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GASTRIC CANCER AND HELICOBACTER PYLORI INFECTION

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The Nobel prize in Physiology and Medicine in 2005 was presented to Barry Marshall and Robin Warren for their discovery of Helicobacter pylori (Hp), but only the involvement of this germ in gastritis and peptic ulcer has been mentioned in the award sentence, while numerous epidemiological, clinical and experimental studies and reports emphasized the crucial role of Hp in pathogenesis of gastric cancer (GC). This review is based on the old concept proposed by P. Correa much before the discovery of spiral bacteria in the stomach, postulating the cascade of mucosal changes from acute/chronic gastritis into the atrophic gastritis with intestinal metaplasia and finally to dysplasia and GC. It is now widely accepted view that Hp infection is the major initiator of the inflammatory and atrophic changes in gastric mucosa accompanied by an over-expression of certain growth factors such as gastrin as well as of cyclooxygenase-2 (COX-2) and anti-apoptotic proteins including survivin and B-cl₂, leading to proliferation of mutated atrophic cells, excessive angiogenesis, inhibition of apoptosis and formation of gastric tumour. All the morphological and biochemical changes associated with the transformation of mucosal cells into the cancer cells can be traced in excellent experimental model of gastric cancerogenesis induced by infection of Hp in Mongolian gerbils. Since the eradication therapy was proved in several prospective clinical trials to greatly reduce the incidence of GC and this was confirmed on the gerbil model of Hp-induced GC, it has been postulated; a) that Hp is the major causal factor in pathogenesis of GC and b) that the only rational approach in attempt to reduce the occurrence of GC is the global eradication of Hp.

Key words: gastric cancer, Helicobacter pylori, gastrin, COX-2, survivin, Mongolian gerbils

EPIDEMIOLOGY

Gastric cancer (GC) is the fourth most common cancer and the second cause of cancer-related death worldwide, accounting for nearly 1000,000 new cases
annually and over 850,000 deaths at the same time (1). An overall GC incidence is constantly decreasing, possibly due to the fall in the Hp prevalence caused by increasing living standard level. Unfortunately, 2/3 of the GC patients (pts) are diagnosed in advanced stage of which outcome is poor prognosis.

Histologically, 95% of GC are adenocarcinoma either well-differentiated, intestinal type, related to corpus-dominant chronic atrophic gastritis dominating in developing countries with high Hp prevalence and undifferentiated diffuse type of GC originating from pangastritis without widespread atrophy and more uniform geographic distribution (1-5) (Fig. 1). In general, the Hp prevalence in different countries concurs with the occurrence of GC (1-5). According to Crew and Newgut (6), the distant, predominantly intestinal, type of GC predominates in the developing countries, among blacks and those with lower socio-economic status, whereas proximal tumors are more common in developed countries, among whites and higher socioeconomic classes. There is little doubt that the main risk factors for distal gastric cancer include Hp infection and inappropriate diet, whereas gastroduodenal reflux disease (GERD) and obesity play an important role in development of proximal gastric cancer.

Fig. 1. Geographic variations of GC death rate (upper panel) and Hp prevalence (lower panel). Modification of Crew and Neugut (6).
Cancer geography and risk factors

Overall GC incidence and mortality fell dramatically over past 7 decades (7), but despite of that decline, gastric cancer is fourth most common cancer and second leading cancer-related death worldwide (8, 9). The two main cancer sites are proximal portion of stomach (cardia) and distal portion (non-cardia). Despite a decline in distal non-cardia, proximal cardia cancers have been increasing since 1970s, especially in males in western countries (10, 11). These differences between cardia and non-cardia cancer suggest that they represent distinct diseases with different etiologies (Fig. 2).

About 90% of stomach tumors are adenocarcinoma which can be subdivided into: 1) well-differentiated or intestinal type, and 2) undifferentiated or diffuse type. The intestinal type is related to corpus-dominant gastritis with mucosal atrophy and intestinal metaplasia, whereas the diffuse type usually originates from pangastritis without atrophy. The intestinal type tumors predominate in countries with high prevalence of Hp such as East Asia, while diffuse type tumors has more uniform geographic distribution (12).

It is of interest that while the gastric cancer, particularly its non-cardia localization shows overall decline, gastric cardia tumors show relative rise and is

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*Note:* +, positive association; ++, strong positive association; -, negative association; ?, ambiguous;

Fig. 2. Epidemiological risk factors for cardia and non-cardia GC.
accompanied by rising trends in distal, esophageal, gastroduodenal reflux disease (GER) and Barrett’s esophagus that according to recent opinion of Blaser (13), results from the eradication of Hp, whom he considered as “endangered species” that should not be eradicated world-wide as it lives in symbiosis for centuries in human stomach without inducing changes in majority of infected people and, in fact, preventing certain diseases such as esophago-cardiac cancer, Barrett’s esophagus or GERD (Fig. 3). As some prominent gastroenterologists such J. Misiewicz consider, the most favorable Hp for human health as “death germ”, the question is open for discussion. Indeed, Graham (15) e.g. believes that there is an erroneous and unproven concept regarding Hp and adenocarcinoma of esophagus and this problem is discussed in details by P. Thor in his issue of journal.

Similarly, the widely spread opinion that there is no causal relation between the Hp infection and gastric cancer is that in some African countries, where standard living is very low and Hp infection very high, gastric cancer occur not frequently. Recently, Agha and Graham (16) showed on prospective studies on African countries and prospective endoscopic studies on African population that so called African enigma is non-existing phenomenon (Fig. 4).

Fig. 3. With decrease of Hp prevalence in populations and the decline in occurrence of GC, there is also an increase in the incidence of GERD, Barrett’s esophagus and esophageal carcinoma. Modified from Blaser (13).
GC is a multifactorial disease, so in addition to marked geographic variations, the environmental or life style factors are the major contributors to the etiology of this disease. As shown on Fig. 2, there is multitude of factors among which low socio-economic status, Hp infection in family members living in crowded house-shelters and poor sanitation are the most common conditions favoring Hp transmission from person to person and cancer risk. As countries with high rates of GC rates typically exhibit also high Hp prevalence include the developing as oppose to developed countries (17-22). In our studies based on Polish population considered as partly developed showed 10 years ago relatively high Hp infection rate this Hp infection rate in GC patients (~90%) exceeded significantly that in age-matched non-GC patients (60%) and interestingly in all GC the plasma levels of anti-CagA IgG were about twice higher than in controls (23) (Fig. 5). Furthermore, plasma levels of cytokines such as IL-8 and gastrin concentrations and their PG expression in cancer tissue were remarkably higher than in healthy age-matched controls (23). In subsequent studies (24) is was revealed that unlike intact gastric mucosa, cancer tissue was found to be accompanied by highly elevated plasma levels of gastrin and progastrin and their overexpression in tumor cells (23), suggesting that this hormone that is well established oxyntic mucosal cells growth promoting factor, may contribute to gastric carcinogenesis. Another factor, highly important for gastric cancerogenesis was found in our hands to be overexpression of cyclooxygenase-2 (COX-2) and prostaglandins (PG),

![Estimates of the worldwide mortality from GC by region](image)

Fig. 4. Estimates of world-wide mortality from GC by regions (modified from 16).
especially PGE\textsubscript{2} in the cancer tissue and in the margin of tumor but not in intact mucosa (24). Furthermore, overexpression of growth factor such as hepatocyte growth factor and transforming growth factor (TGF-\(\alpha\)) in gastric tumor was detected by RT-PCR (25) (Fig. 6). The finding that tumor tissue is capable to express large amounts of antiapoptotic proteins including survivin, Bcl-2, combined with downregulation of proapoptotic protein Bax (26), support and extend the original Correa’s paradigm (27) (Fig. 7). According to this concept Hp, already recognized in 1994 by the International Agency for Research on Cancer (IARC) to serve as definite carcinogen in human beings (28), triggers the progressive sequence of gastric lesions from chronic gastritis, gastric atrophy, intestinal metaplasia, dysplasia and finally gastric cancer (29). These progressive gastric mucosal changes and their irreversibility have been confirmed by our group recently (30, 31) and Hp eradication combined with high dose of vitamin C permitted at least in part to normalize excessive production of gastrin, growth factors and PGE\textsubscript{2} by the mucosa as well as on increase in gastric acid secretion (30,

Fig. 5. Serum anti-Hp IgG and anti-CagA IgG in GC patients and healthy age-matched controls. Each column represents 20-30 subjects. Asterisk indicates significant change from the control value (unpublished results).
31). At present our concept of gastric cancerogenesis, while confirming the original Carrea’s model, draws attention to growth factors (gastrin, HGF, TGF-α, bFGF and VEGF) that seems to be responsible for excessive proliferation of tumor cells and discovery of large amounts PGE₂ and anti-apoptotic proteins (B-cl₂) with reduction of apoptotic Bax explains the molecular mechanism of gastric cancerogenesis (Fig. 7).

The most convincing evidence supporting the crucial role of Hp and described above biochemical changes originated from our studies in collaboration with K. Marlicz on MALT-lymphoma gastric tumors, which were infected in almost 100% with Hp and which healed completely following eradication of this germ (32, 33). With the removal of infecting germ not only gastric tumor disappeared but also tumor promoting proliferation of lymphoid tissue vanished and almost 5 years after the Hp eradication all investigated patients enjoy good health (Fig. 8).

Several case-controlled studies have shown significant association between Hp infection and GC risk with about 2.1 to 16.7-fold greater risk compared to seronegative beings (34-36). Prospective studies have also supported the association between Hp infection of GC risk (37, 38). Perhaps the most compelling evidence for the link between Hp infection and GC comes from
Modified „Correa’s cascade”

Normal mucosa

Chronic Gastritis

Atrophic Gastritis

Genetic Defects

Mutation and activation of Kras

H. pylori

GASTRIN, TGFα, HGF, bFGF, VEGF

COX-2 PG & INOS, NO

p53 mutation

Intestinal Metaplasia

Dysplasia

Vit C, Carotene

Gastric cancer (diffuse type)

Gastric Cancer (intestinal type)

1-2 %

Fig. 7. Modified Correa’s cascade proposed in 1996 and present modification in 2005.

Fig. 8. Schematic presentation of the results of Hp eradication in subjects with Hp infection and accompanying peptic ulcers, MALT lymphoma and gastric cancer. Note that eradication was effective in all pathologies except gastric cancer.
prospective studies on 1526 Japanese Hp infected pts in which the GC developed during 7 years of observation in 2.9%, but none in uninfected subjects (29). In Hp infected pts with non-ulcer dyspepsia GC developed in 4.7% (39) (Fig. 9).

Cofactors and virulence factors responsible for the occurrence of GC in H. pylori infected stomach

There is a long list of cofactors (40) determining higher GC in Hp-infected individuals. The imbalance between Hp and host, especially excessive expression of CagA (41) was observed also in our earlier studies (27). Host factors associated with higher risk of GC include genetic polymorphism and high level of expression of certain cytokins such as IL-1β, TNFα. Hp-related gastric tumors are mostly non-cardia cancers, localized in distal stomach, however such cofactors as excessive smoking (42) and obesity (43) seem to promote GC in cardia area. The story that infection with CagA expressing Hp prevents the development of GC in cardia and in esophagus (44, 45) seems to be controversial as more recent publications (46-50) failed to confirm that Hp eradication increases the risk of esophagitis and gastric cardia adenocarcinoma. The global

Fig. 9. Development of GC in humans after Hp eradication occurs after 7 years at significantly lower rate than in those remaining Hp infected and GC occurs at significantly higher rate with increase of mucosal atrophy (Insert) (Based on the data of Uemura et al (39).
approach to Hp eradication seems to be the only reasonable way of making the GC a rare disease as advocated recently by Graham and Shiotani (51).

Since COX-2-PGE₂ system plays a role in cell proliferation, apoptosis and angiogenesis, all involved in carcinogenesis (52, 53) and this system starts to operate in the gastric mucosa following Hp infection and progression from atrophic gastritis to intestinal metaplasia (54), it is obvious that inhibition of this system by non-steroidal anti-inflammatory agents (NSAID) seems to be fully justified (55-57). Our recent studies (58) are also compatible with the above-mentioned finding (Fig. 10).

As reactive oxygen species (ROS) are produced in excessive amounts and enhance the atrophic gastritis, we found that prolonged treatment with large dose (2g/d) of vitamin C delays the progress of inflammatory and atrophic mucosal changes and restored in part the exocrine and endocrine functions of the stomach disordered by Hp infection (58). The use of specific COX-2 inhibitors was found to be highly effective confirming an overall opinion that NSAID reduced the risk of Hp-associated non-cardia GC (59).

Final question regarding the pathogenesis of GC is whether affecting of expression and action of gastrin might affect the development of gastric tumor. So far no study was performed with auto-antibodies for gastrin or with antagonists

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**Fig. 10.** Role of COX-1 and COX-2-prostaglandin systems in gastric carcinogenesis.
of their CCK₂-R but both approaches may be worthy consideration. The application of gastrimmune, a complex of diphtheria toxin with gastrin (G-17) was reported to increase the production of gastrin antibodies and to delay the colorectal carcinogenesis (60), which also was found to express the gastrin and its receptors (61). In the stomach the use of gastrimmune against GC is unlikely to be effective as gastrin is produced by G-cells in variety of molecular forms including 71-aminoacid, progastrin, 34-aminoacid “big” gastrin, 17-aminoacid “little” gastrin and glycine-extended G17. Before gastrimmune capable to raise the endogenous production of antibodies against all these forms of gastrin is available, the attempts to prevent or delay in the development or metastasis of GC seem to be questionable. In contrast, the use of safe and side-effects free specific gastrin receptors (CCK₂-R) antagonist seems to be justified.

The experimental evidence for the causal role of Hp in carcinogenesis originates from the induction of GC in various experimental model (62). The most suitable model in this respect appears to be Mongolian gerbil, which responds within few months with atrophic and precancerous gastritis (63) and after about one year with GC. In this model, Hp alone without any combination

![M. gerbil with GC and associated expression of genes involved in carcinogenesis](image)

*Fig. 11.* The induction of gastric cancer by infection with Hp expressing CagA and VacA in Mongolian gerbil. Mucosa of oxyntic gland area in healthy control animals and following Hp infection and cancer formation.
with chemical carcinogen results in the progressive atrophic changes of gastric mucosa accompanied by hypochlohydria, hypergastrinemia and overexpression of COX-2, anti-apoptotic protein and proinflammatory cytokines as well as ROS (Fig. 11). The eradication of Hp and addition of probiotics reversed the functional changes in the gerbil stomach and reversed the precancerosis is the stomach (64). It remains to be established whether the therapy applied in gerbils will be equally effective in precancerosis caused by Hp in humans.

REFERENCES


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