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REVIEW ARTICLE

Why is the coexistence of gastric cancer and duodenal ulcer rare? Examination of factors related to both gastric cancer and duodenal ulcer

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Abstract The coexistence of gastric cancer with duodenal ulcer has been found empirically to be rare, but why it is rare is difficult to explain satisfactorily. To elucidate this question, we carried out a literature review of the subject. The frequency with which the two diseases coexist is 0.1–1.7%, and the main factor associated with both gastric cancer and duodenal ulcer is *Helicobacter pylori* infection. However, there are marked differences between the disorders of hyperchlorhydria in duodenal ulcer, and hypochlorhydria in gastric cancer. The most acceptable view of the reason for the difference may be that the acquisition of *H. pylori* infection occurs mainly in childhood, so that the time of acquisition of atrophic gastritis may be the most important, and if atrophic gastritis is not acquired early, high levels of gastric acid may occur, and consequently acute antral gastritis and duodenal ulcer may occur in youth, whereas, in elderly individuals, persistent *H. pylori* infections and the early appearance of atrophic gastritis may be the causes of low gastric acid, and consequently gastric cancer may occur. In patients with duodenal ulcer, factors such as nonsteroidal anti-inflammatory drugs (NSAIDs) and *dupA-H. pylori* strains may contribute to preventing the early acquisition of atrophic gastritis, while acid-suppressive therapy and vascular endothelial growth factor and other entities may inhibit atrophic gastritis. In contrast, in gastric cancer, factors such as excessive salt intake, acid-suppressive therapy, polymorphisms of inflammatory cytokines, and the *homB-H. pylori* strain may contribute to the early acquisition of atrophic gastritis, while factors such as NSAIDs; fruits and vegetables; vitamins A, C, and E; and good nutrition may inhibit it.

Keywords Gastric cancer · Duodenal ulcer · *Helicobacter pylori* · Polymorphism · Gastric acid

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Introduction

Recently, we encountered a patient with gastric cancer that was histologically of the diffuse type and in whom the active bleeding of a duodenal ulcer had been successfully treated by an endoscopic procedure 4 months before the diagnosis of the gastric cancer.

However, it has been shown empirically that the coexistence of gastric cancer with duodenal ulcer is a rare phenomenon [1]—indeed, the frequencies of gastric cancer and gastric and duodenal ulcers are about 0.15, 2, and 1%, respectively, in Japanese mass surveys. But the coexistence of gastric cancer and duodenal ulcers is very rare. Several studies have demonstrated the low frequency of this combination, and the question about this coexistence has been variously discussed for a long time, leading to a small flood of opinions at each report of a new finding regarding causation, such as *Helicobacter pylori*, H2-blockers, proton pump inhibitors (PPIs), and so on, but still no satisfactory answer has been found.

H. pylori infection, in particular, is an etiological factor common to both diseases and may be one of the major causative factors in both, and so it is reasonable to expect a strong, direct relationship between the two diseases, and a frequency of coexistence that is more than fortuitous. That is to say, a strong association between them would be

unsurprising. And yet, the diseases have different phenotypes and they rarely coexist. Why?

To shed some light on this question, we investigated the relationship between gastroduodenal peptic ulcers and gastric cancer by reviewing the literature on the subject.

Frequencies of duodenal ulcer and gastric cancer

H. pylori infects approximately half of the world's population [1], and in 1994, the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) concluded that *H. pylori* is a definite carcinogen in humans [2].

Labigne and de Reuse [3], Graham [4], and Stemmermann and Fenoglio-Preiser [5] have reported that *H. pylori* infection is a causative agent of superficial gastritis, peptic ulcer, atrophic gastritis, and gastric cancer. Graham [4] and Uemura et al. [6] reported that approximately 20% of *H. pylori*-infected individuals develop clinically significant diseases, and the frequency of duodenal ulcers in individuals with *H. pylori* infection is thought to be approximately 16% [4]. Although Fischer et al. [7] found 48 cases of concomitant gastric cancer while reviewing 45000 patients with duodenal ulcer (0.1%), Miwa et al. [8] stated that six patients with gastric cancer among their 356 patients (1.7%) also showed duodenal ulcers, and Take et al. [9] and Kamada et al. [10] reported that gastric cancer did not develop in patients with duodenal ulcer. Uemura et al. [6] conducted a 5-year follow-up of many Japanese subjects with *H. pylori* infections and found that all those with duodenal ulcers were also infected with *H. pylori*; however, none of the patients with duodenal ulcer developed gastric cancer, although 3.4% of the patients with gastric ulcer did, and gastric cancer subsequently appeared in 5% of the patients with *H. pylori* infections. Fuccio et al. [11] indicated that the risk of gastric cancer was higher in patients with gastric ulcer than in those with duodenal ulcer. Therefore, gastric cancer concomitant with duodenal ulcer appears to be very rare.

We examined the factors related to both gastric cancer and duodenal ulcer.

Exogenous factors (Fig. 1)

Various *H. pylori* strains (Figs. 1, 4)

It is gradually becoming clear that there is a wide variety of *H. pylori* infections, and that there are some bacterial strains that may well be more likely to cause duodenal ulcer disease, and others that may promote the development of gastric cancer [12].

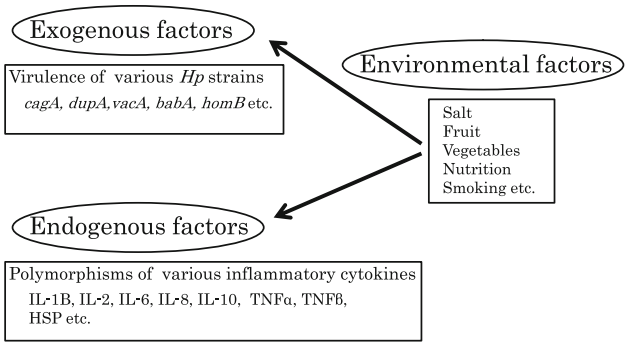

Fig. 1 Risk factors of gastric cancer and duodenal ulcer. *Hp*, *Helicobacter pylori*; *IL*, interleukin; *TNF*, tumor necrosis factor; *HSP*, heat shock protein

Atherton [13], Atherton et al. [14], Censini et al. [15], Prinz et al. [16], and Li et al. [17] have reported that *H. pylori* strains containing various bacterial virulence factors—such as the cytotoxicity-associated gene pathogenicity island (*cag*PAI), the vacuolating cytotoxin (*vacA*) gene, and the blood group antigen binding adhesion (*babA*) gene—are associated with more severe inflammation and an increased risk of developing cancer. Marrelli et al. [18] have reported that the *vacA* gene encodes the vacuolating cytokine VacA, which induces epithelial cell injury, and the degree of heterogeneity in *vacA* may be useful as a marker for peptic ulcer diseases.

Odenbreit et al. [19] have reported that the *cagA* gene is located in the right half of the PAI, and encodes the CagA protein, which is translocated into the gastric epithelial cells that deleteriously affect host cell physiology. Huang et al. [20], Kuipers et al. [21], and Hatakeyama [22] have indicated that the *cagA* gene increases the risk of atrophic gastritis and gastric cancer, and Yamaoka et al. [23] reported that subgroup analysis suggested that Japanese *H. pylori* strains with the type C pattern of repeats (1 FR region and 2 JSR regions) in CagA + *H. pylori* strains were associated with atrophy and gastric cancer. Moreover, Graham [4] reported that, in the presence of low acid secretion, highly virulent *H. pylori* (due to the presence of *cagA*) might lead to atrophic gastritis and a concomitant increase in the risk of developing cancer. However, Nomura et al. [24] and Atherton et al. [14] stated that individuals infected with CagA + *H. pylori* were at higher risk of developing duodenal ulcers than those infected with other *H. pylori* strains.

Meanwhile, Lu et al. [25] and Argent et al. [26] reported that the expression of the duodenal ulcer-promoting gene A (*dupA*) may be associated with an increased risk of duodenal ulcer and a reduced risk of gastric cancer, because the pathogenic mechanism of *dupA* appears to involve the induction of high interleukin (IL)-8 production in the antrum, leading to antrum-predominant gastritis, a well-

recognized characteristic of duodenal ulcer. However, Hussein [1] reported that *dupA* promotes duodenal ulceration in some populations and gastric ulcer and gastric cancer in others, and Argent et al. [26], Nguyen et al. [27], and Arachchi et al. [28] indicated that about 40% of *H. pylori*-infected patients with duodenal ulcer do not have the *dupA* gene, so that they required further investigation into the effects of the *dupA* gene.

However, recently, Jung et al. [29] have reported that, although *cagA* status was associated with inflammation and atrophy both in the antrum and in the corpus, *homB* (one of the *hom* family of *H. pylori* outer-membrane proteins) status was associated with inflammation and atrophy only in the corpus, so that *homB* gene status may be used as a factor for discriminating between the risk of gastric cancer and that of duodenal ulcer.

In this way, various *H. pylori* strains have been reported and various opinions concerning them are prevalent, but no consensus has existed, and at present, it is impossible to answer the questions that prompted this study merely on the basis of differences of virulence between *H. pylori* strains. However, if unknown types of *H. pylori* strains that induce gastric cancer and duodenal ulcer independently are discovered in the future, it is possible that current views will undergo great changes. Therefore, major developments of research in this field can be expected.

Effects of acid-suppressive therapy (Fig. 2)

Camels et al. [30] reported that atrophic gastritis in which there is a loss of gastric acidity contributes to the promotion of the endogenous formation of *N*-nitroso compounds by the gastric bacterial flora, and Sanduleanu et al. [31] indicated that profound acid-suppressive therapy can be associated with bacterial overgrowth with non-*H. pylori* species within the stomach, so that these factors may be some of the causative factors of gastric cancer.

Moreover, Lamberts et al. [32] and Klinkenberg-Knol et al. [33] indicated that the profound reduction in gastric acid secretion induced by PPIs leads to increased secretion of gastrin, and most PPI users have moderate hypergastrinemia; Havu [34], Gillen and McColl [35], and Kuipers [36] indicated that hypergastrinemia has been associated with an increased risk of gastric cancer.

Kuipers [36] and Kuipers and Sipponen [37] stated that PPI therapy in *H. pylori*-positive patients changes the gastritis pattern from antral-predominant to corpus-predominant pangastritis, and in antral-predominant gastritis, inflammation of the antral mucosa stimulates gastrin secretion, which maintains acid production at a normal to high level and thus keeps the acid production pattern intact, in contrast with corpus-predominant gastritis, in which inflammation of the gastric corpus mucosa further impairs acid secretion, despite the increase in gastrin. These authors [36, 37] concluded that, in patients with *H. pylori* infection, long-term PPI use is associated with an increased incidence of atrophic gastritis, which is a precursor of gastric cancer. Similarly, vagotomy, a procedure used mainly for duodenal ulcers, may increase the risk of gastric cancer [38], as may treatment with cimetidine [39] (Fig. 3).

Elder et al. [40] proposed that cimetidine is converted to its nitroso analog which structurally resembles other known gastric carcinogens, but Muscroft et al. [41] contended that cimetidine is unlikely to cause gastric cancer, as a result of their finding low concentrations of gastric juice nitrite in patients taking the drug.

Lin et al. [42] reported on the anticancer activity of cimetidine (Fig. 3), and noted that the perioperative use of cimetidine in gastric cancer patients could help restore diminished cellular immunity. Milito and Fais [43], Dillman et al. [44], and Jiang et al. [45] were in agreement with this opinion, but Langman et al. [46] reported that

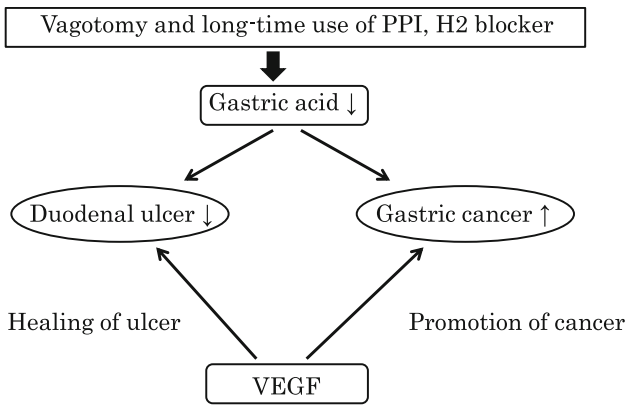

Fig. 2 Effects of acid-suppressive therapy. *PPI* proton pump inhibitor, *VEGF* vascular endothelial growth factor

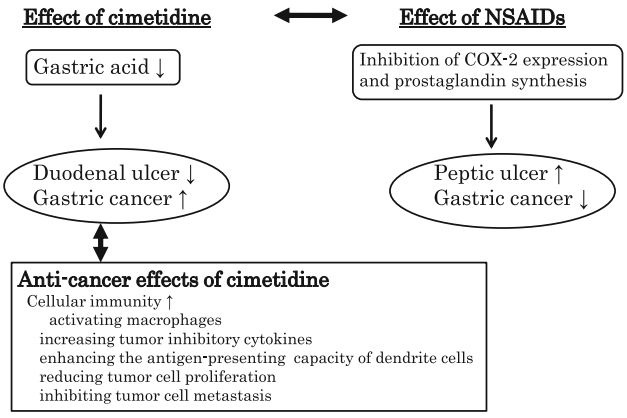

Fig. 3 Effects of cimetidine and nonsteroidal anti-inflammatory drugs (*NSAIDs*). *COX-2* cyclooxygenase-2

cimetidine did not show significantly more influence on the survival of patients with gastric cancer than placebo. Therefore, further investigation is required into the effects of cimetidine.

Effects of nonsteroidal anti-inflammatory drugs (Fig. 3)

Gridley et al. [47] and Thun et al. [48] indicated that nonsteroidal anti-inflammatory drugs (NSAIDs) may protect patients against gastric cancer as well as colorectal cancer. Wang et al. [49] reported that NSAID use has been associated with a reduced risk of gastric cancer and speculated that it is possible that NSAIDs may inhibit the replication and proliferation of *H. pylori* [49, 50], while Takahashi et al. [51] and Hudson et al. [52] reported that NSAIDs may neutralize the increased cyclooxygenase-2 (COX-2) expression and prostaglandin synthesis associated with *H. pylori* infection, thereby reducing the risk of gastric cancer. However, these drugs may also cause peptic ulcers [53], so that long-term NSAID use may be associated with an increased risk of gastroduodenal ulcer and a reduced risk of gastric cancer, but there are some negative opinions about this association [54, 55], and so there is no consensus regarding the anticancer effects of NSAIDs.

Effects of diet (Fig. 1)

Graham [4] indicated that fresh fruits and vegetables may prove to have been a critical factor in delaying or preventing the progression of superficial gastritis to atrophic gastritis; Correa et al. [56] named this phenomenon "the banana hypothesis" and concluded that environment is more important than genetics in determining the outcome of an *H. pylori* infection.

Parsonnet et al. [57], Correa et al. [58], and Kobayashi et al. [59] indicated that dietary factors that have been suspected to increase risk, such as nitrates, carbohydrates, and salt, could potentially amplify the risk of mutation beyond that due to inflammation alone, whereas fresh fruits and vegetables, and vitamins A, C, and E are dietary antioxidants that may limit inflammation-related oxidative damage.

Consumption of fresh fruit and vegetables may diminish the risk of acute antral gastritis, but it has no effect on more advanced cases of atrophy such as atrophic body gastritis, and therefore, it is considered that the consumption of fresh fruits and vegetables may also be of little value in the improvement of severely advanced mucosal atrophy.

Of interest, Correa et al. [58] reported that salty foods may be another risk factor for gastric cancer, excessive salt perhaps amplifying the virulent carcinogenetic factors of *H. pylori*.

Other exogenous risk factors (Fig. 1)

Chen et al. [60] and Sierra et al. [61] indicated that male gender and smoking were associated with an increased risk of duodenal ulcer in *H. pylori*-infected patients. Graham [4] speculated that poor nutrition in childhood and low parietal cell function may leave *H. pylori*-infected patients open to gastric cancer, whereas good nutrition in childhood and high parietal cell function may precede the development of duodenal ulcer. Moreover, childhood infections such as diphtheria, tonsillitis, and so on are associated with a marked decrease in acid secretion, and this is also considered to be a causative factor in gastric cancer [62–64].

Endogenous factors

Polymorphisms of inflammatory cytokines (Figs. 1, 4)

Suzuki et al. [65] and Murakami et al. [66] have reported that *H. pylori* increases the production of inflammatory cytokines such as IL-1β, IL-2, IL-6, IL-8, and tumor necrosis factor alpha (TNF-α), and that toxic metabolites and lysosomal enzymes released from neutrophils are also responsible for gastric mucosal injury, while Takashima et al. [67] reported that decreased acid secretion was accompanied by an elevation of IL-1β messenger RNA levels in the *H. pylori*-infected gastric mucosa. Esplugues et al. [68] and Kondo et al. [69] reported that the acid-inhibitory effect of IL-1β appears to involve nitric oxide synthesis and may be mediated by the inhibition of gastric histamine mobilization.

The examination of gastric acid secretion is very important because a significant difference in gastric acid secretion exists between duodenal ulcer and gastric cancer; namely, hyperchlorhydria in duodenal ulcer and hypochlorhydria in gastric cancer.

Furthermore, El-Omar et al. [70], Furuta et al. [71], Figueiredo et al. [72], and Camargo et al. [73] indicated

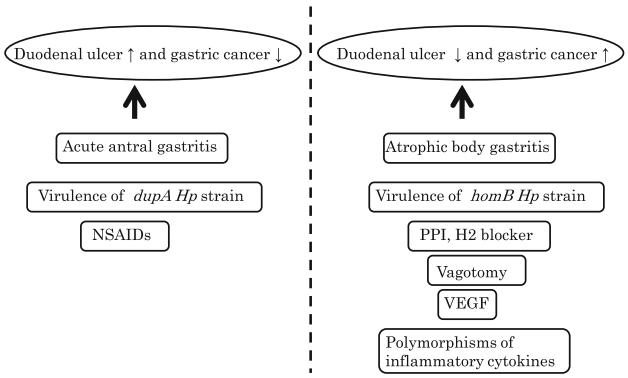

Fig. 4 Possible causative factors of gastric cancer and duodenal ulcer

that IL-1 genetic polymorphism may induce a reduction in acid secretion, may cause gastric inflammation and atrophy, and may contribute to *H. pylori*-related gastric carcinogenesis. Moreover, Camargo et al. [73], Zambon et al. [74], and El-Omar et al. [75] stated that polymorphisms in genes associated with the inflammatory response in the gastric mucosa, such as IL-1β, TNF-α, and IL-10, have been shown to be associated with higher risks for duodenal ulcer and gastric cancer. However, Kato et al. [76], Lee et al. [77], Gatti et al. [78], and Kamangar et al. [79] did not agree with these opinions, and Chang et al. [80], in particular, indicated that mucosal inflammatory cytokines were related to gastroduodenal phenotypes, not to IL-1β genotypes, and they noted that *H. pylori* infection was a more important factor in the development of gastroduodenal phenotypes than IL-1β polymorphisms. Partida-Rodríguez et al. [81], however, reported that genotype TNF-β G/G showed a significant gene-dose effect with gastric cancer, and heat shock protein (HSP) 70-1 C/G showed significant association with both gastric cancer and duodenal ulcer.

Thus, opinions vary considerably, but it is not possible to explain the causes of gastric cancer and duodenal ulcer by the notion of polymorphism alone. Nevertheless, examination of the polymorphisms of inflammatory cytokines is very important because hitherto unknown polymorphisms of some cytokines which have significant roles in gastric acid secretion may be found in the future.

Effect of vascular endothelial growth factor (Figs. 2, 4)

Jones et al. [82] and Suzuki et al. [83] stated that enhanced vascular endothelial growth factor (VEGF) gene expression was identified to contribute to the healing of peptic ulcer, whereas Takahashi et al. [84] and Maeda et al. [85] reported that gastric cancer frequently displayed high levels of VEGF expression associated with intramucosal microvessel density, and Feng et al. [86] indicated that high levels of VEGF expression have also been observed in gastric premalignant lesions such as chronic atrophic gastritis and intestinal metaplasia. Moreover, Tahara et al. [87] indicated that the VEGF 1612A polymorphism was associated with an increased risk of gastric cancer.

Failure to notice lesions

In addition to the above factors, failure to detect gastric cancer during the follow-up periods for gastroduodenal ulcers may also play a part in the reported lack of gastric cancer coexistent with duodenal ulcer. Especially in cases of duodenal ulcers that are, for instance, large, deep, bleeding, or concomitant with severe acute antral gastritis, gastric cancer of the antrum may easily be missed. Indeed, Takatsu et al. [88] reported that 0.98% (9/920) of gastric cancers were missed in panendoscopy; moreover, Hosokawa et al. [89] reported that in 41/250 (16.4%) cases, gastric cancer may have been overlooked. Therefore, the problem of failure to notice a lesion should also be included in our title question, because in patients with multiple lesions, minor lesions tend to be easily overlooked in various examinations.

Etiology of duodenal ulcer and gastric cancer (Fig. 5)

Although gastric cancer and duodenal ulcer have the same major causative factor (*H. pylori* infection), the phenotypes of the diseases are greatly different. Why and how do *H. pylori* infections lead to different diseases?

To help answer this question, we examined the etiology of these two disorders involving the various factors related to these disorders mentioned above.

Mabe et al. [90] reported that cases of duodenal ulcer are more prevalent in younger individuals than gastric cancer cases and that gastritis in duodenal ulcer was primarily antral and spared the gastric corpus, allowing continued high levels of acid secretion. Corpus inflammation, however, has long been known to suppress acid, and low acid allows *H. pylori* to interact with the mucosa to cause more inflammation and to establish a vicious cycle leading to the loss of glands and to atrophy. Correa [91] speculated that atrophic gastritis starts in the antrum and may extend upwards towards the gastric body, often resulting in more severe atrophic gastritis with increased age. Uemura et al. [6], Khulusi et al. [92], Sipponen et al. [93], and Wu et al. [94] have indicated that antral-predominant gastritis is associated with hyperchlorhydria and duodenal ulcer, whereas corpus gastritis leads to hypochlorhydria and atrophy and an increased risk of distal gastric cancer. Miwa et al. [8] stated that the low incidence of gastric cancer coexistent with duodenal ulcer was assumed to depend on the fact that intestinal metaplasia is slight in stomachs carrying duodenal ulcers, and that gastric cancers occur less frequently and grow more slowly in stomachs with

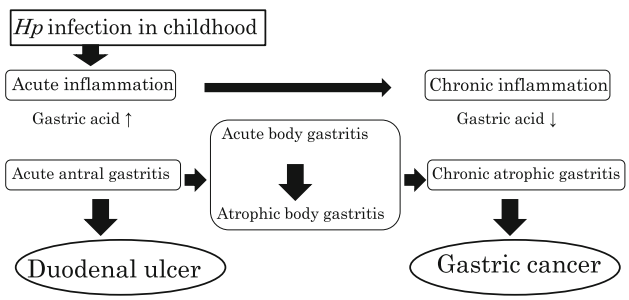

Fig. 5 Mechanisms of gastric cancer and duodenal ulcer

high acid secretion activity than in stomachs with low acid secretion.

Hwang et al. [95] reported that peptic ulcer patients had lower atrophy scores than patients with simple gastritis, whereas Brooks [96] reported that patients with gastric ulcer generally have more severe atrophy than do duodenal ulcer patients, and furthermore, Fuccio et al. [11] reported that many patients with gastric ulcer also have atrophic gastritis or intestinal metaplasia. Hussein [1] has shown that gastric ulcer is associated with a high risk, but duodenal ulcer with a low risk, of gastric cancer, and patients with gastric ulcers typically have atrophic gastritis and corpus-predominant gastritis, whereas patients with duodenal ulcers have antral-predominant gastritis, but few atrophic changes.

Parsonnet et al. [57] and Hussein [1] indicated that the rapid turnover of cells resulting from *H. pylori* infection-related injury increased the risks of DNA damage, predisposing the mucosa to transformation by ingested or endogenous mutagens, and they also noted that endogenous byproducts (especially free radicals) of inflammation, such as superoxide and hydroxyl ions, and nitric oxide, nitrates, and nitrosamines produced by macrophages caused oxidative damage, mutation, and malignant transformation [97]. They noted that these mechanisms are not mutually exclusive, and a combination of mechanisms is likely.

Hussein [1] also indicated that, in patients with gastric cancer, the infiltration of leukocytes into the gastric mucosa, combined with an alkaline pH in gastric juice, results in low levels of ascorbic acid and a diminished ability to block the N-nitrosation process; however, the gastric juice of patients with duodenal ulcers shows high levels of ascorbic acid.

Fuccio et al. [11] appropriately summarized the mechanisms of gastric cancer and duodenal ulcer after *H. pylori* infection as follows: *H. pylori* infection is usually established during childhood, so that antral gastritis and duodenal ulcers are common among young patients with a relatively short history of *H. pylori* infection; they speculated that continuous infection with *H. pylori* may result in the development of corpus gastritis in patients with antral gastritis associated with duodenal ulcer, so that middle-aged and elderly patients with duodenal ulcer often have gastritis in the corpus, and these conditions may place a patient at high risk of the development of gastric cancer. This explanation is considered to be widely accepted at the present time.

These contrasting etiologies may be the main reasons for the rare frequency of the coexistence of gastric cancer and duodenal ulcer. Another important factor in this phenomenon is the age at which the *H. pylori* infection is acquired. Graham [4] hypothesized that the acquisition of *H. pylori* infection in early childhood would lead to an increased prevalence of gastric atrophy in young adults and that duodenal ulcer disease would be rare in that population. However, it is now recognized that *H. pylori* is typically a childhood-acquired infection; Kubo and Imai [98] indicated that the best association with gastric cancer is not the age of acquisition of *H. pylori* infection but the age of acquisition of atrophic gastritis, because cases of early acquisition of atrophic gastritis may lead to gastric but not duodenal ulcer; this opinion is now widely accepted.

Factors in the early acquisition of atrophic gastritis may include salty foods; acid-suppressive therapy; polymorphisms of inflammatory cytokines and VEGF; and the presence of the *homB H. pylori* strain, whereas the factors that inhibit atrophic gastritis may include NSAIDs; fresh fruits and vegetables; vitamins A, C, and E; good nutrition; and the presence of the *dupA-H. pylori* strain.

Figure 5 shows a summary of the processes described in this section; we note that because of the contrasting etiologies of gastric cancer and duodenal ulcer, their coexistence may be unusual.

In addition, for gastric cancer to coexist with duodenal ulcer, an unrelated cause of mucosal atrophy must play some part, and the diffuse type of gastric cancer may be predominant in such cases [6, 93, 99].

Conclusions

Individuals with infections caused by the same *H. pylori* strain do not all show the same phenotypes of diseases, so that some amplifying factors are necessary. At present, then, we consider that the time of acquisition of atrophic gastritis is the most important factor in the final clinical outcome, and the characteristics of the infecting *H. pylori* strains and genetic characteristics of the host, as well as environmental factors, may all be involved in this outcome. Therefore, environmental factors such as diet, nutrition, and smoking are still important.

In the future, if bacteria other than *H. pylori*, or atypical *H. pylori* strains, or unfamiliar mutations of *H. pylori*, or unknown endogenous factors of the host, for example, are discovered, then the current outlook may be amended, and an accurate understanding may arise. We therefore look forward to further developments in molecular biology in this field.

In addition, the frequency of *H. pylori* infections is expected to decrease in the future, and whatever kinds of alterations may occur should be carefully observed.

Summary

Gastric cancer rarely coexists with duodenal ulcer, and one of the most acceptable views at present as to why this is so

is the following: in many cases of childhood infections by *H. pylori*, the time of acquisition of atrophic gastritis is the most important factor as regards the phenotypes of diseases, and if there is no early acquisition of atrophic gastritis, high levels of gastric acid can occur, and consequently, acute antral gastritis and duodenal ulcer may be seen when the subjects are in their teens or twenties. NSAIDs, smoking, and the *dupA H. pylori* strain may be among the factors promoting duodenal ulcer. In contrast, in elderly individuals, persistent *H. pylori* infections and early acquisition of atrophic gastritis may be the cause of low gastric acid, and consequently gastric cancer can occur. Factors such as salty foods; acid-suppressive therapy; polymorphisms of inflammatory cytokines and VEGF; and the *homB H. pylori* strain appear to promote gastric cancer, whereas factors such as NSAIDs and fresh fruits and vegetables are thought to inhibit this disease. In these ways, gastric cancer and duodenal ulcer may have contrasting etiologies, and their risk factors may also be contrasting. Therefore, the coexistence of these two disorders is unusual, and such cases may occur only as a result of a factor unrelated to mucosal atrophy; thus, the diffuse type of gastric cancer is probably predominant in such cases. However, these speculations are open to the possibility of marked amendments, if striking new factors should be discovered.

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