers as predictors of *H. pylori* preneoplastic gastric lesions progression. In a certain study conducted in Narino, Columbia, subjects with atrophic gastritis were enlisted to take parts in a chemoprevention trial. Participants were randomly allotted to intervention therapies, which included eradication of *H. pylori* infection complied by daily dietary supplementation with antioxidant micronutrients in a 2 × 2 × 2 factorial design. A systematic sample of exam-

Table 2. Data that do not indicate a positive relation between *H. pylori* infection and gastric cancer (From Imrie *et al.*, Ref # 62)

Location	Yr. of investigation	Study type	Mean Follow-Up Period (Years)	Cases Total	Cases Infected(%)	Controls Total	Controls Infected	OR (CI 95%)
United States	1991	c	n/a	69	52	252	38	1.63 (0.79-3.37)
Japan	1993	c	n/a	29	83	58	67	2.14 (0.72-6.4)
Greece	1993	c	n/a	47	72	50	68	1.23 (0.51-2.95)
Taiwan	1995	ncc	3.1	29	69	220	59	1.55 (0.68-2.56)
Japan	1995	c	n/a	282	76	767	74	1.04 (0.73-1.49)
Germany	1995	c	n/a	111	59	111	51	1.39 (0.82-2.36)
China	1996	ncc	2.4	85	54	255	56	0.93 (0.57-1.54)

ncc indicates nested case-control study; c, case-control study; n/a, not applicable

ple subjects was chosen from each of the eight treatment combinations. They were asked to donate their DNA. The first exon of KRAS was amplified by polymerase chain reaction, and mutations were determined. At year 3, the data suggested that subjects with KRAS mutations in their baseline premalignant gastric biopsies were 3.7 fold likely to advance to a higher premalignant stage than those who did not have baseline KRAS mutations [43]. Nevertheless, after 6 years, the investigation group reported the both KRAS mutations at baseline and 72-month biolosies in the same study sample pool failed to predict histologic development [59].

H. pylori and gastric lymphoma

According to previous studies, gastric B-cell lymphomas, namely MALT (mucosa associated lymphoid tissue) lymphomas, has an epidemiologic association with *H. pylori* infection [105,138]. These forms of lymphomas are quite scarce, by only 0.71 cases/100,000 per year in the United States [114]. Treatment of the *H. pylori* infection readily leads to reduction of gastric MALT lymphomas in adults [131]. *H. pylori* eradication is now indicated for low-grade gastric MALT lymphoma.

The role of *H. pylori* infection in gastric carcinogenesis

Cag*A*-positive *H. pylori* has a major role in gastric carcinogenesis

Recent reports have proposed that *CagA*-positive strains of *H. pylori* display a significantly increased incidence of gastric cancer. Compared to those patients carrying *CagA*-negative strains, they exhibit higher rate of gastric cancer breakout [23,116]. *CagA* protein is a highly immunogenic protein which is one of the most researched virulence factors of *H. pylori*. The *CagA* gene is located on a pathogenicity island (PAI) namely the *cag* PAI. The *cag* PAI is comprised of 31 genes. Although *H. pylori CagA*-positive from the United States and Japan cause similar IL-9 and apoptosis displays [1], the levels of gastric atrophy (and therefore, the risk of gastric cancer) is higher in East Asian *CagA*-infected cases [140]. Nevertheless, in Asian sample, most of the infected subjects carry *CagA*-positive strains, which immediately trigger logical questions about the correlation of this virulence factor as a standard of the relative risk of gastric carcinogenesis in such populations.

A group of researchers suggested that risk of gastric cancer is still notably higher in those cases with *CagA*-negative *H. pylori* infections than in uninfected group, although patients with *CagA*-positive strains possess the greatest risk [49]. A meta-analysis of the correlation between *CagA*-seropositivity and gastric cancer suggested that infection with *CagA*-positive *H. pylori* increased the rate of gastric carcinogenesis over that with sole *H. pylori* infection.

CagA is transported to epithelial cell through the *cag* type IV secretion system, phosphorylated one tyrosine residues and fixed to the eukaryotic signal transduction cascades that play a significant role in *H. pylori*-host cell interactions and pathogenesis (Fig. 1) [3,96,112,124]. *CagA* causes cellular spreading and elongation, namely the 'hummingbird' phenotype in the gastric epithelial cell. This phenotype is assumed to have a essential role in the pathogenesis of *CagA*-positive *H. pylori* infection. This morphological modification of gastric epithelial cells demands src homology 2 domain-containing protein tyrosine phosphatase-2 (SHP-2) [92]. SHP-2 has a central role in the intracellular signal transduction evoked by a variety of cytokines, growth factors and hormones [129]. *CagA*-SHP-2 communication may cause apoptosis and increase the epithelial cell turnover related to *CagA*-positive *H. pylori* infection [102]. Needless cycles

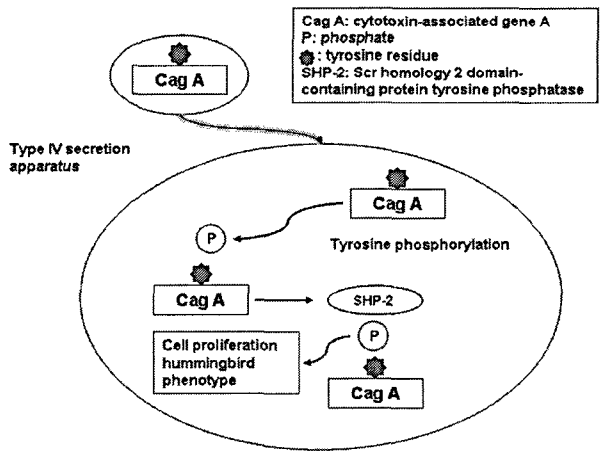

Fig. 1. *CagA* relevant deregulation of SHP-2 trosine phosphatase. Bacterial type IV secretion system is the primary method of *CagA* delivery.

of DNA replication may raise the opportunity of genetic mutation, which might eventually lead to abnormal cell proliferation.

A study conducted in Japan reported the correlation of a frequent single nucleotide polymorphism (SNP, JST057927, G-to-A) in the PTPN11 gene that encrypts SHP-2 with gastric abnormalities [44]. The investigators suggested that this polymorphism elevated the rate of gastric atrophy and gastric carcinogenesis among *H. pylori*-seropositive subjects. A distinct increased risk of atrophy was displayed in the subjects with *G* allele of *PTPN11*, while the *A/A* genotyped subjects were protective. The SHP-2-binding reaction of *CagA* affects its own virulence in the induction of gastric atrophy, which is a major predecessor of gastric cancer. *PTPN11 G/A* SNP may compose a genetic trait making the hosts susceptible to gastricatrophy among those infected (Fig 2). *CagA*-SHP-2 structure formation might cause unnatural proliferation and metastasis of gastric epithelial cells. These cellular may develop into gastric atrophy and eventually, gastric carcinoma.

Possible role of *H. pylori* infection in gastric carcinogenesis.

Recent animal experiments have proved that long-term colonization by *H. pylori* caused gastric adenocarcinoma in Mongolian gerbils [52,54]. In human populations, *H. pylori* infection has been demonstrated to be notably increased if *N*-nitroso compounds were given [125]. *H. pylori* induced gastric carcinogenesis include the inflammatory cascade of cytokines, free radical production, over- and under- expression of growth factors and receptors and abnormal acid secretion, all of which result from gastric atrophy and intestinal metaplasia [119].

H. pylori infection induces a strong host inflammatory and immune responses [26]. However, these responses are not able to eliminate the infection and make the host susceptible to endogenously and extraneously detrimental factors such as bacterial overgrowth, induction of *N*-nitroso compounds from the dietary salt, nitrates or nitrites, less ascorbic secretion, less anti-oxidants, drinking and smoking, etc. The effect of these factors on development of gastric cancer varies among populations and individuals according to the genetically different susceptibility.

H. pylori infection-induced gastritis patients exhibit significantly decreased antioxidant levels in the gastric juice and inclined free radical production [141]. Nitrogen oxides, a well-renowned mutagen, are produced from several sources in cases with *H. pylori*-induced gastritis [79]. Excess amount of nitrosamines can induce apoptosis and gastric mucosal DNA damage. These degradations cause the host to be susceptible to have altered cell cycle controlling, cell loss, atrophy, intestinal metaplasia, dysplasia, and eventually, gastric carcinoma. This cascade can be stopped by eliminating the infection with antibiotics [79,90].

The clinical consequences of *H. pylori* infection primarily depend upon two conditions; the host secretory status and *H. pylori* strains [60]. *H. pylori*-associated gastritis and gastric acid secretion share a mutual interaction [83]. The infection in subjects who had high levels of acid production before prior to the infection can lead directly to antral predominant gastritis with relatively little or no gastritis in the stomach body. Antral gastritis causes the gastrin production to increase, and this successively induces excessive acid secretion and increase the risk for duodenal ulcer [83].

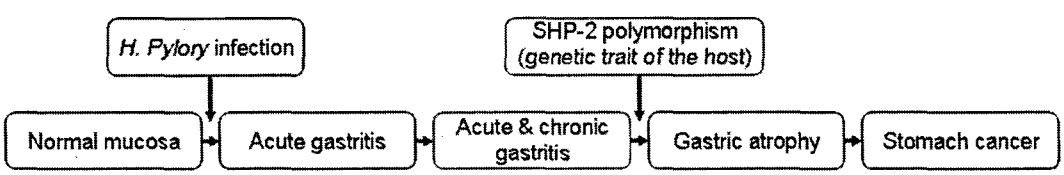

Fig. 2. Gastric cancer progression - a multistage model.

However, in subjects who had low acid production before the infection, *H. pylori* may cause a sequence of gastritis in both the body and antrum of the stomach, thus a relatively little amount of acid secretion. In patients with gastritis, hypochlorhydria tends to increase the risk of gastric carcinogenesis [127]. Still, this is distinct from pharmacological hypochlorhydria caused by anti-secretory treatment that never causes gastritis when *H. pylori* infection is not exhibited.

Conclusion

Although its pathological role in gastric carcinogenesis has been questioned by several studies, *H. pylori* infection has a notable contribution in gastric carcinogenesis. Especially, *CagA*, one of the virulence of *H. pylori*, acts as a direct oncogenic factor. Particularly in Korea where significant prevalence of *H. pylori* infection still exists, it plays a crucial role in the development of gastric cancer. Nevertheless, as tumor progression requires great accumulation of environmental and genetic carcinogens, the position taken by *H. pylori* infection has still more aspects to be scrutinized.

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초록 : *Helicobacter pylori*와 위암발생

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*H. pylori*가 공식적인 발암인자로 지정된 이후, 많은 연구가 *H. pylori* 감염과 위암종 발생간의 연관관계를 지지해 왔다. 비록 몇몇 연구가 위암종 발생에 대한 *H. pylori* 감염의 부정적인 영향에 대한 증거를 제공하기는 했지만, 이들 연구가 *H. pylori* 감염률을 과소평가했다는 새로운 증거들이 제시되고 있다. 이 종설에서는 위암과 *H. pylori*의 역학적인 생태, *H. pylori* 감염과 위암종 발생의 연관관계를 지지하는 증거들, 제시된 위암종 발생의 기작, 그리고 *H. pylori* 감염의 위암종 발생에서의 잠재적인 병리학적 역할을 기존 연구들을 바탕으로 살펴보았다. 결론적으로 *H. pylori* 감염은 위암종 발생과 긍정적인 연관관계를 가진다는 것을 밝힐 수 있었다.