Gastric cancer: Past, present and future

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AO-O Chan, BC-Y Wong, S-K Lam. Gastric cancer: Past, present and future. Can J Gastroenterol 2001;15(7):469-474. Gastric cancer remains a major cause of cancer mortality in the world. However, in the past 10 decades, the view of gastric cancer has been changing. This includes the unexplained decline in the incidence of the cancer, the proximal shift of the cancer in the stomach, the identification of Helicobacter pylori as an etiological agent, rapid development in molecular tumour biology, new treatment modalities and the adoption of mass screening for prevention. This article reviews the changing views of gastric cancer and the latest developments.

Key Words: Gastric cancer; Helicobacter pylori

EPIDEMIOLOGY AND DISEASE PATTERN

The incidence of gastric cancer has declined rapidly over the past few decades; this decline took place globally (1-5). The cause for this decline in the incidence of gastric cancer is still a medical mystery, and occurred before the discovery and eradication of H pylori. The decline took place earliest in countries with low gastric cancer incidence such as the United States in the 1930s, whereas the onset of decline in countries with a high incidence such as Japan was slower. In China, the decline was less dramatic than in other countries. Zheng et al (6) reported that in Shanghai, despite an overall decrease in gastric cancer incidence, an increase had been observed in the oldest and the youngest groups, and a less remarkable decline was observed in women than in men. The rise in incidence of gastric cancer among those 25 to 34 years of age is noteworthy, because this may signal the introduction of new environmental factors; as well, the age of onset of developing gastric cancer in the Chinese population is younger than that in the Western population.

This mini-review was prepared from a presentation made at the 1998 World Congress of Gastroenterology, September 6 to 11, 1998, Vienna, Austria
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Received for publication October 1, 1999. Accepted October 6, 1999
The diffuse and intestinal types of gastric cancer are classified by Lauren (7) as two biological entities that are different with regard to epidemiology, etiology, pathogenesis and behaviour. While there was a decline in the worldwide incidence of the intestinal type of gastric cancer in the past few decades, a gradual increase in the diffuse type to the overall incidence of gastric cancer, a gradual increase in the diffuse type was observed, which has accounted for approximately 30% of gastric carcinoma in some reported series (8).

An explosive increase in the incidence of gastric cancers confined to the cardia has been observed (9-12). A shift from distal to proximal stomach cancers was partially due to the decrease in distal cancers. Proximal tumours share demographic and pathological features with Barrett’s associated esophageal adenocarcinoma and are more likely to occur in men; this parallels the male predominance in the increasing incidence of lower-third esophageal carcinoma. Proximal tumours differ from distal tumours in that they are not associated with a severe form of gastritis, characterized by atrophy and/or intestinal metaplasia. They tend to be more aggressive than those arising from distal sites. It has been proposed that environmental factors or chemical carcinogens, eg, cigarettes and alcohol, have been particularly associated with cardiac carcinoma (13). In fact, it has been proposed that carcinoma at the cardia is a different entity from the rest of the gastric carcinomas.

The incidence of gastric cancer varies with different geographic regions as well. A high incidence is noted in Asian countries such Japan, Korea and China; parts of Europe such as Ireland; and South American countries such as Chile and Columbia. A difference in incidence and mortality from north to south has been observed in several countries, with the northern prefectures having a higher mortality risk than those in the south. This gradient is particularly marked in the northern hemisphere (14-16); in the southern hemisphere, the mortality risk tends to be higher in the southern parts (17,18). It appears that higher geographic latitudes are associated with a higher gastric cancer risk.

**ENVIRONMENTAL RISK FACTORS AND H PYLORI**

Risk of gastric cancer is associated with socioeconomic status. Subjects from a lower socioeconomic class had approximately twice as much risk of developing intestinal-type gastric cancer as subjects from a higher socioeconomic group (1,14,19,20). On the contrary, proximal gastric cancers were associated with higher socioeconomic class (12).

Large epidemiological studies demonstrating the association between diet and gastric cancer were mainly based on the amount of food imported and produced rather than the actual food consumption (21). This does not take into account the losses during storage, distribution and consumption of food, nor any ethnic dietary differences. The association between N-nitroso compounds and gastric cancer was summarized by Bartsch et al (22) in 1987. The risk of gastric cancer induced by N-nitroso compounds has been demonstrated in animal experiments (23-25). An increase in gastric nitrite was observed in patients with intestinal metaplasia, dysplasia and gastric cancer (26-28). The use of nitrate-based fertilizers (27,29,30) and pickled foods that contain nitrosated products (31,32) has been shown to positively correlate with gastric cancer. High salt intake has been shown to damage stomach mucosa and increase the susceptibility to carcinogenesis in rodents (33-35). The positive correlation between nitrate intake, salt excretion and gastric cancer has recently been shown in the Intersalt study involving 24 countries from 39 populations (36).

The World Health Organization’s International Agency for Research on Cancer has recently classified H pylori as a group 1 or definite carcinogen (37). The etiological role of H pylori in gastric cancer was based on Correa’s (38,39) model: chronic atrophic gastritis to intestinal metaplasia, dysplasia and finally carcinoma. H pylori has been shown to be strongly associated with gastric atrophy and intestinal metaplasia (40-42). Large case control and cohort studies have shown the relationship between H pylori and adenocarcinoma (41,43-46) in both the intestinal and the diffuse types of gastric cancer. H pylori infection has been estimated to increase the risk of gastric cancer sixfold (47). Tsugane et al (48) found that in a Japanese population, higher salt intake correlated with a higher prevalence of H pylori infection. It was postulated that gastric mucosal damage caused by high salt intake facilitated H pylori infection. The gastric juice of H pylori-positive individuals had a lower concentration of vitamin C than H pylori-negative individuals, but the concentration returned to normal when H pylori was eradicated (49). Therefore, vitamin C could play an important role in preventing the damage caused by H pylori through its antioxidant effect (49). Lower socioeconomic status was associated with a higher prevalence of H pylori (50). However, large interventional studies are needed to directly prove the causative role of H pylori in gastric carcinogenesis (51). On the other hand, the association of H pylori with cancer of the gastric cardia is more controversial (41,43,44,52).

Despite the proposal of dietary and environmental factors, and the identification of H pylori, the rapid global decline in gastric cancer is still not fully explainable. An interesting hypothesis that has been proposed as a pivotal point for the decline is the popularization of refrigerators (53,54). Refrigerators improve the storage of food, thereby reducing salting for preserving food, and preventing bacterial and fungal contamination of food. Refrigeration also enables fresh food and vegetables to be more readily available, which may be a valuable source of antioxidants important for cancer prevention.

**MOLECULAR BIOLOGY**

Recent advances in molecular biology lead to a better understanding of the carcinogenesis of gastric cancer. It is the accumulation of multiple gene abnormalities that result in the transformation of a normal epithelial cell to a malignant cell (55). Progressive accumulations of genetic changes have been evidenced in the different stages of
Correa's model. Microsatellite instability (56,57) and telomerase reactivation (58) occurred in early carcinogenesis. Mutation of p53 (59) and adenomatous polyposis coli genes (60), and amplification and overexpression of c-myc (61,62) and cyclin E genes (63) are found in advanced gastric cancer. Unlike colon and pancreatic cancers, gastric cancer rarely involves k-ras mutation (64). Multiple autocrine and paracrine loops interact with each other in the progression of advanced gastric cancer. These include hepatocyte growth factor (65) and the c-erbB-2 or HER-2/neu genes (66-71); and epidermal growth factor and the c-erbB-2 or HER-2/neu genes (68-71); and epidermal growth factor (EGF)/transforming growth factor-alpha and EGF receptors (72). In addition, E-cadherin (73,74), and CD44 (75,76) have been shown to play an important role in metastasis.

Genetics events further reinforced the observation that two different pathways exist in the intestinal and diffuse types of gastric cancer. Mutations of the p53 gene were essentially restricted to the intestinal type in the early phase but were involved in both types in the advanced stage (77,78). Loss of heterozygosity, mutations of the adenomatous polyposis coli (60) and the 'deleted in colon cancer' (79) genes, and amplification of the c-erbB-2 gene (67) were frequently associated with intestinal-type gastric cancers but were seldom found in the diffuse type. Microsatellite instability was found in 64% of the diffuse type but only 17% of the intestinal type (80). Amplification of c-met and k-sam tyrosine kinase receptor genes, as well as overexpression of the EGF family, transforming growth factor-beta, platelet-derived growth factor, insulin-like growth factor-II and fibroblast growth factor, are frequently found in diffuse type carcinomas (67,72). The involvement of the cadherin gene, an invasion suppressor gene, took place at an early stage in the diffuse type. Decreased expression of E-cadherin has been found in most diffuse-type gastric cancer. Germ-line mutation of the E-cadherin gene has been found in familial carcinoma of the stomach (81).

The relationship between H pylori and molecular changes may be another way to study the role of H pylori in gastric carcinogenesis. Kuniyasu et al (82) found that the degree of H pylori infection correlated with the level of human telomerase RNA expression and telomerase positivity in 26 carcinoma tissues. Moss et al (83) showed that apoptotic cells occurred in about 2.9% of epithelial cells in uninfected gastric tissue samples, located in the most superficial aspect of gastric glands. Apoptotic cells were found in 16.8% of infected gastric tissues throughout the depth of gastric glands, and the value fell to 3.1% after H pylori eradication. Similar results have been obtained by others (84,85). Accumulation of mutant p53 protein at the regenerating zone of gastric pits was significantly decreased in the H pylori-eradicated group compared with the noneradicated group (86). Downregulation of the E-cadherin protein has been shown to be significantly associated with H pylori infection in patients with normal gastric mucosa, gastritis, gastric ulcer and duodenal ulcer (87). Studies on whether eradication of H pylori results in reversion or halting of the molecular events is important both in the understanding of gastric carcinogenesis and in the management of patients.

**TREATMENT**

**Surgery:** The surgical strategy of the Japanese Research Society for Gastric Cancer was based on gastric lymphatic drainage. D2 radical gastrectomy has been advocated and practised as standard surgery in Japan for the past 30 years. In D2 radical gastrectomy, all of the lymph nodes are retrieved from the resection specimen and examined for micrometastasis, which sometimes may be difficult to see intraoperatively. This is in contrast to the Western world, where conventional limited D1 radical gastrectomy is more commonly performed. Japanese series demonstrated a survival benefit using D2 resection (88). However, this was not proven in the Western world (89). In a recent prospective, randomized controlled trial, D2 resections were associated with significantly higher mortality and morbidity, which may nullify the survival benefits from D2 procedures (90).

Further, the difference could also be accounted for partially by understaging in the Western world, where less regional lymph nodes were resected (91). In addition, the number of tumors diagnosed in Japan could have been overstaged, because some of the stage I carcinomas diagnosed in Japan were reported to be dysplasia by Western pathologists (92).

**Endoscopic treatment:** Therapeutic endoscopy for gastric cancer is a minimally invasive procedure that aims for complete cancer removal in early gastric cancer, palliation by recanalization or hemostasis of cancer bleeding. Endoscopic mucosal resection proposed by Tada et al (93) has been performed in patients with early gastric cancer in the absence of lymph node involvement, whereas the endoscopic laser ablation technique offers high efficacy in treating deeper invasive cancers.

**Chemotherapy:** Adjuvant chemotherapy after curative surgery has not been able to show a prolonged disease-free interval or overall survival by meta-analysis (94). A recent prospective study compared one of the newer chemotherapy regimens, consisting of 5-fluorouracil, leucovorin and epideroxorubicin, with surgery alone in node-positive patients; the result was a significantly improved median survival and delayed time to recurrence in the chemotherapy-treated patients (95). Further follow-up to determine long term survival benefit is necessary. Neoadjuvant chemotherapy aims at reducing tumour bulk, thus downstaging the primary tumour to increase resectability rates. But at the same time, it may delay operation in those patients with early gastric cancer who do not benefit from neoadjuvant chemotherapy. Further trials on neoadjuvant chemotherapy is necessary. New second-generation combinations of chemotherapy protocols were developed for palliative care. These include etoposide plus cisplatin; methotrexate; etoposide plus 5-fluorouracil plus leucovorin; continuous infusion of 5-fluorouracil plus cisplatin; and high dose methotrexate plus 5-fluorouracil plus doxorubicin (96-98). Currently, promising results have been achieved in
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