8 *Helicobacter pylori* Infection and Gastritis

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8.1 Introduction

Since *Helicobacter pylori* (*H. pylori*) was first cultured from gastric mucosa in 1983, it has been found to cause not only peptic ulcers and chronic gastritis but also malignant gastric mucosal lymphoma and gastric cancer. Thus, peptic ulcers, which had been classified as an intractable disease due to complications such as frequent recurrence and bleeding, have become a treatable infectious disease. *H. pylori* is a gram-negative, spiral bacterium that infects more than 50% of the world population. The innate and adaptive immune response proceeds vigorously after exposure to *H. pylori*, but in most cases, the infection lasts for a lifetime unless artificial eradication is performed [1]. A 1998 study on the prevalence of serum *H. pylori* among all ages in South Korea reported that the prevalence increased steadily until the age of 49 (Fig. 8.1a), but when the prevalence according to sex was compared, there was no difference in *H. pylori* infection by sex until the age of 15, whereas *H. pylori* infection became significantly more common among males than among females after the age of 16 [2] (Fig. 8.1b). This phenomenon was also found in a 2016–2017 epidemiological study [3]. Males also had a higher rate of *H. pylori* eradication than females [3], but the rate of reinfection after *H. pylori* eradication was also higher among males than females [4], suggesting that the disproportionately higher *H. pylori* infection rate among males will most likely remain stable. Eighty percent of individuals infected with *H. pylori* do not experience any issues for their lifetime, but 1–3% develop gastric cancer, which is twice more prevalent among males than females worldwide. Environmental factors such as consumption of tobacco or alcohol may be responsible for this sex/gender difference, but it has been hypothesized that a partial cause is the sex/gender difference in gastritis due to *H. pylori* infection. The higher prevalence of atrophic gastritis and intestinal metaplasia among males supports this hypothesis [5]. In the past 15 years, atrophic gastritis and intestinal metaplasia decreased among females but remained steady among males [6], indicating that environmental factors such as tobacco and alcohol together with *H. pylori* infection contribute to atrophic gastritis and intestinal metaplasia. An interesting fact is that *H. pylori* infection increases the risk of metabolic syndrome [7]. Total cholesterol was significantly higher among males, while a reduction in high-density lipoprotein (HDL) cholesterol was clearly observed in females [8], indicating that the systemic effects of *H. pylori* infection are different by sex/gender. This section examines the

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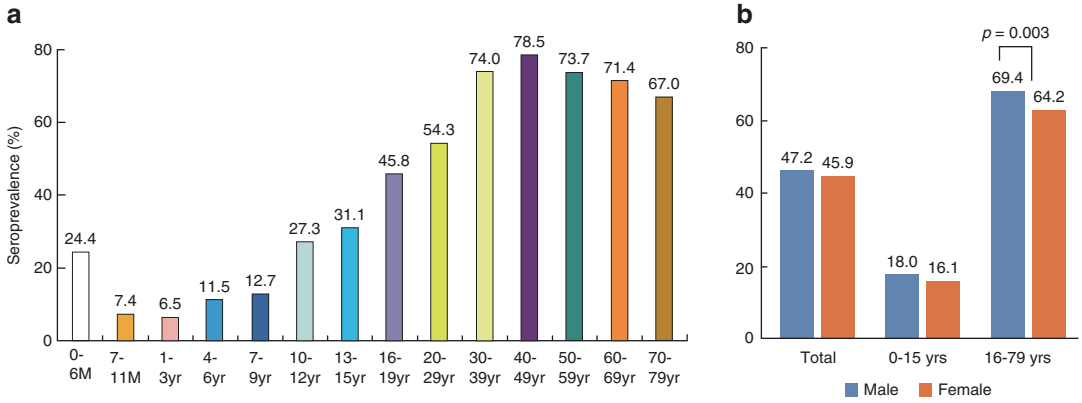

Fig. 8.1 (**a**) Prevalence of *H. pylori* by age and sex in the 1998 national epidemiological study. The prevalence of *H. pylori* increased with age and peaked in the 40–49 age group. (**b**) The serum prevalence of *H. pylori* among children younger than 16 of age and those older than 16. The prevalence among males was significantly higher than that among females in the 16 and above age group. $*p < 0.05$; *M* month, *yr* years (adapted from Kim et al. [2])

epidemiology of *H. pylori* infection, re-infection after eradication, and atrophic gastritis and intestinal metaplasia from *H. pylori* infection, as well as sex/gender differences in lipid metabolism.

8.2 Sex/Gender Differences in the Epidemiology of *H. pylori*

A research society dedicated to *H. pylori* (currently the Korean College of Helicobacter and Upper Gastrointestinal Research) conducted a study with 102 nationally gathered researchers and a total of 5732 participants (2336 individuals in the 0–15 age group and 3396 individuals in the 16–79 age group) who were asymptomatic to obtain insights into the prevalence of *H. pylori* infection in South Korea in 1998 [2, 9]. The most prominent strength of this study is that the study sample included all ages from infants according to the national demographic distribution. A high percentage (24.4%) of infants showed *H. pylori* immunoglobulin G (IgG) obtained from the mother's placenta until 6 months after birth. *H. pylori* IgG disappeared from 7 to 12 months, with a prevalence of 7.4% in this age group, and the prevalence was lowest at 6.5% from age 1 to 3 [2] (Fig. 8.1a). The prevalence increased again until it peaked at 78.5% among individuals in their 40s and decreased to 67.0% among those in their 70s [2] (Fig. 8.1a). The prevalence of *H. pylori* increased gradually from 7 months after birth to the age of 9 years (12.7%), dramatically to the 10–12 age group (27.3%), and by around 1.7% each year until the 31–40 age group (74.0%). This trend was predominantly interpreted as reflecting a cohort effect (i.e., an effect pertaining to a defined population group tracked after estimation at a certain time point) by which the infection occurs before the age of 5 and lingers for a lifetime, rather than as indicating that new infections steadily occurred [10, 11]. The prevalence did not show a significant sex/gender difference in individuals younger than 15 (18.0% among males and 16.1% among females) but was significantly higher among males than females (69.4% and 64.2%) in individuals older than 16 ($p = 0.003$) [2] (Fig. 8.1b). This finding was confirmed repeatedly in epidemiological studies conducted in 2005 [12], 2011 [13], and 2016–2017 [3], indicating that *H. pylori* infection continues to occur after the age of 15 [3] (Fig. 8.2). A multivariate analysis of risk factors related to *H. pylori* infection found that among adults (older than 16), the number of people sharing a room while growing up (during elementary or middle school age) and economic status while growing up were associated with significant differences in the prevalence of

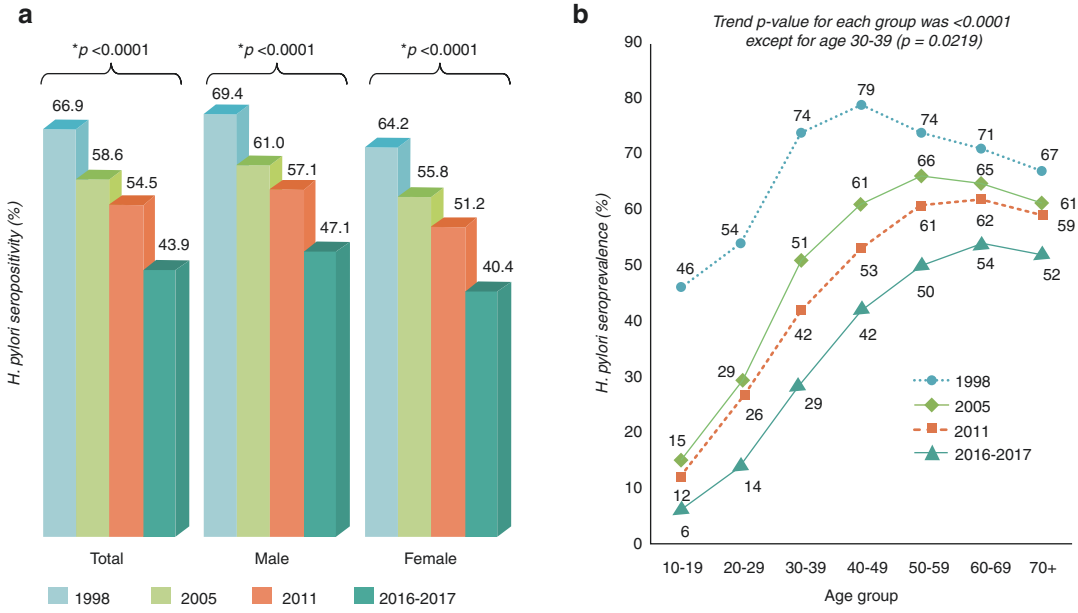

Fig. 8.2 (**a**) Changes in the serum prevalence of *H. pylori* among individuals older than 16 without a history of *H. pylori* eradication in South Korea in 1998, 2005, 2011, and 2016–2017. A sex/gender analysis shows that the prevalence was significantly higher in males than females at all four time points. (**b**) Changes by age demonstrate that the serum prevalence of *H. pylori* steadily decreased (*p for trend <0.05) (adapted from Lim et al. [3])

H. pylori infection, while among children (younger than 15), the maternal education level, household income, and drinking water showed significant associations [9]. In both children and adults, socioeconomic status and the living environment in adolescence were found to be important factors in *H. pylori* infection. This result is similar to the findings from a study conducted in Turkey among preschool-age and school-age children that reported low income, density of children per household, and use of a heater as important risk factors [14]. In other words, it can be inferred that *H. pylori* infection occurs directly from person to person due to contacts in a dense living environment and poor socioeconomic status during adolescence. Higher *H. pylori* prevalence among men older than 16 years of age than among women of the same age indicates that close contacts are more common or that hygiene is poorer among school-age boys compared to girls. Another interesting finding is that the re-infection rate after *H. pylori* eradication through the standard triple therapy including a proton pump inhibitor (PPI) was also higher among males [4]. In that study, the re-infection rate was calculated for 331 individuals who received the standard triple therapy from 2003 to 2010 and tested negative 1 year after eradication with 18–95 months of follow-up (average of 37.1 months). Risk factors for re-infection, including sex/gender, age, tobacco consumption, alcohol consumption, income, education level, digestive symptoms, atrophic gastritis and intestinal metaplasia, and resistance to clarithromycin, were analyzed. Thirty-six of the 331 participants were re-infected, reflecting a 3.51% re-infection rate per year [4]. The risk factors identified in multivariate analysis were male sex (hazard ratio [HR] 2.28; 95% confidence interval [CI], 1.05–5.00; p = 0.037) and low income (≤$5000 vs. >$5000) (HR 3.54; 95% CI, 1.08–11.67; p = 0.038) [4]. As such, the risk factors for *H. pylori* re-infection were identical to the risk factors for *H. pylori* infection, suggesting that infection and re-infection are both more active among males above the age of 16.

8.3 Sex/Gender Differences in Chronic Gastritis

Gastritis refers to inflammation found through upper gastrointestinal (GI) endoscopy or in the GI mucosa and is categorized into acute gastritis and chronic gastritis. Gastritis presenting with acute inflammation or special types of gastritis are not difficult to diagnose as they demonstrate characteristic findings on endoscopy. However, there are some controversies regarding the endoscopic diagnosis and categorization of chronic gastritis, which is the most common type. In 1936, Schindler [15] categorized types of chronic gastritis based on gastroscopy findings into superficial gastritis, atrophic gastritis, hypertrophic gastritis, and post-gastric surgery gastritis and stated that there are major differences in the disease course and prognosis according to the type [15]. As endoscopy developed after the 1980s, researchers suggested various categorizations, most of which were based on histopathological characteristics rather than gross findings. The Sydney categorization [16], which was revised in 1996, has relatively detailed descriptions of the endoscopic diagnostic criteria of gastritis, but it has not been widely used due to its limits in expressing endoscopic findings and its complexity. After *H. pylori* was first cultured in 1983, *H. pylori* infection was found to be an important cause of peptic ulcers and a cause of gastritis. The finding that chronic active inflammation of the gastric mucosa is observed in most patients with *H. pylori* infection increased interest in chronic gastritis.

8.3.1 Sex/Gender Differences in the Distribution of Chronic Gastritis

The largest study about the distribution of gastritis was based on endoscopic findings among 25,536 individuals who received upper GI endoscopy at 40 hospital health check-up centers around South Korea from January to June 2006, conducted by the Korean College of Helicobacter and Upper Gastrointestinal Research [17] (Table 8.1). Among the 25,535 patients who remained after excluding those who had a history of surgery due to diseases related to the digestive system or who received treatment for chronic diseases other than hypertension and diabetes, 3593 (14.1%) had normal findings while 21,942 (85.9%) had at least one finding of gastritis finding. Gastritis was diagnosed based on mucosal erythema, exudate, edema, erosion, color change, increased vascular fluoroscopy, and nodular change. Superficial gastritis was most common (7983, 31.3%), followed by atrophic gastritis (6918, 27.1%), erosive gastritis (6054, 23.7%),

Table 8.1 Characteristics of 25,536 participants who received upper gastrointestinal endoscopy at 40 hospital health check-up centers around South Korea in 2006 (adapted from Park et al. [17])

Variable category	*n*	%
Sex		
Male	15,180	59.5
Female	10,356	40.5
Age (y)		
≤39	6976	27.3
40–59	15,001	58.8
≥60	3549	13.9
Area (province)		
Seoul	9525	37.3
Gyeonggi	3085	12.1
Kangwon	1965	7.7
Chungcheong	3094	12.1
Kyungsang	3646	14.3
Cholla	3759	14.7
Jeju	462	1.8
Social habitus		
Current smoking[a]	6529	26.0
Alcohol (≥once per week)[a]	10,479	41.0
Medical history		
NSAID medication for ≥1 month[a]	1616	6.0
Antibiotics history within 1 month[a]	253	1.0
Epigastric pain or discomfort during last 1 year[a]		
Yes	12,921	51.6
No	12,143	48.4
Endoscopic findings		
Normal	3593	14.1
Superficial gastritis	7983	31.3
Erosive gastritis	6054	23.7
Atrophic gastritis	6918	27.1
Intestinal metaplasia	1811	7.1

n number of subjects
[a]Some data were missing due to incomplete record

and intestinal metaplasia (1181, 7.1%) [17] (Table 8.2). There were no sex/gender differences in superficial gastritis, which was the most common type. Superficial gastritis decreased significantly with increasing age, with a prevalence of 36.8% (2556) in the age group of 40 and below, 31.3% (4704) in the 40–60 age group, and 20.4% (723) in the above 60 age group ($p < 0.001$). Unlike superficial gastritis (Table 8.2a), erosive gastritis (Table 8.2b), atrophic gastritis (Table 8.2c), and intestinal metaplasia were more prevalent among males than females ($p < 0.001$, Table 8.2d). The prevalence was highest in the above 60 age group, demonstrating an increasing frequency with age ($p < 0.001$) [17] (Table 8.2).

Table 8.2 Distribution of gastritis among 25,536 participants who received upper gastrointestinal endoscopy at hospital health check-up centers in 2006 by sex and age (adapted from Park et al. [17])

Variable categories	*n*	%	*p*-value[a]
a. Superficial gastritis			
Sex			
Male (*n* = 15,180)	4720	31.1	
Female (*n* = 10,356)	3263	31.5	0.483
Age (y)			
≤39 (*n* = 6976)	2556	36.8	
40–59 (*n* = 15,011)	4704	31.3	
≥60 (*n* = 3549)	723	20.4	<0.001
b. Erosive gastritis			
Sex			
Male (*n* = 15,180)	3983	26.2	
Female (*n* = 10,356)	2071	20.0	<0.001
Age (y)			
≤39 (*n* = 6976)	1396	20.0	
40–59 (*n* = 15,011)	3744	24.9	
≥60 (*n* = 3549)	914	25.8	<0.001
c. Atrophic gastritis			
Sex			
Male (*n* = 15,180)	4215	27.8	
Female (*n* = 10,356)	2703	26.1	0.003
Age (y)			
≤39 (*n* = 6976)	1039	14.9	
40–59 (*n* = 15,011)	4335	28.9	
≥60 (*n* = 3549)	1544	43.5	< 0.001
d. Intestinal metaplasia			
Sex			
Male (*n* = 15,180)	1262	8.3	
Female (*n* = 10,356)	549	5.3	<0.001
Age (y)			
≤39 (*n* = 6976)	187	2.7	
40–59 (*n* = 15,011)	1187	7.9	
≥60 (*n* = 3549)	437	12.3	<0.001

[a]*p*-values for χ^2 test

8.3.2 Sex/Gender Differences in Atrophic Gastritis and Intestinal Metaplasia

Chronic inflammation damages cells and transforms them into various stages. Precancerous tissues associated with chronic inflammation are characterized by neutrophils, macrophages, monocytes, mast cells, eosinophils, dendritic cells, and lymphocytes, which form the tumor microenvironment [18]. The inflammation-related cells that compose the tumor microenvironment produce cytokines, reactive oxygen, and reactive nitrogen and become involved in the initiation, promotion, and metastasis of cancerous mutations [18]. These factors contribute to carcinogenesis by promoting cellular mutations and modifying the functions of enzymes and proteins in tissues by damaging cellular DNA, RNA, and proteins through chemical reactions such as oxidation, nitrogenation, and halogenation. Many factors are known to cause gastric cancer, but the most important factor is *H. pylori* infection. Other factors include old age, male sex, family history of gastric cancer, salty food, smoked food, tobacco consumption, alcohol consumption, atrophic gastritis, and intestinal metaplasia [19]. Many studies have been published on the gastric cancer risk posed by atrophic gastritis and intestinal metaplasia. For example, gastric cancer incidence was 4.9 times higher among *H. pylori*-positive atrophic gastritis patients than among *H. pylori*-positive patients without atrophic gastritis and 14.5 times higher than among *H. pylori*-negative patients without atrophic gastritis [20, 21]. The risk was even higher among patients with intestinal metaplasia. The incidence of gastric cancer among *H. pylori*-positive intestinal metaplasia patients was 6.4 times or 10.9 times higher than that among *H. pylori*-positive patients without intestinal metaplasia [21, 22], suggesting that atrophic gastritis and intestinal metaplasia

are important precancerous lesions of gastric cancer. A 2011 national multicenter study with 4023 participants who received health check-ups at 8 medical centers in South Korea confirmed the 2005 results that atrophic gastritis and intestinal metaplasia in endoscopic findings were more prevalent among males than females [5] (Tables 8.3 and 8.4). In this national multicenter study, the prevalence of atrophic gastritis confirmed by endoscopy was 40.7%, and the prevalence of intestinal metaplasia was 12.5%. The most important risk factor was age, followed by sex. The prevalence of atrophic gastritis (odds ratio [OR] 1.38; Table 8.3) and intestinal metaplasia (OR 1.88; Table 8.4) was significantly higher among males than among females [5]. Another interesting finding was that in participants with a family history of gastric cancer, intestinal metaplasia (a risk factor of gastric cancer) was significantly more common (OR 1.48; Table 8.3) [5]. A Japanese study that conducted follow-up endoscopy for 17 years also found that intestinal metaplasia was more common among males than among females [23]. The gastric antral intestinal metaplasia grade from the biopsy before *H. pylori* eradication according to the Sydney system was higher among males (0.67 ± 0.94) than among females (0.44 ± 0.77) (p = 0.003). The gastric body intestinal metaplasia grade was also higher among males (0.20 ± 0.62) than among females (0.047 ± 0.21) (p = 0.0027), a difference that was consistently observed during the study duration [23].

Table 8.3 Multivariate analysis of risk factors of atrophic gastritis diagnosed in 4032 individuals who received an upper gastrointestinal endoscopy at health check-up centers in 2011 (adapted from Joo et al. [5])

Variables	B	S.E.	*p*-value	Exp(β)	95% confidence interval	
					Lower limit	Upper limit
Age (y)						
<40				1.00		
40–59	1.039	0.165	< 0.001	2.55	2.05	3.18
≥60	1.980	0.203	< 0.001	5.00	3.71	6.74
Male	0.603	0.155	< 0.001	1.38	1.17	1.64
H. pylori IgG positivity	0.377	0.112	< 0.001	1.41	1.19	1.66
Intestinal metaplasia	1.309	0.147	< 0.001	4.29	3.35	5.50
Education below college	−0.131	0.216	0.046	1.35	1.01	1.79

B estimate, *SE* standard error, *Exp(β)* odds ratio, *H. pylori Helicobacter pylori*

Table 8.4 Multivariate analysis of risk factors of intestinal metaplasia diagnosed in 4023 individuals who received upper gastrointestinal endoscopy at health check-up centers in 2011 (adapted from Joo et al. [5])

Variables	B	S.E.	*p*-value	Exp(β)	95% confidence interval	
					Lower limit	Upper limit
Age (y)						
<40				1.00		
40–59	1.150	0.205	<0.001	3.16	2.11	4.72
≥60	1.178	0.236	<0.001	3.25	2.05	5.15
Male	0.631	0.154	<0.001	1.88	1.39	2.54
H. pylori IgG positivity	0.775	0.119	<0.001	2.17	1.72	2.74
Atrophic gastritis	1.303	0.113	<0.001	3.68	2.95	4.60
Relatives of gastric cancer	0.395	0.143	0.006	1.48	1.12	1.96
Smoking	0.170	0.138	NS	1.19	0.91	1.55
Alcohol	0.112	0.131	NS	1.20	0.87	1.45
Education below college	−0.384	0.162	0.018	1.47	1.06	2.00
Consumption of dairy product	0.338	0.116	0.004	1.40	1.12	1.76

B estimate, *SE* standard error, *Exp(β)* odds ratio, *H. pylori Helicobacter pylori*

8.3.3 Sex/Gender Differences in 15-Year Changes in Atrophic Gastritis and Intestinal Metaplasia

With improvements in the socioeconomic conditions of South Korea, *H. pylori* infections have rapidly declined. When the sex/gender differences in atrophic gastritis and intestinal metaplasia diagnosed in biopsy were examined, the decline was significant among women, but no decline was found among men. This result can be interpreted as reflecting the importance of tobacco consumption, alcohol consumption, and diet beyond *H. pylori* for the incidence of atrophic gastritis and intestinal metaplasia [6]. That study was conducted among 2002 individuals from 2003 to 2018, examined atrophic gastritis and intestinal metaplasia through biopsies, and analyzed risk factors such as sex, family history of gastritis, alcohol consumption, tobacco consumption, diet, and socioeconomic status in 3 different phases (2003–2007, 2008–2012, and 2013–2018). The prevalence of *H. pylori* infection declined over the 15-year period, from 49.2% to 40.2% and 36.0% [6]. However, no significant changes were found in the prevalence of various atrophic gastritis and intestinal metaplasia grades from the histological examination of the gastric antrum and gastric body (Fig. 8.3a). Nonetheless, the grades of gastric body atrophic gastritis (p = 0.048) and intestinal metaplasia (p = 0.010) declined significantly among *H. pylori*-negative women, and the grade of gastric body intestinal metaplasia also declined significantly among *H. pylori*-positive women (p = 0.002) [6] (Fig. 8.3b). The changes in the prevalence of atrophic gastritis and intestinal metaplasia were similar to the changes in the grades of atrophic gastritis and intestinal metaplasia. When only the prevalence, rather than the grades, of atrophic gastritis and intestinal metaplasia was examined, there were no changes in the prevalence of atrophic gastritis and intestinal metaplasia among men (Fig. 8.3c), but the prevalence of atrophic gastritis (p = 0.024) and intestinal metaplasia (p < 0.001) declined significantly over the 15-year period in *H. pylori*-positive women [6] (Fig. 8.3d). These differences in the prevalence of atrophic gastritis and intestinal metaplasia are caused by differences in tobacco consumption, alcohol consumption, and diet, indicating that lifestyle habits have a major influence on gastric cancer risk factors beyond *H. pylori* infection. According to the Korea National Health and Nutrition Examination Survey conducted by the Ministry of Health and Welfare, the percentage of smokers was 38.1% among males and 6.0% among females in 2017 (http://www.index.go.kr/unify/idx-info.do?idxCd=4237), and the percentage of monthly binge drinkers was 52.7% among men and 25.0% among women (http://www.index.go.kr/unify/idx-info.do?idxCd=4238). According to national and international literature, women tend to consume more vegetables and fruit than men [24, 25]. According to a multivariate analysis of risk factors for atrophic gastritis and intestinal metaplasia, the risk of atrophic gastritis and intestinal metaplasia increased with age and *H. pylori* infection. Smokers had a particularly high risk of intestinal metaplasia in the gastric antrum [6]. In summary, *H. pylori* infection and tobacco consumption are important risk factors for chronic gastritis, and their effects accumulate over time and with age. Recent South Korean public health policy is shifting toward active interventions to prevent gastric cancer through *H. pylori* eradication therapy. The results suggest that attention should also be given to smoking cessation, moderation in alcohol consumption, and diet.

8.3.4 Sex/Gender Differences in Atrophic Gastritis and the Reversibility of Intestinal Metaplasia After *H. pylori* Eradication

The exact mechanism of intestinal metaplasia is not completely understood, but in recent studies, expression of the *CDX* gene, which codes for a specific transcriptional factor in the intestinal tract from the duodenum to the rectum, has been hypothesized as an important factor for both intestinal metaplasia itself and its progression to

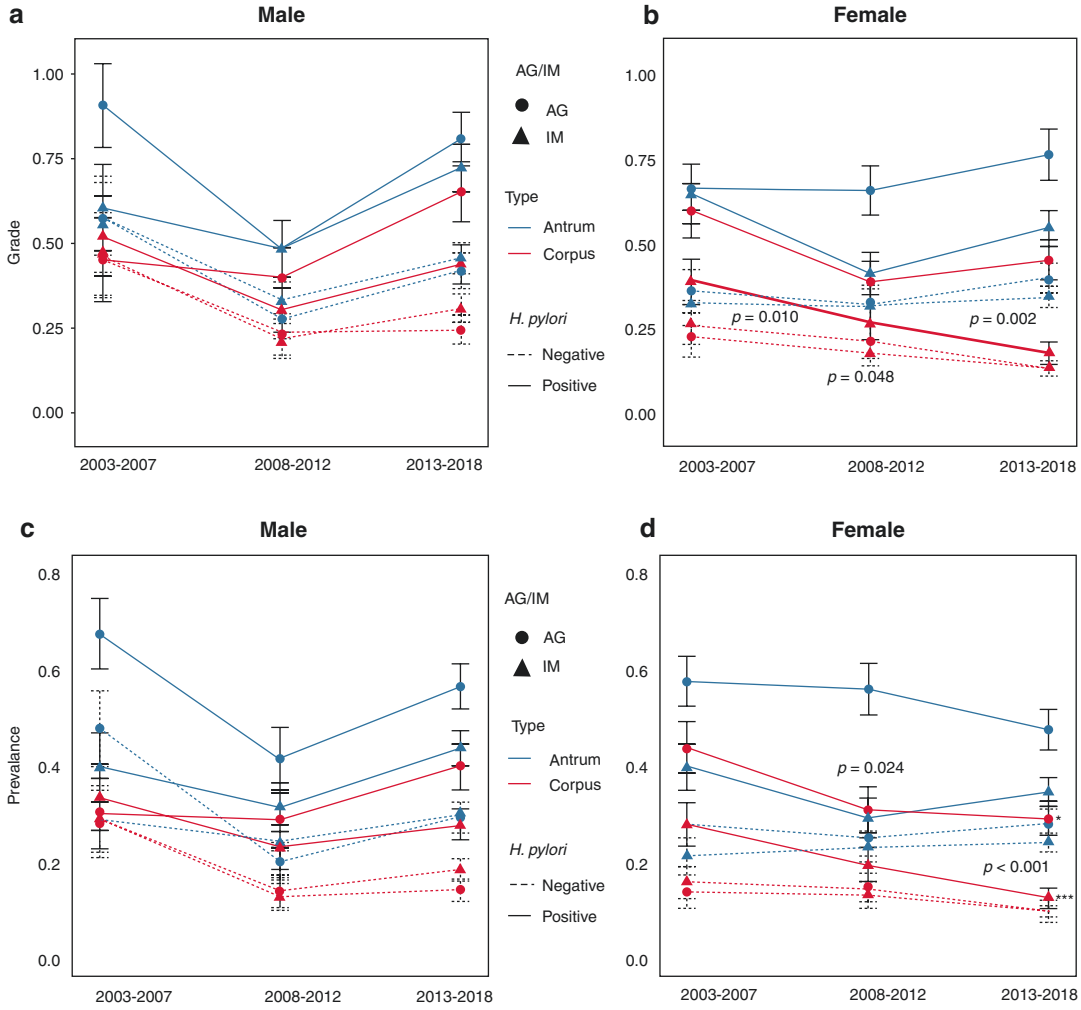

Fig. 8.3 Changes in the grade and prevalence of atrophic gastritis and intestinal metaplasia from histological examinations of the gastric antrum and gastric body in three phases over 15 years (2003–2007, 2008–2012, 2013–2018). (**a**) There were no changes in the grades of atrophic gastritis and intestinal metaplasia among men over 15 years. (**b**) Among *H. pylori*-negative women, the grades of atrophic gastritis ($p = 0.048$) and intestinal metaplasia ($p = 0.010$) in the gastric body declined significantly. The grade of gastric body intestinal metaplasia also declined significantly among *H. pylori*-positive women ($p = 0.002$). (**c**) There were no changes in the prevalence of atrophic gastritis and intestinal metaplasia among men. (**d**) The prevalence of atrophic gastritis ($p = 0.024$) and intestinal metaplasia ($p < 0.001$) declined significantly over 15 years in *H. pylori*-positive women (adapted from Kwon et al. [6])

dysplasia or gastric cancer [26]. The author investigated *CDX1* and *CDX2* gene expression using real-time polymerase chain reaction (PCR) after categorizing 270 participants by *H. pylori* infection status, intestinal metaplasia, dysplasia, and gastric cancer. *CDX1* and *CDX2* were not expressed in the normal gastric mucosa of the control group but were expressed when there was intestinal metaplasia. *CDX2* expression was also significantly higher in the gastric tissue of the *H. pylori* infection group than in the non-infected group [27]. *CDX1* and *CDX2* expression increased when the degree of intestinal metaplasia was more severe, and *CDX2* expression was significantly higher in incomplete intestinal metaplasia [27]. *CDX1* was expressed more in

the dysplasia group than in the control group, and *CDX1* and *CDX2* were both more strongly expressed in the gastric cancer group compared to the control group, supporting the hypothesis that CDX1 and CDX2, which are transcriptional factors, cause intestinal metaplasia and become involved in the mechanism of gastric cancer [27]. A study with an average follow-up of 33.7 months after *H. pylori* eradication reported that improvement in gastric body intestinal metaplasia was associated with reduced *CDX2* mRNA expression [28], providing evidence for an association between intestinal metaplasia and CDX2 and the reversibility of intestinal metaplasia through *H. pylori* eradication. In addition to endoscopic atrophic gastritis and intestinal metaplasia, histological atrophic gastritis and intestinal metaplasia were also found to be more severe among males than among females, suggesting that reversibility after eradication might be greater in females than in males.

A study analyzed a total of 24 factors that can impact the improvement of atrophic gastritis and intestinal metaplasia including environmental factors, single-nucleotide polymorphisms in host factors that regulate inflammatory responses, and genetic polymorphisms in *H. pylori* virulence factors by following up 778 participants for 10 years [29]. Since environmental factors, host factors, and genetic polymorphisms—as factors other than *H. pylori* eradication therapy or the follow-up period after therapy—contribute to improvements in atrophic gastritis and intestinal metaplasia, 11 environmental factors (sex, age, *H. pylori* infection and eradication status, tobacco consumption, history of alcohol consumption, blood type, salty food, spicy food, history of gastric cancer, education level, and economic status), 10 host genetic polymorphisms, and 3 *H. pylori* virulence factor polymorphisms were examined [29]. *H. pylori* eradication was statistically significantly associated with improvement in atrophic gastritis in the gastric antrum and gastric body, and gastric antrum intestinal metaplasia improved significantly in cytotoxin-associated gene A (*cagA*)-positive patients and patients who received *H. pylori* eradication [29]. *H. pylori* eradication was significantly associated with improvement of gastric body intestinal metaplasia [18]. When these findings were examined according to *H. pylori* infection status, *cagA* positivity and age younger than 65 were significant factors associated with improvements in atrophic gastritis and intestinal metaplasia among *H. pylori*-positive patients. In the *H. pylori* eradication therapy group, young age and economic status were significant factors associated with the improvement of atrophic gastritis and intestinal metaplasia [29]. *H. pylori* infection usually occurs at age 5 or below [30]; therefore, since the total time of exposure to *H. pylori* is shorter for younger individuals, it is suspected that atrophic gastritis and intestinal metaplasia improve more readily [29]. In order to confirm the significance of other factors excluding *H. pylori* eradication, which is the most important factor, further analyses were conducted after grouping *H. pylori*-positive patients, *H. pylori*-negative patients, and patients in whom *H. pylori* eradication was successful (Tables 8.5 and 8.6). In the *H. pylori*-positive group, age and *cagA* were significantly associated with the improvement of atrophic gastritis and intestinal metaplasia [29] (Table 8.5). Patients who were cagA antibody-positive had a significantly higher prevalence of atrophic gastritis and intestinal metaplasia [31]. Interestingly, in that study, atrophic gastritis and intestinal metaplasia showed meaningful improvement in *cagA* PCR-positive patients [29]. In the *H. pylori* eradication group, economic status had a significant influence on the improvement of atrophic gastritis, and age below 65 was a significant factor associated with the improvement of intestinal metaplasia [29]. Environmental factors such as age and economic status impact not only the incidence of *H. pylori* infection, atrophic gastritis, and intestinal metaplasia but also their improvement after eradication treatment [18]. *H. pylori* eradication was found to be a common factor that influenced the improvement of both atrophic gastritis and intestinal metaplasia, but there were factors not common to both. An explanation for this finding is that the risk factors of atrophic gastritis and intestinal metaplasia are different [18]. The risk factors of atrophic gastritis are *H. pylori* infection, old age, *H. pylori* virulence factors,

Table 8.5 Analysis of factors associated with the improvement of atrophic gastritis and intestinal metaplasia among *H. pylori*-positive patients (adapted from Hwang et al. [29])

		Improvement	No improvement	Uni-variable *p*-value	Multivariable *p*-value	OR (95% CI)
AG in antrum						
cagA	Negative (ref)	58 (50.9)	75 (68.8)			
	Positive	56 (49.1)	34 (31.2)	0.006	0.01	0.48 (0.28–0.84)
AG in body						
cagA	Negative (ref)	54 (58.1)	37 (80.4)			
	Positive	39 (41.9)	9 (19.6)	0.009	0.023	0.37 (0.16–0.87)
IM in antrum						
Age	≥ 65 years (ref)	54 (28.1)	89 (41.8)			
	< 65 years	138 (71.9)	124 (58.2)	0.004	0.017	0.55 (0.34–0.90)
cagA	Negative (ref)	88 (59.5)	108 (71.1)			
	Positive	60 (40.5)	44 (28.9)	0.035	0.072	0.64 (0.39–1.04)
IM in body						
cagA	Negative (ref)	71 (59.7)	66 (78.6)			
	Positive	48 (40.3)	18 (21.4)	0.005	0.055	0.62 (0.38–1.01)

Data are presented as number (%)
AG atrophic gastritis, *IM* intestinal metaplasia, *OR* odds ratio, *CI* confidence interval

Table 8.6 Analysis of factors associated with the improvement of atrophic gastritis and intestinal metaplasia after *H. pylori* eradication (adapted from Hwang et al. [29])

		Improvement	No improvement	Uni-variable *p*-value	Multivariable *p*-value	OR (95% CI)
AG in body						
Monthly income	<25,000 (ref)	20 (27.4)	9 (52.9)			
(dollar)	≥25,000	53 (72.6)	8 (47.1)	0.042	0.048	0.34 (0.11–0.99)
IM in antrum						
Age	≥65 years (ref)	45 (26.5)	54 (38.6)			
	<65 years	125 (73.5)	86 (61.4)	0.023	0.024	0.57 (0.35–0.93)

Data are presented as number (%)
AG atrophic gastritis, *IM* intestinal metaplasia, *OR* odds ratio, *CI* confidence interval

male sex, and education level, while the risk factors of intestinal metaplasia are *H. pylori* infection, old age, male sex, history of tobacco consumption, spicy food consumption, and family history of gastric cancer [5, 32]. It was hypothesized that improvements in atrophic gastritis and intestinal metaplasia after *H. pylori* eradication will be more likely among males than among females whose atrophic gastritis and intestinal metaplasia grades were lower, but sex was not a statistically significant factor. This finding might be related to fact that males more actively received eradication treatment and that among females, atrophic gastritis and intestinal metaplasia improved regardless of *H. pylori* infection [6]. A more definitive conclusion can be reached after further research from multiple perspectives.

8.4 Sex/Gender Differences in the *H. pylori*-Eradicated Population

Comparing the eradication trends in 2005, 2011, and 2016–2017 based on a national study that reported the *H. pylori*-positive rate and the eradication rate for 18 years, it was found that a history of eradication became more common in the older population, reflecting the trend for an increasing number of patients to receive eradication therapy in the 40–49, 50–59, 60–69, and above 70 age groups [3] (Fig. 8.4a). This trend could be explained by a greater interest in health with increasing age, which might be accelerated by health policies that actively promoted eradication by publicizing research results that found *H. pylori* infection promotes gastric cancer. Eradication in younger populations is desirable to prevent gastric cancer. It is not recommended to place an age limit on eradication therapy for the following reasons: (1) *H. pylori* eradication improves various indicators of the tumor microenvironment (e.g., *H. pylori* eradication reduced the proportion of patients with a pepsinogen I/II ratio of 3 or less, a biomarker of atrophic gastritis, in a group of patients with gastric cancer and dysplasia [conditions that are more common in the elderly] to the point that no significant difference was observed from a control group) [33]; (2) the survival rate of gastric cancer surgery patients after *H. pylori* eradication has recently increased [34]; and the average life expectancy in South Korea continues to increase. The eradication rates were 15.4%, 21.3%, and 26.7% among men in 2005, 2011, and 2016–2017, respectively, which were significantly higher than the corresponding rates of 12.2%, 16.8%, and 19.7% among women, suggesting more active eradication among men [3] (Fig. 8.4b). This finding can be interpreted as a result of more frequent health check-ups, more *H. pylori* tests conducted, and more exposure to information about the necessity of *H. pylori* eradication among men. Insurance coverage for *H. pylori* eradication in South Korea expanded in January 2018, and atrophic gastritis became a condition that prompts recommendation for eradication; therefore, eradication has recently become active in the private sector. In Japan, 600,000 individuals were treated with *H. pylori* eradication drugs annually, and after *H. pylori*-positive gastritis was covered by insurance in March 2014, the population that received eradication increased 2.3-fold to 1,400,000 [35]. Similarly, the proportion of the population receiving *H. pylori* eradication in South Korea is expected to increase further from the proportion of 23.5% in 2016–2017 [3].

8.5 Sex/Gender Differences in the Changes of Lipid Metabolism After *H. pylori* Infection

In 1969, Gallin et al. [36] found that the bacteria-induced systemic inflammatory response causes changes in lipid metabolism. Studies based on epidemiological research, such as various studies that examined the relationship between *H. pylori* infection and lipid metabolism, have been reported since. A study reported that among patients with coronary artery disease diagnosed by angiography, there were no changes in total cholesterol and low-density lipoprotein (LDL) cholesterol, but significantly lower HDL cholesterol levels, in *H. pylori* antibody-positive

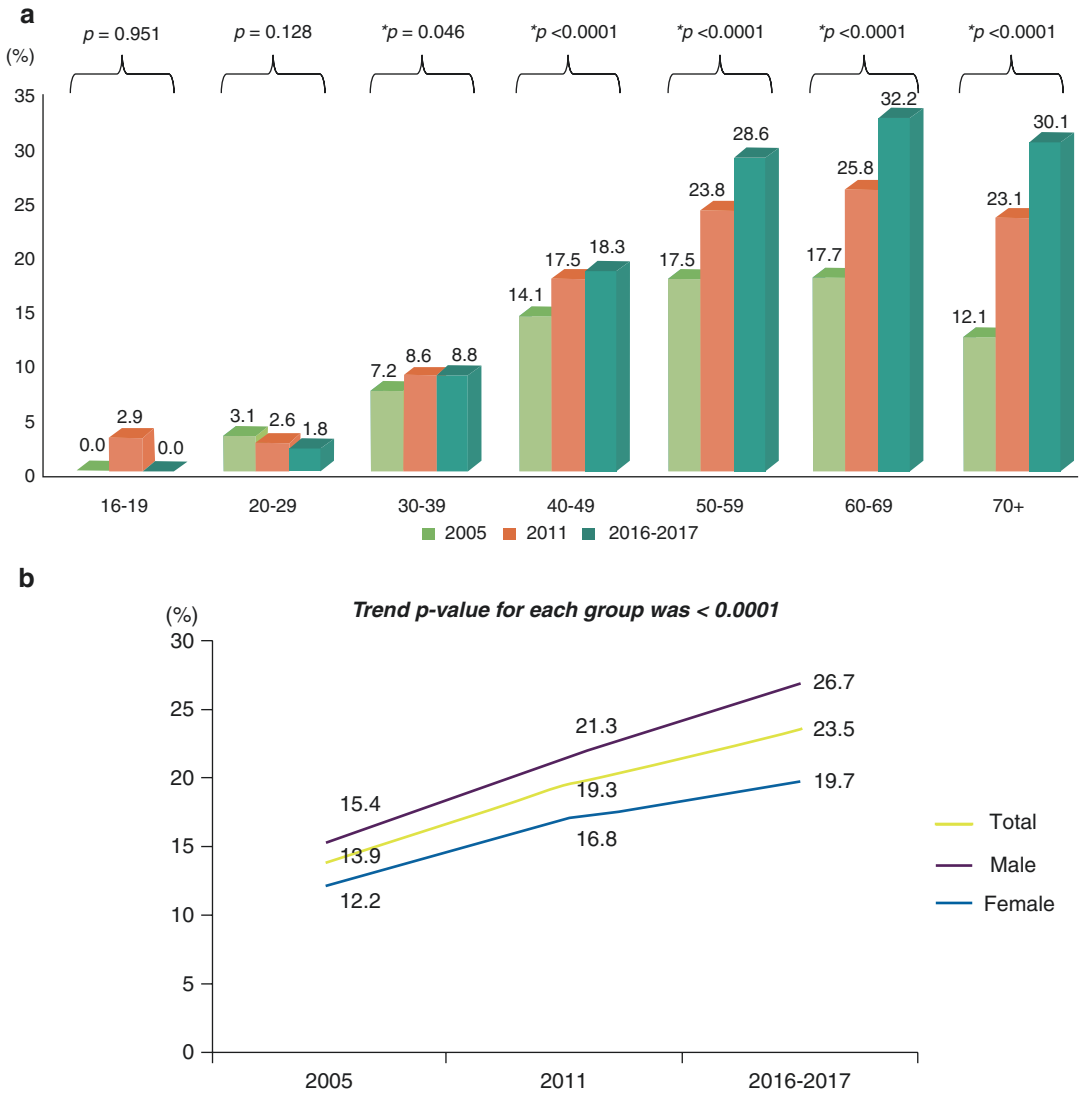

Fig. 8.4 Increase in the number of *H. pylori*-eradicated population in South Korea in 2005, 2011, and 2016–2017. (**a**) The rate of eradication increased rapidly with age. (**b**) When the *H. pylori*-eradicated population was compared by sex, the number was significantly higher among males than among females. *p value for trend (adapted from Lim et al. [3])

patients [37]. Another study reported that *H. pylori* infection was associated with higher triglyceride levels and lower HDL cholesterol levels [38], while a different study did not find such association [39]. A study of healthy adult males rather than patients found higher LDL cholesterol levels and lower HDL cholesterol levels in the *H. pylori* antibody-positive group than in the negative group [40]. A recent study in South Korea analyzing 15,195 participants in health check-ups reported that body mass index, waist circumference, total cholesterol, and LDL cholesterol levels were higher and HDL cholesterol levels were lower in the *H. pylori*-positive group than in the negative group [41]. Studies of the association between *H. pylori* infection status and lipid metabolism indicators are diverse in terms of their designs, samples, and results.

Summarizing studies that reported significant associations between *H. pylori* infection status and changes in lipid metabolism indicators, *H. pylori* infection is associated with higher levels of total cholesterol, LDL cholesterol, triglycerides, and apolipoprotein B, and lower concentrations of HDL cholesterol and apolipoprotein A1 [37, 38, 40, 41]. These results are explained by the increase in the activity of lipoprotein lipase in adipose tissue and fatty acid synthesis and lipolysis in the liver caused by the increased release of cytokines related to *H. pylori* infection such as IL-1 or IL-6, IFN-α, and TNF-α [42, 43]. A study reported sex/gender differences in such changes [8]. A recent South Korean study of 1065 individuals reported that in the *H. pylori*-positive group (663, 62.3%), total cholesterol ($p = 0.003$), LDL ($p = 0.046$), and triglyceride ($p = 0.029$) levels were significantly higher, and HDL cholesterol levels were significantly lower ($p = 0.032$) [8]. In the multivariate analysis, males in the *H. pylori*-positive group had higher total cholesterol levels (OR 1.007; 95% CI, 1.002–1.011), while females had lower HDL cholesterol levels (OR 0.983; 95% CI, 0.968–0.998) [8]. This result is related to the reports that metabolic syndrome is more common in *H. pylori*-positive individuals, males, and older individuals [44] and that diabetes was more common only among males in the *H. pylori*-positive group, suggesting a relationship with sex hormones [45]. *H. pylori* infection affects lipid metabolism and diabetes incidence differently by sex/gender, and further studies are needed in this area.

8.6 Conclusions

H. pylori is transmitted at a young age when the immune system is not fully mature, and unless artificial eradication is attempted, the infection lasts for a lifetime. Sex/gender differences have been found in the epidemiology of *H. pylori*, chronic gastritis, the eradication rate, and lipid metabolism. There were no sex/gender differences in *H. pylori* infection until the age of 15 according to a 1998 study of the serum prevalence of *H. pylori* in all age groups conducted in South Korea, but the *H. pylori* infection rate among males become significantly higher than that among females after the age of 16. This phenomenon was observed in the 2016–2017 epidemiological survey as well. This finding cannot be explained completely by a cohort effect and indicates that *H. pylori* infections occur among males, who have higher exposure after the age of 15. Moreover, in a 2006 national multicenter study with 25,513 individuals, erosive gastritis, atrophic gastritis, and intestinal metaplasia were significantly more common among males than among females. The same result was found for atrophic gastritis and intestinal metaplasia in a 2011 national, multicenter study with 4023 participants of health check-ups. The prevalence of *H. pylori* infections is rapidly decreasing in South Korea. The histological findings of atrophic gastritis and intestinal metaplasia decreased among females from 2003 to 2018, but they did not decrease among males, indicating that tobacco consumption, alcohol consumption, and diet are important factors other than *H. pylori* infection contributing to the incidence of atrophic gastritis and intestinal metaplasia. The eradication rate of *H. pylori* is higher in older age groups, as older adults are more interested in maintaining health. The eradication rates were 15.4%, 21.3%, and 26.7% in 2005, 2011, and 2016–2017 among males, which were significantly higher than the corresponding rates of 12.2%, 16.8%, and 19.7% among females, suggesting active *H. pylori* eradication among males. A systemic inflammatory response to bacteria causes changes in lipid metabolism. Total cholesterol levels were higher in *H. pylori*-positive males, and HDL cholesterol levels were lower in *H. pylori*-positive females, indicating sex/gender differences in lipid metabolism post-*H. pylori* infection. Considering the differences in epidemiology, chronic gastritis, and lipid metabolism by sex/gender after *H. pylori* infection, tailored therapy including decisions about the timing of eradication therapy is recommended.

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