Development of Gastric Cancer and Its Prevention

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Abstract
Gastric cancer is a heterogeneous disorder; genetic factors, \textit{H. pylori} infection and various environmental factors contribute to its development. Advanced atrophic corpus-predominant gastritis provides the histological base for its genesis. Low socio-economic status and poor hygienic conditions, smoking habits, heavy alcohol consumption, high salt and low intake of vegetables and fruits are important external factors for the occurrence of gastric cancer. For its prevention, the eradication of \textit{H. pylori} infection at an early age is mandatory for subjects at high risk or those living in areas with high prevalence of gastric cancer. Given that an increased serum level of Pepsinogen II is a good biomarker for the presence of gastritis, it seems reasonable to screen all infected subjects at risk of gastric cancer with increased serum pepsinogen II at an early age (at around 30 years) to eradicate \textit{H. pylori}. An endoscopy should be performed for subjects at an older age (40 years and older), when increased serum pepsinogen II level is associated with decreased serum pepsinogen I and pepsinogen I to II ratio.

Keywords: Gastric cancer, pathogenesis, pepsinogen II, prevention


Introduction
Gastric cancer is highly prevalent in countries such as Japan, Korea, China, Iran and some countries of South America, although the prevalence of distal gastric cancer has decreased dramatically during the last three decades in the Western world.\(^1\) This remarkable decrease in distal gastric cancer in Western countries and the increased prevalence of proximal gastric and cardiac cancer\(^2–4\) are concurrently associated with the decrease of the prevalence of \textit{H. pylori} infection.\(^3\) This phenomenon shows that changing environmental factors can account for the increased development of colorectal cancer and the regression of distal gastric cancer in Western countries. Epidemiological studies have not considered the localization of cancer in the stomach and no distinction has been made between proximal and distal gastric cancer. Due to \textit{H. pylori}-induced gastritis, all types of gastric cancer are developed in a mucosa with deep changes associated with atrophy and intestinal metaplasia. The aim of this review article is to discuss the pathogenesis of gastric cancer irrespective of its localization and morphology, the important factors contributing to its development and measures, which are relevant for its prevention.

The molecular biology of gastric cancer and the biomarkers relevant for its prognosis are not addressed in this article. The prevention of gastric cancer is very important, given that gastric cancer is usually diagnosed when it is already at an advanced stage and its surgical removal is currently associated with a survival span of 5 years.\(^6\)

Gastritis as precursor of gastric cancer
There is no doubt that chronic inflammation of an organ is considered as the first step in the development of cancer in various organs. The inflammation of gastric mucosa is more specific than the homogeneous inflammatory process in other organs. Due to different morphology and functions of upper and lower stomach, \textit{Helicobacter pylori} inflames the antral region first (antral gastritis). The spread of inflammation from the antrum upwards occurs with advancing age under some conditions (corpus-predominant gastritis). With the predominance of gastritis in the antrum, duodenal ulcer or prepyloric ulcer disease can be developed. When the gastritis progresses from the antrum to the corpus with advancing age in some people and with the regression of inflammation in the antrum, corpus-predominant gastritis occurs.\(^7\) While gastritis restricted to the antrum occurs without \textit{H. pylori} infection, the expansion of gastritis to the corpus (antrum-predominant and corpus-predominant gastritis) is associated with \textit{H. pylori} infection in 80% of the patients.\(^8\) With the atrophy of mucosa in the corpus, the parietal cells disappear slowly. Thus, the secretory capacity of acid secretion will be decreased (Achlorhydria). When the inflammation advances in the corpus and with the appearance of atrophy of mucosa, a change of mucosa to metaplastic type (intestinal metaplasia) develops. This process is associated with a complete lack of parietal cells and the cessation of acid secretion (Achlorhydria). When there is a lack of acid secretion, \textit{H. pylori} cannot survive and disappears. Thus, the bacteria coming from oral or intestinal route can colonize the stomach and help to induce an environment capable of producing the oncogenic compound nitrosamine, which seems to be important for the occurrence of dysplasia and neoplasia in gastric mucosa.\(^9\) Corpus predominant infiltration of neutrophils and mononuclear cells and any appearance of intestinal metaplasia in the antrum or corpus were found to be important risk factors for the development of early gastric cancer.\(^10\)
Genetic host factors in the development of gastric cancer

Gastric cancer is a heterogeneous disorder; multiple factors play a role in its genesis. Less than 10% of the cases of gastric cancer can be traced back to the inheritance of factors relevant for gastric cancer development. Among these is familial inheritance of E-Cadherin, which is a host factor that causes the hereditary diffuse gastric cancer, in which this neoplasia occurs with high percentage with no influence of environmental factors under the age of 50 years. A prophylactic gastrectomy is indicated for subjects who have this mutation at an early age. This genetic factor is very rare in the population and therefore cannot play an important role in the occurrence of gastric cancer in the population.

In a meta-analysis, interleukin-1B-511T allele and IL-1 RN*2 VNTR were significantly associated with increased risk of developing gastric carcinoma and even more significantly with non-cardia gastric carcinoma or intestinal-type of gastric carcinoma. Both are significantly associated with increased risk of developing gastric carcinoma among Caucasians, but not Asians or Hispanics. In a different meta-analysis, this association, however, was not present.

Patients with Peutz-Jaggers syndrome as an autosomal dominant inherited disorder are at risk of the development of various malignant conditions. Genetic cancer is one type of cancer affecting these patients. Patients with hereditary non-polyposis colorectal cancer (Lynch syndrome) might develop gastric cancer. Carriers of this syndrome may have a lifetime risk of 8% in males and 5.3% in females for gastric cancer. In a study of the role of smoking in gastric cancer, Ladeiras-Lopes, et al. found forty-two articles that addressed smoking as an important factor. In a hospital-based study, smoking one or more cigarettes per day was associated with a risk of gastric cancer of 2.3 (95% CI, 1.4 – 3.5; P < 0.001) with more diffuse-type than intestinal-type tumors (P < 0.05).

In a meta-analysis on the role of smoking in development of gastric cancer, Ladeiras-Lopes, et al. found forty-two articles for systematic review. Comparing current smokers with non-smokers, the summary RR estimates were 1.62 in males (95% CI: 1.50 – 1.75; 18 studies) and 1.20 in females (95% CI: 1.01 – 1.43; nine studies); the RR increased from 1.3 for the lowest consumption to 1.7 for the smoking of approximately 30 cigarettes per day in the trend estimation analysis; smoking was significantly associated with both cardia (RR = 1.87; 95% CI: 1.31 – 2.67; nine studies) and non-cardia gastric cancer (RR = 1.60; 95% CI: 1.41 – 1.80; nine studies).

A total of 1,071 Japanese men aged 40 years or higher were followed up prospectively for 14 years. Compared with current nonsmokers, the hazard ratios of gastric cancer for smokers increased with the number of daily cigarettes; the HR values for 1 – 9, 10 – 19, and > or = 20 cigarettes per day were 1.36 (95% CI: 0.50 – 3.71), 1.93 (95% CI: 1.01 – 3.67), and 1.88 (95% CI: 1.02 – 3.43), respectively. The risk of gastric cancer increased steeply for subjects who had both a smoking habit and H. pylori infection compared with those who did not have both risk factors (HR = 11.41, 95% CI 1.54, 84.67). In a hospital-based study, smoking one or more cigarettes per day was associated with a relative risk of 4.8 for gastric cancer with confidence limit of 0.6 – 14.8. The consumption of red wine with smoking increased the relative risk to 9.3 with 95% confidence limit of 4.6 – 19.0. In a prospective cohort of 18,244 middle-aged men in Shanghai over 20 years of follow-up, 391 incidences of gastric cancer were identified. Smokers had an increased risk of gastric cancer (HR = 1.59; 95% CI: 1.27 – 1.99) compared to nonsmokers after adjustment for alcohol intake and other

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confounders. Among non-drinkers, smokers had 80% increased risk of gastric cancer (HR = 1.81; 95% CI: 1.36 – 2.41). Conversely, heavy drinkers experienced a statistically significant increase in risk of gastric cancer (HR = 1.46; 95% CI: 1.05 – 2.04) among all subjects and a statistically non-significant 80% increased risk among smokers. In a cohort study of 7150 men in Lithuania over 30 years, 185 cases of gastric cancer were detected. Higher intake of wine more than 0.5 liter per occasion compared with less intake was associated with gastric cancer with HR of 2.95 for men (95% CI: 1.30 – 6.68). Higher consumption of beer or vodka was not associated with gastric cancer risk. After adjustment for smoking, education level, body mass index and ethanol intake, no excess risk of gastric cancer was found in association with total acetaldehyde intake.37 In an European prospective investigation and nutrition cohort study with the occurrence of 444 cases of gastric cancer, heavy alcohol consumption at baseline was positively associated with gastric cancer risk (HR = 1.65; 95% CI: 1.06, 2.58), whereas lower consumption (< 60 g/d) was not.38 Intestinal non-cardia carcinoma was associated with heavy alcohol intake.

In a population-based cohort study in Korea over 6.5 years with 3452 detected cases of gastric cancer, a positive association was found between alcohol consumption and distal (RR = 1.3; 95% CI: 1.2 – 1.5) and all total gastric cancer (RR = 1.2; 95% CI: 1.1 – 1.4). Combined consumption of high levels of tobacco and alcohol increased the risk estimates further; cardia and upper-third gastric cancers were more strongly related to smoking than distal gastric cancer.39

In a meta-analysis of 44 case-control and 15 cohort studies, including a total of 34557 gastric cancer cases, compared with non-drinkers, the pooled relative risk (RR) was 1.07 (95% CI: 1.01 – 1.13) for alcohol drinkers and 1.20 (95% CI: 1.01 – 1.44) for heavy alcohol drinkers. This meta-analysis provides definite evidence of a lack of association between moderate alcohol drinking and gastric cancer risk. There was, however, a positive association with heavy alcohol drinking.40 In a further meta-analysis, of the 11 cohort studies evaluated, nine showed no association between alcohol drinking and gastric cancer, and one study showed a strong positive association among men. None of the 11 case-control studies found any association between alcohol drinking and gastric cancer.41

By comparing smoking habit and alcohol intake, it became evident that smoking has definite influence on the development of gastric cancer, while alcohol intake did not affect the development of gastric cancer in the majority of studies. Heavy intake of alcohol could affect the occurrence of gastric cancer. As heavy drinkers usually smoke and since this was not considered as a confounding factor in the majority of studies, it cannot be ruled out that this effect could be due to smoking habit of drinkers, too. In all these epidemiological studies, the H. pylori co-infection rate of the populations was not examined. It is very probable that the subjects with risk factors were also infected with H. pylori.

Role of salt intake in the etiology of gastric cancer

The remarkable decrease of gastric cancer in the last three decades appears to be the consequence of changing nutritional habits that coincide with a change in life style due to better hygiene and the use of refrigerators for preserving meat and food without conserving it. During the same time period, the H. pylori infection rate of Western populations has decreased considerably. In almost all clinical studies, the reduction of daily salt intake by preserving meat and food without the use of salt as a conserving compound has decreased the progression of gastric mucosa towards precancerous conditions and gastric cancer. The varying mortality rates of gastric cancer in many countries are closely associated with the consumption of salt and urine salt concentration.42 In a meta-analysis in 2012 (total population: n = 2076498; events: n = 12039), the combined odds ratio showed a significant positive association between high salt intake and gastric cancer compared with low salt intake (OR = 2.05, 95% CI: 1.60 – 2.62).43 In another meta-analysis with seven studies and inclusion of 268 718 participants, 1474 gastric cancer cases were identified over a follow-up of 6 – 15 years. In the pooled analysis, “high” vs. “low” salt intake was associated with a corresponding risk of gastric cancer with RR = 1.68 (95% CI: 1.17 – 2.41) and “moderately high” vs. “low” salt intake with RR = 1.41 (95% CI: 1.03 – 1.93).44 The association between salt intake and gastric cancer occurrence was observed in another case and control study in Portugal regardless of H. pylori infection status and virulence, smoking, tumor site or histological type.45 However, in the follow up study of the government employees over 6 – 7 years in Korea, this association was marginal.46 In another study, this association was found in those having a combination of H. pylori infection and atrophic gastritis.47

Role of vegetables and fruits as antioxidants

Intake of vegetables and fruits and occurrence of cancer has been extensively studied in many cohort and population- and hospital-based case and control studies in a variety of sites. Sufficient fruit and vegetable intake reduces the prevalence of cancer in various organs, including the intestinal tract. In a meta-analysis which considered 16 studies, a favorable effect on gastric cancer was found for a “healthy diet” rich in vegetables and fruits with an odds ratio (OR) of 0.75 (95% CI: 0.63 – 0.90) for the highest versus the lowest category and an unfavorable role emerged for the ‘Western/unnhealthy’ dietary pattern, with an OR of 1.51 (95% CI: 1.21 – 1.89).48 In four areas of Korea, mortality due to gastric cancer over 15 years was negatively associated with use of refrigerators and intake of fruit but not vegetables.49

From 29 case-control studies carried out in Latin America, fruit and total vegetable consumption were each associated with a moderately decreased risk of gastric cancer.50 In a case and control study from Italy, among the four major dietary patterns, named “animal products”, “vitamins and fiber”, “vegetable unsaturated fatty acids”, and “starch-rich”, a positive association was found between gastric cancer risk and the “animal products” (OR = 2.13; 95% CI: 1.34 – 3.40, for the highest versus the lowest score quartile) and the “starch-rich” dietary pattern (OR = 1.67; 95% CI: 1.01 – 2.77). The “vitamins and fiber” pattern (OR = 0.60; 95% CI: 0.37 – 0.99) was inversely associated with gastric cancer.51

In a large case and control study in European countries over 3 ½ years, subjects with gastric cancer occurrence had lower plasma levels of antioxidant micronutrients such as carotenoids and tocopherols compared with controls.52 In a meta-analysis published recently on the dietary fiber intake and gastric cancer, from 21 articles containing 580,064 subjects in 19 case-control
and 2 cohort studies, the odds ratio of dietary fiber intake was 0.58 (95% CI: 0.49 – 0.67).

Prevention of gastric cancer
As gastric cancer is a heterogeneous disorder and the susceptibility of each individual to the various pathogenetic factors is different depending on genetic, geographic and environmental factors, its eradication and prevention might be difficult to assess. Unintended change of life style and habits in the last decades have remarkably decreased the prevalence of gastric cancer in Western Europe, North- and South America. Many factors play an important role in this decrease. On the one hand, the improvement of life style conditions and hygiene have diminished the prevalence of H. pylori infection as the main cause of gastritis and precondition for cancer development. On the other hand, the improvement of economic status, availability of refrigerators preserving fresh healthy food, omitting salting and conserving ingredients in meat led to a dramatic decrease in gastric cancer. Smoking patterns as a further factor contributing to the occurrence of gastric cancer has hardly changed in either the developed or the developing countries.

Hereditary gastric cancer
Genetic factors with high penetrance must be treated differently from other causes. Any family with two documented cases of gastric cancer in the first or second degree relatives, with the tumor occurring in at least one member under the age of 50 years, or in three members in the first or second degree relatives at any age must be considered as genetically predisposed to gastric cancer. Early gastric resection in the case of high penetrance of gastric cancer at an early age must be the main measure of prevention if there is a diagnosis of genetic deficiency. In other cases, the risk must be assessed on the basis of mucosal changes by histology of the antrum and corpus and eradication of H. pylori through further surveillance in different intervals.

Chemoprevention of gastric cancer
No randomized controlled studies exist so far on the long term effect of NSAID alone on the development of gastric cancer. In a meta-analysis (eight case-control and one cohort study) with a total of 2831 gastric cancer patients, NSAID users had a reduced risk of gastric cancer, with odds ratio of 0.78 (95% CI: 0.69 – 0.87). Users of aspirin only (OR = 0.73, 95% CI: 0.63 – 0.86) and non-aspirin NSAIDs (OR = 0.74, 95% CI: 0.55 – 1.00) experienced similar levels of risk reduction. It is probable that the anti-angiogenesis and apoptosis-promoting effects of NSAID play a role in inhibition of cancer genesis in the stomach as it does in patients with colon polyp. There are many ongoing cohort and population studies for prevention of cardiovascular diseases in which multiple compounds, including low dose aspirin, were administered to subjects in various countries. The results of these large and long-term studies will clarify in the future the effect of aspirin on the prevention of gastric cancer.

Interventional measures to decrease H. pylori prevalence by eradication
As H. pylori infection is the main cause of gastritis and the precondition for development of precancerous conditions like atrophic gastritis and intestinal metaplasia, its eradication remains a logical step in the strategy of gastric cancer prevention. Various studies on the prevention of development of precancerous conditions and gastric cancer have shown that intestinal metaplasia is severely reversible by eradication of Helicobacter pylori. However, gastric cancer development cannot be easily prevented by the eradication of H. pylori, when the gastritis has progressed to advanced precancerous conditions. As this progression takes a long time and occurs at an older age, the eradication of H. pylori must be carried out long before the atrophic gastritis associated with intestinal metaplasia develops. This means that the eradication of H. pylori could have an effect on preventing gastric cancer when it is performed at an earlier age. In our double-blind, randomized prospective and controlled study, successful eradication of H. pylori did not lead to regression but ended the progression of intestinal metaplasia after 4 ½ years compared to the non-eradicated group. It is not known whether the end of progression of precancerous condition influences the reduction of development of dysplasia and gastric cancer.

In a multi-center, randomized controlled study over 3 years in patients with a condition after endoscopic resection of early gastric cancer (272 patients in each group), H. pylori eradication prevented, irrespective of length of follow-up, the incidence of recurrence of metachronous gastric carcinoma. The odds ratio for metachronous gastric carcinoma was 0.353 (95% CI: 0.161 – 0.775; p = 0.009). Prevention of recurrent gastric cancer through H. pylori eradication suggests that the intervention was efficacious in this study despite the presence of precancerous conditions.

Some population-based controlled studies have addressed the effect of H. pylori eradication on development of gastric cancer. None of those studies was able to prove the decrease of gastric cancer. By pooling the results of 6 studies, 37 of 3388 treated patients (1.1%) developed gastric cancer compared with 56 of 3307 untreated participants (1.7%) over 4 to 10 years. The relative risk for gastric cancer was 0.65 (95% CI: 0.43 – 0.98). All studies were performed in areas with high incidence of gastric cancer, mostly in Asia.

On the other hand, as gastritis is very common in most developing countries and few subjects develop gastric cancer, mass eradication of H. pylori in all members of these societies with high prevalence of infection, even in areas with high risk for gastric cancer, seems to be impossible. Beside high costs, various side effects of therapy and the occurrence of bacterial resistance must be taken into consideration. In addition to these unfavorable aspects, the development of esophageal and cardia carcinoma, as well as esophagitis are associated with negative H. pylori infection. Therefore, long-term sequelae of interventional H. pylori eradication in the population for gastric cancer prevention remain to be studied. The harm could outweigh the probable benefit of eradication in subjects at normal risk. Thus, mass eradication of H. pylori for gastric cancer prevention is not justified for individuals living in high risk areas. Therefore, the advantage of H. pylori eradication must be evaluated against the probable hazard in any individual, which can occur many years or some decades later. H. pylori eradication can only be carried out in the first degree relatives of gastric cancer patients and in those having an individually high risk of developing gastric cancer, like corpus-dominant gastritis.
Screening of individuals with high risk for gastric cancer by measuring serum Pepsinogen II

In spite of the remarkable decrease in gastric cancer in Europe and North America, it occurs in all countries with a different prevalence. As mentioned above, a strategy for gastric cancer prevention would be to identify the subjects at risk in any society and in any area irrespective of the prevalence of gastric cancer. Except individuals carrying genetic deficiency with high penetrance for gastric cancer, who need special surveillance and should undergo gastrectomy at appropriate time, all other subjects at risk should be selected among the population. Endoscopic surveillance with taking biopsy specimens from the antrum and corpus for diagnosis of corpus-predominant gastritis or routine radiology in areas with high risk for gastric cancer are very cost-intensive and not practicable in developing countries. Many people at risk in developing countries are not willing to undergo this uncomfortable surveillance procedure at different time intervals.

Low serum pepsinogen I level (< 70 μg/L) and low ratio of pepsinogen I to pepsinogen II (< 5 or 3) have been proposed for screening those with atrophic gastritis by some Japanese authors. However, this strategy was not adopted in the guideline of Eastern Asian Societies.

Pepsinogen II is decreased when extensive atrophic gastritis and intestinal metaplasia occur in the corpus by remarkable loss of acid producing parietal cells associated with hypo- or achlorhydria. Thus, by measuring these biomarkers, individuals at earlier stages of atrophic gastritis in the corpus will be missed in screening. In a study, we found that serum pepsinogen II is increased to at least more than 1 ½-fold of the normal value with the occurrence of gastritis with 80% sensitivity and specificity (using a cut-off value of 7.5 μg/mL for pepsinogen II), which has been confirmed by others. As atrophic gastritis advances, the level of serum pepsinogen II, unlike the level of pepsinogen I, remains high or increases further, decreasing the ratio of pepsinogen I to pepsinogen II. Individuals with increased pepsinogen II and normal pepsinogen I level have gastritis without atrophic change and are eligible for H. pylori eradication. As successful eradication leads to regression of gastritis, the level of pepsinogen II decreases to normal level after eradication.

With the measurement of pepsinogen II in serum, it is possible to screen subjects with gastritis in the population as well as to evaluate the success of H. pylori eradication in terms of the decrease of serum level after therapy. The measurement of antibody to H. pylori is for additional confirmation that increased serum pepsinogen II level is due to the presence of infection. The normal serum pepsinogen II level together with lack of H. pylori antibody in serum is a sign of the presence of normal gastric mucosa and lack of advanced atrophic gastritis. In this case, no H. pylori eradication is necessary.

Screening can be started at the age of 30 years, at which atrophic gastritis can hardly be present. In case of positive serology for H. pylori antibody by high serum pepsinogen II level, the prophylactic eradication of H. pylori can be performed. In case
of normal pepsinogen II, the examination can be repeated at 5 year intervals, as the progression of gastritis to atrophic gas-
tritis cannot occur over a few years. At the age of 40 years, when pepsinogen II increases, the measurement of pepsinogen I should be additionally performed. In case of normal serum pepsinogen I and increased pepsinogen II, the eradication of H. pylori will be performed. When pepsinogen I is decreased and the ratio of pepsinogen I to pepsinogen II is low (< 5), atrophic gastritis in the corpus is probable. At this time period, in addition to H. pylori eradication, endoscopy should be performed to evaluate the extent and severity of precancerous lesions and to exclude dys- or neoplasia. Further work-up and follow-up of patients depend on the histologic findings and the severity of atrophic gastritis in the the corpus. For individuals with a normal level of pepsinogen II, further control examination should be performed at 5-year intervals up to higher age by following the procedure outlined here (see Figure 1).

This strategy will remarkably reduce the number of endo-
scopic examinations and the costs of all prevention procedures for gastric cancer. The validity of this plan has to be proven in prospective population-based trials for prevention of gastric cancer.

In conclusion, various factors appear to feature in the develop-
ment of gastric cancer. Chronic infection induced by Helico-
bacter pylori is the beginning of the process, to which vari-
ous environmental factors like smoking habit, a salty diet with little intake of vegetable and fruits might contribute over long decades to the change of gastric mucosa to precancerous les-
sions and the development of gastric neoplasia. The prevention of gastric cancer could be achieved through eradication of H. pylori at younger age before the development of atrophy and intestinal metaplasia in the corpus occurs. Increased serum pep-
sinogen II might be a marker of H. pylori-induced gastritis for selection of individuals at high risk of gastric cancer.

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