

# The thinking to the huge disease burden of gastric cancer in China and the increasing tendency of esophagogastric junctional adenocarcinoma

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Gastric cancer is one of the most common cancer and leading cause of cancer death worldwide (1). Although the overall incidence has been declining globally in recent years, gastric cancer remains a disease with high incidence and mortality, especially in Eastern Asia (1). In a recent issue of *Gut* (2), Colquhoun *et al.* has described the worldwide incidence patterns of cardia and non-cardia gastric cancer separately. It has been reported that the highest estimated regional rates of gastric cancer occurred in Eastern/Southeastern Asia (2). The high incidence of gastric cancer in these areas may result from *Helicobacter pylori* (*Hp*) infection and bad dietary habits, including excessive ingestion of smoked or salty foods. In addition, the national screening programs in Japan and Korea and the wider application of endoscopy also contribute to the high incidence of gastric cancer.

Particularly, the incidence of gastric cancer is much higher in China than in any other countries. China accounts for nearly 45% of new cases and 40% of cancer related deaths worldwide. Therefore, the prevention and treatment of gastric cancer are urged to be emphasized, especially in China. Relative to the high incidence of gastric cancer, the long-term survival rates of advanced cases in China are still unsatisfactory although it has been improved with the implementation of standard D2 lymphadenectomy and development of chemotherapy as well as new targeted drugs in recent years (3-5).

It's well known that advanced stages of cancer as the main reason contribute to the poor survival of patients. However, the proportion of early gastric cancer is still

too low and advanced gastric cancer remains the leading health burden and cause of cancer-induced mortality in China (6). Benefiting from the national population-based gastric cancer screening programs, in the contrast, Korea and Japan where gastric cancer are the most frequently diagnosed cancer reported a gradually increasing incidences of early gastric cancer and relative high 5-year survival rates being around 70% in recent years (7,8). Consequently, establishment of a formal and specialized nationwide screening program for gastric cancer in China should be advocated to promote early detection.

Surgery is the mainstay of treatment for patients with gastric carcinoma. As the publication of the 15-year follow-up results of Dutch trial, the benefiting role of standard D2 lymph node dissection for the treatment of gastric cancer has been realized and accepted by the majority of surgeons (3). In Chinese hospitals, however, D1 or D1+ lymphadenectomy was frequently performed for some patients with less advanced gastric cancer in the earlier decades and standard D2 lymphadenectomy was selectively performed for medically fit patients with advanced stage (9). Furthermore, the dissection sometimes might be not standard sufficiently in a so-called "D2 lymphadenectomy". Fortunately, the gastric cancer surgery has been becoming more and more standard in recent years through making efforts on the training and spread of D2 lymphadenectomy in China. Our data demonstrated that the increased proportion of D2 lymphadenectomy was found to be accompanied by increased surgical duration, the number of harvested lymph nodes and overall survival from 2000–2005 period to 2006–

2010 period in West China hospital (9), which also justified the survival benefit brought by D2 lymphadenectomy. Therefore, training and spread of D2 lymphadenectomy and generalization of standard treatment are urgently advocated in China. Moreover, further attentions should be paid to the spread and education about chemotherapy, the invention of new drugs or regimens with lower toxicity, and the appropriate application of chemotherapy, since the role of adjuvant chemotherapy in gastric cancer patients after D2 gastrectomy have been established by two large randomized controlled trials in Asia (ACTS-GC trial and CLASSIC trial) (4,10).

Esophagogastric junctional adenocarcinoma (EGJA) is usually regarded as a distinct entity from the distal cancer, including epidemiology and risk factor profiles (11). In recent years, different changing trends in the incidence of EGJA and non-EGJA have also been observed (2). The incidence of EGJA has been increasing in the ensuing years since there has been a proximal migration of carcinoma in the world, especially in Central Asia; while the incidence of non-EGJA decreased annually (2). The increasing tendency of EGJA is also found in China (12). The reasons for these changing trends are not very clear, but may reflect the change of risk factors. Several factors might be responsible for this phenomenon (13-15).

Cigarette smoking and possibly heavy alcohol consumption as risk factors have been identified in case-control studies of patients with esophageal or cardia gastric adenocarcinoma. The fact that smoking could increase the risk of esophageal adenocarcinoma may partly explain the reason why men had higher estimated rates than women, particularly for EGJA. Obesity has also been considered as a major risk factor for EGJA. Unfortunately, the percentage of overweight population increased dramatically. The diet habit also has been changing to the unhealthy foods. There is some evidence that dietary factors, including low intake of fruits and vegetables and high intake of red meat, fat, and calories, may be involved in the carcinogenesis of EGJA. These are accordance to the finding that a slight gradient across Human Development Index (HDI) categories was observed, with the highest rates found in high HDI countries (2). *Hp* infection is considered as an important risk factor for distal gastric cancer. Paralleled by a falling in the prevalence of *Hp* infection, the incidence of distal gastric cancer is decreasing in the developed world, which suggests that the reduction in the rate of *Hp* infection is partly responsible for the proximal migration of the location of gastric cancers. However, it has also been reported

that there was a positive association between *Hp* infection and EGJA (2). And considering the high prevalence of *Hp* infection in some Central Asia countries where the highest estimated rates of EGJA have been observed, it is also possible that *Hp* infection may play a role in the high incidence of EGJA in those populations. In addition, the increased acceptability of upper gastrointestinal endoscopy and its widespread application in the population have made the detection rate of EGJA and esophageal cancer increased.

The role of the gastroesophageal reflux disease (GERD) in the carcinogenesis of EGJA is still controversial. Basically, long-term gastroesophageal reflux might injure the epithelium of esophagus and EGJ, and gradually lead to the occurrence of Barrett's esophagus, then dysplasia, and finally progress to the adenocarcinoma (16). Therefore, gastroesophageal reflux was regarded as an important risk factor of Barrett's esophagus, esophageal and EGJA, which has been supported by epidemiological studies (16). The prevalence of GERD in Asia has been detected to be increasing year by year, although it is still lower than that of Western countries. In some Asian regions, the prevalence of GERD has been reported up to 48% (12). The statistical data showed that the increased trend of GERD in Asian population might be accompanied with the increased prevalence of esophageal adenocarcinoma in Eastern countries (12). Also, the annual incidence of type I EGJA seemed to be positively associated with reflux esophagitis in time trend (17,18). Recently, our team retrospectively analyzed the changes of EGJA and GERD among 5,053 surgical patients from 1988 to 2012 in a Chinese high-volume hospital (12). We found the increasing trends of EGJA, as well as the prevalence of GERD. At the same time, there was an upward tendency with significant difference between the proportion of EGJA and the prevalence of GERD. Instead of type II and type III tumors, there was a positive correlation with change in GERD for type I tumors. Therefore, a great number of studies tended to think that there was a strong and probable causal relation between gastroesophageal reflux and esophageal adenocarcinoma, as well as EGJA (19).

On one hand, however, cohort studies demonstrated that symptoms of GERD were found monthly in almost 50% of US adults and weekly in nearly 20%, but EGJA was not popular in these patients (19). And in our study, the positive correlations with change in GERD for type II and type III tumors have not been observed (12). On the other hand, some study considered that the similarities in change over time in the rate of detection of EGJA and reflux esophagitis

could not easily account for causal relationship (18). Therefore, we consider that probably GERD plays an important role in the development of EGJA, but the evidence is inadequate to show the causality between GERD and EGJA.

Besides the epidemiology and risk factor profiles, there are many differences of EGJA from non-EGJA and many issues of EGJA are still less clear and debatable. Therefore, further researches of EGJA should be emphasized and focused on the biological behaviors and treatments aspects, such as the pattern of lymph node metastasis, the proximal resection margin, extent of lymphadenectomy or digestive reconstruction etc.

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### Footnote

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