Different Pathophysiology of Gastritis in East and West? A Western Perspective

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Key Words

Helicobacter pylori · Chronic atrophic gastritis · Pathogenic factors

Abstract

Background: Gastritis results from multifactorial gastric mucosal injury. *Helicobacter pylori* (*Hp*) is the main cause, and associated diseases have typical underlying patterns of gastritis. Gastric ulcer and gastric cancer (GC) develop from chronic atrophic corpus gastritis (CAG) which therefore represents the most important pattern. GC incidences in East Asia are substantially higher than elsewhere, and this should be also reflected by higher prevalences of CAG and characteristic differences in pathophysiology compared to the West. **Summary:** The few available comparative studies of gastritis in Eastern and Western patients are summarized. The main pathogenic factors of gastritis are discussed together with their limitations to explain local differences in disease outcome. Emphasis was put to also include less well-established pathogenic host and environmental factors of possible impact. **Conclusions:** CAG is more prevalent in East Asian areas with high GC incidences than the West. Geographic heterogeneity of associated diseases is due to differences in *Hp* prevalence and virulence as well as modulating host and environmental factors. The following may contribute to the higher burden of CAG in the East: ABD type of CagA with *vacA* s1 and *babA2* alleles of *Hp*, host Lewis(b) expression in *sej/sej* nonsecretors, *H. heilmannii*, low parietal cell mass, high sodium and nitrate intake, preferences in

vegetable and fruit consumption, cigarette smoking, air pollution, alcohol. Conversely, green tea, nonfermented soy products and rice may confer protective effects. *Hp* is on the decline, but also in a world cleared from this bacterium, differences in host genetics will continue to modify gastric disease outcome together with maintained customs as part of cultural diversity.

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Definitions and Introduction

Gastritis denotes (cellular) inflammation due to gastric mucosal injury. Gastropathy referring to gastritis with minimum inflammation was originally described for bile reflux but is similar for other external causes like nonsteroidal anti-inflammatory drugs (NSAIDs), alcohol, chemicals and radiation.

Autoimmune gastritis is corpus-limited and spares the antrum. In contrast, *Helicobacter pylori* (*Hp*) gastritis is antrum-predominant and superficial in the majority, but can spread to the corpus and gradually destroy the gastric glands. Within years to decades, a minority of Western patients undergo a progressive course with atrophy and intestinal metaplasia of the gastric antrum and/or corpus as precancerous condition for noncardia gastric cancer

For an Asian perspective on gastritis, see Suzuki and Mori [Inflamm Intest Dis DOI: 10.1159/000446301].

(GC) [1, 2]. In both forms, the risks grow exponentially with increasing grade and extent of atrophic gastritis and intestinal metaplasia [3–5], which are assessed by histology [6, 7]. The development of atrophy is accelerated after vagotomy [8] and possibly under long-term acid suppression [9].

Classification and Etiologies

Despite recent enthusiasm [10–12], gastritis remains a rather neglected area. This is reflected by the actual ICD-10 classification still lacking *Hp* gastritis. Revision is underway. The tendency points to an etiology-based list of multiple causes. Although outdated, the original ABC classification [13, 14] remains popular, supposedly because of comprehensiveness despite simplicity: A refers to autoimmune, B to bacterial (infectious) and C to chemical, covering the most relevant causes. The Kyoto proposal [10] is built around these main groups. Besides *Hp* and *H. heilmannii*, other infections nonspecific to the stomach can cause gastritis. Similarly, noninfectious systemic diseases can affect the stomach like Crohn's disease, sarcoidosis, vasculitis, allergies, eosinophilia and celiac disease. Gastropathies were mentioned before. A remaining group of unknown etiologies decreases as knowledge increases.

Comparisons of Eastern with Western Gastritis

Representative population-based surveys of the East-West difference (EWD) of gastritis are virtually unavailable. Two comparisons of Japanese versus Canadian or Dutch patients showed more severe and extensive chronic atrophic corpus gastritis (CAG) in Japanese patients based on endoscopy or serum pepsinogens [15, 16]. Chinese versus Dutch patients had more antral atrophy and intestinal metaplasia that occurred at younger age [17]. Intestinal metaplasia in the antrum and corpus of duodenal ulcer (DU) patients was more often among Koreans than Americans, Colombians or South Africans despite equal density of *Hp* and degree of active gastritis [18]. In Japanese versus Swedish DU patients, histologies were essentially identical. Gastric ulcer (GU) patients had more atrophy and intestinal metaplasia in the antrum and corpus than DU patients [19]. In *Hp*-positive nonulcer patients, neutrophilic folliculitis, intestinal metaplasia and atrophy in the antrum but not corpus were more frequent in Koreans and Japanese than Americans [20]. Comparing gastritis of different age cohorts of UK and Japanese

nonulcer dyspepsia patients, corpus predominant gastritis or pangastritis in Japanese patients was more common, and atrophy and intestinal metaplasia more extensive and severe [21]. Differences for corpus atrophy were greatest in the middle and older age groups. *Hp* positivity was equally high: 78 versus 71% in UK versus Japanese patients or 90 versus 88% including serology, indicating low *Hp* or its loss in some.

Conventional Pathogenic Factors and Limitations

Autoimmune (metaplastic atrophic) gastritis is inherited and female predominant, and occurs mainly in northern Europe [22]. In the East, the disease is too rare to explain higher prevalences of CAG and GC. Moreover, GC affects more males than females.

The role of NSAIDs, including aspirin, and the interactions with *Hp* are complex. NSAIDs can induce inflammation, peptic ulcers and possibly mucosal atrophy. But NSAID ulcers can occur in virtually normal mucosa, most long-term users do not develop significant gastritis, and with respect to GC, NSAIDs are protective [23, 24]. Consumption, once maybe higher in the West, is increasing worldwide due to demographics. NSAIDs do not seem to contribute to the EWD of CAG, but CAG influences the risk for NSAID-induced gastroduodenal lesions [25].

Despite the multifactorial pathogenesis of CAG and GC, *Hp* is the main and primary cause. Geographic heterogeneity in *Hp*-associated diseases is generally explained by different prevalences of *Hp*. The mere prevalence, however, is of limited importance because associated diseases correlate poorly. Surprisingly, in epidemiological studies, odds ratios (ORs) for GC in *Hp*-positive Japanese patients were not higher than in Western subjects except for one study [26]. In fact, ORs in 2 of 5 compiled studies from Japan did not [27, 28] and in one [29] only marginally reached significance. In one study, increased GC risk correlated significantly with CAG but not *Hp* positivity [28]. Accordingly, in four prefectures of Japan with different GC mortality ratios, the risks correlated with the local prevalences of CAG but not of *Hp* [30]. The findings suggest that CAG is strongly related to GC development in Japan, but *Hp* infection is not [26, 31]. Also, with advancing atrophy and intestinal metaplasia, colonization density of *Hp* decreases and presumably so does the pathogenic impact [5, 32].

Pathogenicity and carcinogenicity of *Hp* is highly variable. Polymorphisms of bacterial virulence factors like *cag* pathogenicity island, *vacA* and genes for outer mem-

brane proteins and motility [33], as well as of host genes related to inflammatory response (*IL-1B*, *IL-1RN*, *IL-10*, *TNF α*) are important but cannot fully explain different regional, ethnic, gender-dependent and individual disease outcomes [34–38]. Complications occur in only a fraction of infected subjects, whereas the majority remains unaffected despite harboring the same microbes. GC and ulcers occur with all types of *Hp* independent of virulence markers and also without *Hp*.

Most East Asian strains contain the *cag* pathogenicity island, the *vacA* s1 allele and produce CagA of distinctive EPIYA motifs. All have been related to higher pathogenicity [39] and particularly the East Asian ABD types of CagA compared with lower pathogenic Western ABC types [40]. The number and types of CagA EPIYA motifs in addition to *vacA* alleles can better explain geographic and ethnic differences of *Hp*-associated diseases in most but not all regions [41]. In Colombia, GC incidences are high despite *Hp* of Western-type CagA [42], and Mongolians are infected with *Hp* of non-East Asian-type CagA [43]. In Southeast Asia, the magnitudes of differences in GC incidences are incompletely reflected by the prevalences of the CagA EPIYA motifs and *vacA* genotypes, and the differences of genotypes were small or null between patients with gastritis, ulcer disease and GC [41].

Reports about the associations of genetic polymorphisms of *IL-1B* and *IL-1RN*, and GC, CAG and ulcers are conflicting. Subsequent studies after the first descriptions found mostly null results [44–46]. A cumulative meta-analysis tended toward null overall associations but with a significant heterogeneity, and an analysis of Western versus East Asian studies revealed no difference [47].

Epidemiological studies show striking geographic and ethnic differences, migration effects and time trends in CAG, GC and peptic ulcers [5, 26, 35, 38, 48–50]. These started when *Hp* was still unknown and happened too fast to be explained by bacterial or host genetic changes [35, 38]. The studies suggest that *Hp* prevalences started to decline in several regions parallel to economic development [4, 5, 26, 49]. It was hypothesized that environmental factors not only had contributed to the pathogenesis of CAG but also to reduced acquisition of *Hp* [5]. The increasing *Hp* prevalences with age despite acquisition in childhood and rarely thereafter represent a cohort phenomenon [5]. This reflects high acquisition rates in the past and decreasing infection in subsequent generations [49]. The decline of *Hp* prevalences in the last 3 decades has been accelerated by antibiotic treatment.

Concepts and Assumptions

These notions support pathogenic factors in addition to autoimmunity, *Hp* and NSAIDs. Fundamentally changing living conditions in the last two centuries (in the West before the East) and that the dramatic drop of GC incidence worldwide started before the *Hp* era underscore the importance of the environment [5, 26, 32, 35, 36, 51, 52]. Supporting evidence is historic, and studies under today's living conditions tend to overestimate the effects of *Hp*.

The merit goes to D.Y. Graham [35] who years ago proposed a pathogenic model of how the main etiologies of *Hp*-associated diseases interplay and in which the environment more than (host and microbial) genetics determines the disease outcome. Crucial in this model is gastric acid secretion/corpus atrophy and its contributing factors.

Atrophy and its proximal spreading in *Hp* gastritis have been classified decades ago by Kimura and Takemoto [53, 54]. The progression of *Hp* gastritis to CAG and GC (intestinal more than diffuse type) is multifactorial, involving a cascade of events where *Hp* infection in early childhood probably represents the initial key trigger [5, 35]. It was speculated that in the past, favored by malnutrition, low vitamin C and iron, frequent childhood infections, poor living conditions and other factors, episodes of hypochlorhydria occurred. These enabled *Hp* to repeatedly get access to the gastric corpus, cause inflammation, rapid destruction of glands and corpus atrophy already in young adulthood [35].

Information about CAG is partially hidden because studies dealt with ulcers or GC, or atrophy was indirectly assessed (pepsinogen). Using GC as an indicator lesion for CAG helps to spot the relevant literature. Similarly, the GU/DU ratio is useful because of different underlying patterns of gastritis and GC prevalences [55], although somewhat less reliable due to undeclared location and synchronic and metachronic DU and GU. Because GC is more prevalent in East Asia (China, Japan, Korea, Mongolia) than the West [56] and CAG is a precursor, the incidences of GC and CAG are related [57–59]. Due to a long co-pathogenesis, most risk factors probably contribute to both conditions underscoring the relevance of CAG.

An exact geographical definition of East and West was considered less important than the opportunities offered by natural experiments of various environments.

Pathogenic Factors of Gastritis beyond 'ABC'

Additional host and environmental factors of possible relevance for the pathogenesis of gastritis in the East and West are discussed below.

Other Infectious Pathogens

Epstein-Barr virus infection and reactivation have been related to peptic ulcer disease [60] and GC. The virus is highly prevalent (around 90%) in a special type of GC with lymphoid stroma (gastric lymphoepithelioma) [61]. Oral pathogens in periodontal disease were incriminated to carry a higher risk of gastric precancerous lesions [62].

A group of non-*Hp* helicobacters (*H. heilmanni* sensu lato) of zoonotic potential can cause gastritis, ulcers, MALT-lymphoma and GC. Although rare compared with *Hp*, their prevalence can reach 6% in Asia versus <1% in the West [63]. Mixed infection with *Hp* can occur. Changing microbiota outcompeting *Hp* in hypoacidity may drive carcinogenesis after CAG has been established [64]. These pathogens might have a marginal effect on the EWD of CAG.

Host Parietal Cell Mass

Acid secretion co-determines disease outcome in *Hp* gastritis because it defines how far the bacterium can spread and cause inflammation [35, 65]. The more gastric glands, the longer they can resist critical destruction and hypochlorhydria [21, 35]. As long as a minimum acid output is maintained, DU can occur. Gastric acid secretion is higher in DU patients than normal controls, and DU is inversely related to GC risk [55]. Conversely, GU indicates underlying CAG with reduced acidity, and ulcers occur at the proximally spreading front of atrophy [53, 66].

Asians were suggested to possess smaller parietal cell masses than Westerners: Maximum acid output was higher in Scots than Chinese female and male healthy controls and DU patients, and the difference remained after correction for body weight, sex, age, blood groups and other factors [67]. In a previous work, parietal cell counts in addition to acid output of DU patients had been measured, which correlated perfectly with maximum acid output [68]. Compared with an earlier cohort of Scots [69], Chinese subjects had significantly lower parietal cell counts. Acid outputs per 10⁹ parietal cells were similar in both groups, suggesting fewer parietal cells rather than functional impairment caused the difference. Regrettably, no histological data were collected. Studying DU patients born in the 1930s and southern Chinese from Hong Kong suggests that most patients in both groups had antrum-

predominant gastritis due to *Hp* infection with low corpus atrophy. The fact that fasting and postprandial serum gastrin levels did not differ between the two groups supports the assumptions and indicates comparable functional antral G-cells. The data suggest that the effect of more pronounced CAG on acid secretion was small compared to a genetically lower parietal cell mass in Chinese patients. Reports about better responses of Asians versus Caucasians to proton pump inhibitors and histamine-2 receptor antagonists were interpreted to indicate lower acid production/parietal cell mass among Asians [70]. Similarly, lower aspirin-induced gastroduodenal mucosal injury in Japanese versus Western patients was associated with lower gastric acid secretion [71].

Histo-Blood Groups

The ABH-secretor and Lewis (Le) histo-blood group systems are associated with susceptibility to various infections and autoimmune diseases [72]. The rationale for *Hp* is the secretion of antigens into saliva and gastric juice in secretors and gastric expression [73–75].

DU is more common with blood group 0 and nonsecretors [76]. Thus, non-0 blood groups and secretor status could predispose to CAG, GU and GC. This is concordant with data of blood group A being a risk factor for CAG/GU/GC in both Western and Eastern populations [55, 77, 78], and was confirmed in a more recent study of Scandinavian blood donors [79].

Relative risks of Le(a+) versus Le(a-) patients of 1.8 for DU versus 0.7 for GU have been described [80]. This roughly corresponds to previous data [76]. Le antigens are oligosaccharides fucosylated by *Le*- and *Se*-encoded fucosyltransferases. Individuals of the Le(a+b-) phenotype are mainly *Le*/– *se*/*se* nonsecretors. In *Le*/– *Se*/– secretors, conversion to Le(b) is favored, yielding a Le(a–b+) phenotype with little or no Le(a) [74, 75].

Hp variably expresses human blood groups, mainly Le(x) and Le(y) but also A, B, H-1, Le(a), Le(b) and sialyl-Le(x) [81]. Research focused rather on the bacterial counterparts of human gastric blood group antigens: *Hp babA2* (blood group antigen-binding)-encoded adhesin, binding Le(b) and H-1, and *sabA* (sialic acid-binding)-encoded adhesin [82, 83], binding sialyl-Le(x, a) antigens [84].

BabA is associated with an increased risk of DU and GC [85], but reports are inconsistent [34, 86]. Effects may be confounded because BabA is more commonly expressed in *Hp* positive for the *cag* pathogenicity island and *vacA* s1 [34, 83]. Interestingly, clinical outcome differed minimally between East Asian and Western strains using these markers [34]. In a recent meta-analysis, the

only association observed of *babA2* positivity was with DU in Western but not Asian countries [87].

Asians differ from Caucasians in the point mutation *sej* with proposed partially retained secretor activity despite equal rates of nonsecretors [88, 89]. The *sej* allele occurs with a frequency of 40% in Japanese and may enhance gastric attachment of *Hp* in Japanese nonsecretors [89].

SabA positivity of *Hp* was positively related to GC and CAG [85, 90] and negatively to DU. In contrast, in Taiwan, the SabA positivity rates of *Hp* were similar in DU, GU and gastritis and independent of whether atrophy was present or not [91]. SabA-positive strains seem to be less prevalent in Asia [92] and may not contribute to the EWD of CAG despite higher importance of SabA versus BabA in CAG/hypochlorhydria [91, 92].

The complex interactions of shared blood group antigens are still incompletely understood [93]. Blood group A is less prevalent in East Asia than Europe in contrast to CAG and GC. Increased host Le(b) expression combined with almost ubiquitous *babA2+* *Hp* may contribute to higher pathogenicity in East Asia. In contrast, the Le(a-b-) phenotype with no functional *Le* gene is common among Africans [94] and may contribute to lower GC rates via low gastric Le(b) expression.

Other Inherited Host Factors and Appendectomy

Up to 3% of mainly diffuse type GC arise in inherited predisposition syndromes [58]. A higher prevalence of CAG was described among blue- versus brown-eyed non-ulcer patients [95]. This may be related to autoimmune gastritis, which is more prevalent in northern Caucasians.

CYP2C19 polymorphisms with known EWD indirectly influence gastric pathology via metabolism of proton pump inhibitors, although a direct relationship was suggested [96].

Other genetic variants associated with an increased risk of GC and ulcer disease have been proposed: *NOD1* and *NOD2*, *IL-8*, cyclooxygenase-2 gene [97, 98], sodium-dependent vitamin C transporter 2 (*SLC23A2*) [99, 100] and possibly others involved in inflammation and immunity [101]. The *TLR-1* and *FCGR2A* loci were related to *Hp* seroprevalence [102].

An inverse association between blood cholesterol and CAG has been reported [32, 103]. In contrast, a high body mass index and hyperglycemia were related to a higher GC risk [58, 104]. One study reported a lower appendectomy rate among GU versus DU patients and controls, suggesting an unremoved appendix increased the risk for CAG [76]. At the moment, there is insufficient evidence to assume that any of these factors have an impact on the EWD of CAG.

Salt, Nitrate and Food Preservation

High sodium consumption is associated with a higher risk of GC [48, 105–107] and GU but not DU [55]. Refrigeration instead of food preservation with salt and nitrate reduced salt consumption and has been linked to fewer premalignant lesions [32, 108]. In Japan, the use of refrigerators increased from 9 to 91% between 1960 and 1970, and urinary sodium excretion decreased from 360 to 187 mmol/24 h between 1955 and 1987 [109].

A survey of 24-hour urine sodium and nitrate excretions in 24 countries showed significant positive correlations with GC mortality in men and women [109]. East Asian countries belong to those with the highest excretions. In a systematic review, high salt intake increased the GC risk by 68%, and the association was stronger for Japanese and selected salt-rich traditional foods [110].

Short-term ingestion of traditional Japanese salty or vinegary food reproducibly caused reversible gastropathy with a higher mitotic activity in healthy men [111]. In Hawaiian Japanese men, nitrate-rich salty foods were related to gastric intestinal metaplasia [112], and high intake of salted cuttlefish and cod roe increased the age-corrected risk of CAG in Japanese women [113]. In a study of Japanese males from five regions with different GC mortality, CAG was not related to *Hp* but to salt excretion [114].

Salt and *Hp* interact in many ways [107]. High intake was related to higher *Hp* infection rates [106], and a permissive role of salt in *Hp* gastritis was proposed [109]. Reports about meat products are conflicting. The European EPIC trial found a positive association with GC [115], and British vegetarians had a 63% lower GC risk than meat eaters [116]. Conversely, low intake of meat and fish increased the risk in Venezuela [108]. High intake of salt and nitrate with food and seasonings in the East contributes to the EWD of CAG/GC, both synergistically and independent of *Hp*.

Fruits, Vegetables and Vitamins

Fruits and vegetables confer protective effects against cancers, including GC, but results are inconsistent and may differ due to the type of GC (intestinal vs. diffuse) [117–119]. Studying overall consumption may yield negative results due to components with opposite effects. Yellow vegetables and high plasma β -carotene were associated with a lower risk of CAG among male Japanese [114]. Similarly, high intake of light-colored vegetables reduced CAG by 32% independent of *Hp* and age [52]. In Venezuela, high fruit consumption reduced CAG by 40%, dysplasia by 60%, and intestinal metaplasia by 15%.

In contrast, starchy vegetables increased the risk probably due to preparation and contamination [32].

The effects partially depend on vitamin C [120]. Ascorbic acid, the reduced form of vitamin C, is secreted by the normal gastric mucosa depending on plasma levels maintained by dietary intake [121]. Poor vitamin C supply in cold areas may account for higher GC rates in northern versus southern areas [122].

Vitamin C levels were reported to be low in *Hp* gastritis and ulcer patients, but increased after *Hp* eradication [94, 120, 121, 123]. Ascorbic acid reduced *Hp* acquisition [124, 125], *Hp*-induced inflammation and oxidative damage [121], prevalence of GC precursor lesions [117] and formation of carcinogenic N-nitroso compounds in gastric juice. In Colombian high-risk patients, ascorbic acid and β -carotene induced histological regression of gastric atrophy and intestinal metaplasia [126]. Intake of total dietary fiber [127, 128] or cereal fiber [119] was related to a lower GC risk. Most East Asians prefer cooked or preserved vegetables to raw vegetables. This may add to increased susceptibility to CAG and GC in Asia.

Dairy Products, Iron and Rice versus Wheat and Soy

Reports about dairy products and milk are inconsistent. Studies from Louisiana and Venezuela reported an increased risk of CAG [117] or intestinal metaplasia [32] with high intake, others a risk reduction. In a meta-analysis, high intake of dairy products but not milk was protective in Western but not Asian studies [129]. The associations between iron deficiency and GC are confounded by blood loss and low absorption. Still, reports indicate an increased GC risk related also to low iron intake [127].

Higher DU rates in southern versus northern areas related to daily intake of rice, inversely related to wheat flour and independent of *Hp* infection, were reported in China and India [122, 130]. In contrast, rice in Japan was associated with a higher risk of CAG [113] probably due to co-ingested salty food.

Reports about soybean products vary: high intake was related to an increased risk of CAG in a Japanese study [114] but was inversely related to GC death in others [131]. In Korea, a protective effect in females but not males was found [132], and in postmenopausal Chinese women, soy intake was inversely related to plasma levels of IL-6, TNF α and soluble TNF receptors [133].

The effect may differ according to salt content [107], fermented versus nonfermented products, conditions of fermentation, microorganisms [134] and toxigenic contaminants [135]. This may explain discordant results in different regions and in genders [131, 132, 136]. Soy

products are used on a daily basis in East Asia. A beneficial effect on CAG/GC could be confounded by co-ingested irritants and could be gender dependent. Dairy products may be protective in the West.

Smoking, Air Pollution, Alcohol, Tea and Coffee

UK smokers had a higher prevalence of gastritis: 21 and 19% in nonsmokers or pipe and former smokers, 28% with 10–19 cigarettes, and 43% with 20+ cigarettes per day [95]. Smoking is a risk factor of GC [137] and precursor lesions including CAG [78, 105, 112, 117]. Transition to dysplasia was higher in blood group A [78]. In a meta-analysis of 40 studies, the relative risk of GC was higher in men than women (1.6 vs. 1.1), and 11% of GC worldwide were attributed to tobacco smoking [138]. Almost identical numbers were reported in a more recent meta-analysis [139] and in the European EPIC trial [137]. Significant effects started from 10 cigarettes per day, depended on dose and duration and declined after stopping [32, 137]. The risks of smoking and *Hp* for GC [140] and peptic ulcer [141] were additive, and smoking was an independent risk factor for GC in Fujian patients [142].

The higher risk of CAG/GC could be caused by swallowed constituents [95], inhaled toxins and other factors: increased bile reflux [143, 144], increased proinflammatory chemokines [145] and impaired mucosal defense (including low vitamin C [94]) in smokers. In a study from northeastern Japan, 44% of male participants of a health check program smoked versus 2% females [113], or 45 versus 3% in Venezuela [108]. The predominance of precancerous lesions and GC among males may be related to smoking. Few reports related air pollution to GC [146]. Again, swallowed chemicals could be involved.

Alcohol was associated with CAG and GC in some [32, 147] but not all reports [52]. Of UK nondrinkers, 21% had gastritis versus 35% of heavy irregular drinkers, 46% of regular drinkers, and 63% of both heavy drinkers and smokers [95]. Green tea, but not black or Oolong tea, was associated with a 37% reduced risk of CAG after adjustment for *Hp* and other variables in Japan [148]. No relationship was found for coffee, alcohol or smoking. In males of the Japan Self-Defense Forces, green tea was related to a lower risk of CAG. [149]. High intake of hot tea was associated with a higher prevalence of gastritis in the UK population [95, 150]. Smoking and air pollution in concert with alcohol and hot beverages may contribute to the risk of CAG/GC. A stronger inhibition of acid secretion in *Hp*-infected Japanese males than females [25] may be an additional factor.

Conclusion

Differences in CAG and associated diseases observed today reflect differences in *Hp* prevalence, virulence, host and environmental factors in the past. Because of fundamental changes in life conditions, correct evaluation requires a time frame of two centuries. Many secrets, therefore, will remain buried in the past. Still, the pathogenesis of gastritis in the East and West can be assumed to be fairly similar under similar conditions. Equally high GC and presumably CAG rates in Western countries occurred in the past when risk factors were comparable to those in the East. Due to the asynchronous elimination of CAG risk factors from the environment, striking geographic heterogeneity has evolved which will decline with further adoption of westernized lifestyles.

Some differences will continue to modify gastric disease outcomes. In many areas, *Hp* will soon cease to be one of them. What remains are inherited ethnic differences, among which lower parietal cell mass in Asians may be important besides cultural differences in lifestyle that hopefully will also be maintained in the future.

Facts from East and West

Although few East-West comparative studies have been done, the available data suggest that patients from East Asian countries show more severe endoscopic and histological manifestations of CAG compared to those from Europe or North America.

In both Asian and Western countries, the prevalence of *Hp* infection is linked to the incidence of GC. Asian countries, however, exhibit a higher incidence of GC.

Analysis of the *Hp* virulence genes points towards a central role of the CagA and VacA virulence factors. The

Hp strains may be classified into three types: East Asian CagA positive (EPIYA motif ABD type), Western CagA positive (EPIYA motif ABC type), and CagA negative. In particular, the East Asian ABD type CagA strain is associated with higher pathogenicity. The presence of the s1 and/or m2 VacA genotypes is associated with a greater risk of GC and peptic ulcers.

The individual's genetic background, including polymorphisms in several interleukin genes, TNF α , NOD1 and NOD2, may affect disease risk. Other host factors that influence disease risk are parietal cell mass and the ABH-secretor and/or Lewis histo-blood group status. Some Asian populations express point mutations in the *sej* allele, which may facilitate bacterial attachment to the gastric mucosa. Asians have been shown to have smaller parietal cell masses than Western populations, affecting gastric acid secretion and response to treatment with proton pump inhibitors and histamine-2 receptor antagonists.

Data on the protective effect of specific dietary elements remain conflicting. Soy products are widely used in Asia, but data on their beneficial effects depend on their salt content, fermentation and the presence of contaminants. Some Western studies have indicated that ingestion of dairy products may have protective effects on CAG and GC. Consumption of green tea has also been associated with a reduced risk of CAG in Japanese populations.

Environmental factors (such as air pollution) could act in concert with lifestyle factors (such as smoking and diet) to modulate an individual's risk of GAC or GC.

Disclosure Statement

The authors have no conflicts of interest to declare.

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