Minority Medicine

Changes in Incidences of Gastric Cardiac-gastroesophageal Junctional and Sub-cardiac Carcinomas in Nanjing of China: A 20-year Retrospective Study from a Single Tertiary Medical Center

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Abstract

Background: **The incidence of gastric cancer is decreasing worldwide in recent decades, which is credited to higher living standers and improved healthcare. It remains unclear whether it is true in the mainland China where rapid industrialization has been taken place over the past 30 years. The aim of this study was to investigate the relative and absolute incidence of gastric cardiac cancer occurring in the gastric cardiac-gastroesophageal junctional (GCG) and sub-cardiac (GSC) regions in the Nanjing metropolitan area of China over a 20-year period.**

Materials and Methods: **Patient pathology reports were reviewed for the diagnosis of adenocarcinoma on gastroduodenoscopic biopsies collected from 1982 through 2001. All reports and corresponding histology slides were retrieved and reviewed to confirm the diagnosis and tumor locations. The patients were sub-grouped into 5 time segments, ie, 1982-1985, 1986-1989, 1990-1993, 1994-1997, and 1998-2001. Within each segment, we collected and analyzed statistically the data on tumor locations (GCG vs GSC), patients' ages and sexes over time.**

Results: **Among 123,472 gastric adenocarcinomas diagnosed during this 20-year period, 5275 (4.3%) were in the cardiac region with 1885 (35.7%) GCG and 3390 (64.3%) GSC cases, respectively. There were no changes in the trend over time for the incidence of GCG (P>0.05), but a decreasing trend was found for GSC (P < 0.05) that also showed a decreasing tendency in the male-to- female ratio (P < 0.05), but not in GCG (P > 0.05). The age of patients for both GCG and GSC was increasing over time (P<0.05) with a significantly older age observed in GCG than GSC (P < 0.001).**

Conclusions: **The results showed a decreasing trend in incidence for GSC but not GCG and suggested a different tumorigenesis mechanism for cancers in these two different cardiac regions of the stomach in the Chinese patient population**. *[N A J Med Sci. 2009;2(1):35-38.]*

Key Words: *Cancer, Adenocarcinoma, Gastric cardia, China, Stomach, Gastroesophageal Junction, Incidence*

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Introduction

Gastric cancer is the second most frequent and fatal malignancy worldwide, accounting for 8.7% of all cancers and 10.4% of all cancer deaths.[1] The 5-year relative overall survival rates are about 20%. The incidence of gastric cancer is the highest in China, Japan, Eastern Europe, and Central/South America.[2] Recently, most clinical and epidemiological observations demonstrate a clear decreasing trend over time in the incidence of gastric cancers. For the past 30 years in the developed countries such as the United States and Western Europe, the incidence of distal esophageal and proximal gastric cardiac adenocarcinomas involving the gastroesophageal junction (GCG) has been rising dramatically, especially among elderly Caucasian men,[3-6] but that of gastric sub-cardiac adenocarcinoma (GSC) has been steadily decreasing. These changes in the incidence also show a marked worldwide variation among different countries and ethnic populations.[7]

Although China is among the countries with the highest incidence of gastric cancer,[1] the evidence of changes in the incidence of gastric cancers with regard to tumor anatomic locations in the recent years is limited. It remains poorly understood whether there is any change in the incidence of gastric cancers at different anatomic sites in the mainland Chinese patient population. This piece of epidemiologic information is critically important in that gastric cancer is considered primarily as an acquired malignancy in which environmental factors such as dietary components, drinking water, microorganisms, living environment, etc, may play an important role in the tumorigenesis.[8-12]

Like many other major coastal cities in China, the Nanjing metropolitan area with an estimated population of over 8 millions has been undergoing tremendous industrialization development over the past 30 years and the Western lifestyle is getting popular. Therefore, we wish to investigate if these environmental changes affect the incidence of gastric cancers in the cardiac region. As such, we performed a retrospective study on incidences of GCG and GSC over a 20-year period.

Materials and Methods

Patient clinicopathologic information was searched and collected from the files stored in the Department of Pathology of the Affiliated Nanjing Drum Tower Hospital of Nanjing University Medical School from 1982 through 2001. All consecutive cases with the pathologic diagnosis of adenocarcinoma, which included all carcinomas with glandular differentiation and/or mucin production, on gastroduodenoscopic biopsies were selected and reviewed.

All gastric adenocarcinoma cases were recorded and corresponding histology slides were reviewed to confirm the diagnosis. The endoscopic description of adenocarcinoma in each case was reviewed and classified according to the tumor site. Adenocarcinoma with its epicenter in the proximal gastric cardia and crossing the gastroesophageal junction (GEJ) was classified as gastric cardiac-gastroesophageal junctional adenocarcinoma (GCG) regardless of where the bulk of the tumor lies. The tumors located entirely below the GEJ and confined within the proximal gastric cardiac region were classified as gastric sub-cardiac adenocarcinoma (GSC). The tumors located entirely above the GEJ were considered esophageal,[13] which were rare and excluded in the study.

The patients were divided into 5 groups as follows: Group I: all cases from 1982 through 1985; Group II: 1986–1989; Group III: 1990–1993; Group IV: 1994-1997, and Group V: 1998-2001. The changes over time in the incidence of carcinomas by locations were assessed with the Cochran Armiger trend test. The Pearson Chi-square test was used for evaluation of differences in the male-to-female ratio between GCG and GSG. The ANOVA test was used for analyzing the differences in patients' ages between male and female patients, respectively, among different groups. The ages of male or female patients with GCG or GSC were compared with the student t test. The value of $P < 0.05$ was considered statistically significant. The Statistical Package for the Social science (SPSS Inc., Cary, North Carolina, USA) was used for all statistical analyses.

Results

Over the 20-year period from 1982 through 2001, we identified a total of 123,472 gastric adenocarcinomas on gastroduodenoscopic biopsies, among which 12,816 (10.4%) cases were in Group I, 20,868 (16.9%) in Group II, 28,971 (23.5%) in Group III, 29,266 (23.7%) in Group IV, and 31,551 (25.5%) in Group V. Because of ambiguous endoscopic description, 230 cases were disqualified and excluded. On the basis of endoscopic findings, 5275 (4.3%) cases were classified as gastric cardiac adenocarcinomas (GCA), among which 1885 (36%) and 3390 (64%) cases were sub-classified as GCG and GSC, respectively. Therefore, GCG and GSC accounted for only 1.5% (1,885/123,472) and 2.7% (3,390/123,472) of total gastric adenocarcinomas, respectively.

The ages of patients at diagnosis were summarized in **Table 1**. Both types of GCA were predominant in men and accounted for 78.8% and 75.3% for GCG and GSC, respectively. The patients' age at the diagnosis of GCG was significantly older than that of GSC (male: 61.6±9.9 vs 58.8±11.3 years old for GCG and GSC, respectively; female: 60.5±9.6 vs 55.9±13.8 years old) ($P < 0.001$). The incidences of GCG and GSC in each of five time segments were shown in **Table 2** and **Figure 1**. There were no changes in the trend of incidence over the 20-year study period for GCG ($P>0.05$); but a statistically significant decreasing trend was noted for GSC ($P < 0.05$). A decreasing trend in the male-to-female ratio was observed in GSC, which was statistically significantly higher in male than female patients ($P < 0.05$), but not in GCG ($P > 0.05$) (**Table 3**). **Table 4** showed that patient ages at diagnosis were older in GCG than GSC over time ($P < 0.05$), which was not influenced by the differences in genders or types of gastric cardiac cancers.

Discussion

Gastric cardiac adenocarcinoma (GCA) has been defined in various ways.[14] In the mainland China, any tumor with its epicenter located in the proximal gastric cardiac region is classified as GCA, regardless of whether or not it crosses the GEJ. Siewert et al.[15] recently classified adenocarcinomas in the GEJ region into three categories on the basis of the precise location of the tumor epicenter. According to their classification a tumor should be defined as a GCA if its epicenter is located within the area 2 cm below the GEJ. However, Nishi et al.[16] defined GCA as the tumor centered within 2 cm of the GEJ including those crossing the GEJ. The most recent World Health Organization (WHO) Classification[13] divided adenocarcinomas in the GEJ region into three types: (1) carcinoma of the GEJ, (2) distal esophageal carcinoma, and (3) carcinoma of the proximal stomach. It is generally agreed that the gastric cardia is a narrow region where the tubular esophagus joins the proximal stomach. This area is so narrow that it is difficult to estimate precisely the location of the tumor epicenter under

gastroduodenoscopy. In order to overcome the potential problem in distinguishing the tumors arising in the GEJ from those confined within the gastric cardia without the GEJ involvement, we combined the guidelines set forth by the WHO with the popular proposal by Siewert et al to define any cardiac tumor across the GEJ as GCG regardless of where the bulk of tumor lies and any tumor confined within the proximal gastric cardiac region without the GEJ involvement as GSC. This is based on the belief that cancers involving the GEJ may have tumorigenesis mechanisms different from those arising but confined within the gastric cardiac area because the former may be associated with a premalignant columnar and intestinal metaplasia in the distal esophagus, known as Barrett esophagus (BE) that is common in Caucasians but not in Chinese patients.

In general, the incidence of gastric cancers shows changing trends over time by its anatomic location in Western countries,[3-6] but varies geographically in the mainland China. For example, the reports from the Beijing area showed no obviously changing trends in the incidence of gastric cancers.[17,18] However, the epidemiology survey report from the Wu Wei city of the Gansu province in the western part of China showed a much higher incidence of gastric cancers than Beijing and the coastal cities; but the markedly increased incidence of GCG was not observed in the past 20 years in the same study,[19] which was confirmed in the current study. We found that the incidence of GCG was not only lower than that of GSC but also did not change over the 20-year study period for the patients in the Nanjing metropolitan area which is located near the east coast of China and enjoys the most rapid industrialization over the past 30 years. This finding is also consistent with the results derived from the studies in Beijing, Japan, Korea, and Taiwan,[20,21] but different from that reported in the European and North American countries. The discrepancy in the incidence of gastric cancers arising in different regions of the stomach between Asians and Caucasians is unknown. Multiple factors, especially genetic, racial, ethnic differences, and environmental factors[20] may play some roles. First, the most consistent finding for the distal esophageal and GCG carcinomas in Caucasian patients of the Western countries is the strong association with severe gastroesophageal reflux disease (GERD) and BE that is a well-known premalignant condition for esophageal and GCG carcinomas in those countries.[22] In contrast, epidemiological studies have demonstrated a much lower incidence of reflux esophagitis among Chinese than that among Caucasians in the Western countries.[23,24] BE is uncommon in non-Caucasians.[25] At present, accelerated modernization and adoption of Western culture have resulted in marked lifestyle changes among many Asians, which may potentially increase the incidence of GERD and BE. Hence, it is reasonable to speculate that the prevalence of GCG would have increased among the Chinese in the mainland China. However, the data from previously published studies from Korea, Japan, and Taiwan, and the current study do not support this assumption. On the other hand, there is a long clinical interval between GERD and occurrence of distal esophageal or GCG carcinomas. It is estimated that the prevalence of GERD rises dramatically after the age of 40.[26] Furthermore, GCG occurs most commonly around or older than 60 years old in our study. Therefore, it may take 20 to 30 years for the patients with severe GERD to develop distal esophageal or GCG carcinomas. Thus, the 20-year study period in our study may be a bit short for detection of an increasing trend of the incidence of distal esophageal and GCG carcinomas in the mainland China. Second, the effects of H. pylori infection on gastric cancer development vary by gastric anatomic sites. The H. pylori infection especially with cagA+ strains contributes to the tumorigenesis of GSC but not GCG.[27-29] Furthermore, recent studies suggest that gastric H. pylori infection may protect the distal esophagus from development of reflux esophagitis and BE.[30] The prevalence of H. pylori infection is reported to be higher among Chinese than Caucasians with an average H. pylori infection rate of 58.07% among the mainland Chinese. Furthermore, 93.6% of the organisms identified in the Chinese are cagA+ strains.[31] In contrast, the prevalence of H. pylori infection in United States was about 35.4%. The higher H. pylori infection rate in the Chinese may contribute to the lower incidences of GCG and GSC. Additional risk factors for GCG and distal esophageal cancers included smoking, increased body mass index, and lower socioeconomic status, among others. Increased body mass index is known positively associated with adenocarcinomas of distal esophagus and GCG. In contrast to Caucasians, Chinese people have a much smaller body mass index that is negatively associated with GCG.[32,33-35,36,37]

The present study showed a declining incidence trend on GSC over the 20-year period, which is consistent with a worldwide decrease in incidence of gastric cancer. There are several possible explanations. First, living standards and healthcare in the mainland China have been gradually improved during the study period. Fresh food, fruit, and vitamins are amply available to ordinary residents in the Nanjing metropolitan area, which are considered to be protective against the development of GSC. The general improvement in Chinese public healthcare has manifested an obvious trend of older ages of cancer patients at diagnosis over time in our study. Second, effective treatment to H. pylori infection may contribute to the decrease in the incidence of GSC.

In our study, we observed a parallel decreasing trend in incidences of both GCG and GSC for the study period (**Figure 1**), which might result from the hospital expansion construction and thus reduced gastroduodenoscopies observed during the same study period.

In conclusion, the results from the current study showed a decreasing incidence of GSC in the Nanjing metropolitan area of China despite rapid industrialization and lifestyle changes; however, the incidence of GCG remained stable over the same study period. The different trends in incidences of gastric cardiac carcinomas between GCG and GSC support the theories for different etiologies and tumorigenesis

mechanisms. The causes of changes in incidences of GCG and GSC are poorly understood and require further prospective large-scale, population-based epidemiology studies.

References

1. Parkin DM. Global cancer statistics in the year 2000. Lancet Oncol. 2001;2(9):533-543.
2. Pisani P, Parkin DM, Bray F, Ferlay J. Erratum: Estimates of the worldwide mortality from 25 cancers in 1990. Int J Cancer. 1999;83(6):870-873.
3. Devesa SS, Blot WJ, Fraumeni JF Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. Cancer. 1998;83(10):2049–2053.
4. Roder DM. The epidemiology of gastric cancer. Gastric Cancer. 2002;5(Suppl 1):5-11.
5. Zheng T, Mayne ST, Holford TR, Boyle P, Liu W, et al. The time trend and age-period-cohort effects on incidence of adenocarcinoma of the stomach in Connecticut from 1955-1989. Cancer. 1993;72(2):330-340.
6. Botterweck AA, Schouten LJ, Volovic A, Dorant E, Brandt PAVD. Trends in incidence of adenocarcinoma of the oesophagus andgastric cardia in ten European countries. Int J Epidemiol. 2000;29(4):645-654.
7. Corley DA, Buffler PA. Marked global incidence variation of esophageal and gastric cardia adenocarcinomas: an international study. Gastroenterology. 2001;120(1):30-35.
8. Tsugane S. Salt, salted food intake, and risk of gastric cancer: epidemiologic evidence. Cancer Sci. 2005;96(1):1-6.
9. De Stefani E, Correa P, Boffetta P, Deneo-Pellegrini H, Ronco AL, Mendilaharsu M. Dietary patterns and risk of gastric cancer: a case-control study in Uruguay. Gastric Cancer. 2004;7(4):211-220.
10. Tran GD, Sun XD, Abnet CC, et al. Prospective study of risk factors for esophageal and gastric cancers in the Linxian general population trial cohort in China. Int J Cancer. 2005;113(3):456-463.
11. Kondo T, Toyoshima H, Tsuzuki Y, et al. Aggregation of stomach cancer history in parents and offspring in comparison with other sites. Int J Epidemiol. 2003;32(4):579-583.
12. Kelley JR, Duggan JM. Gastric cancer epidemiology and risk factors. J Clin Epidemiol. 2003;56(1):1-9.
13. Parkin DM. Global cancer statistics in the year 2000. Lancet Oncol. 2001;2(9):533-543.
14. Liu Y, Kaneko S, Sobue T. Trends in reported incidences of gastric cancer by tumor location, from 1975 to 1989 in Japan. Int J Epidemiol. 2004;33(4):808-815.
15. Siewert JR, Holscher AH, Becker K, et al. Cardia cancer: attempt at a therapeutically relevant classification. Chirurg. 1987;58(1):25–32.
16. Nishi M, Nomura H, Kajisa T, et al. Surgical problem of carcinoma in the esophagogastric junction. Stomach Intest. 1978;13:1497-1507.???
17. Ding SJ, Chen LF, An BG, Lin SR, Zhou LY. The changing tendency of gastric cancer by endoscopy in 25 years-analysis of clinical epidemiology in 1178 case (in Chinese). Chinese Tumor Clinic and Healing. 2001;8(1):23-25.
18. Gao GJ, Cui Y. Epidemiological analysis of the gastric cancer by endoscopy (in Chinese). Hei Long Jiang Med J. 2002;26:387-398.
19. Li Y, Shi B, Li X, Zhou W, Liu H , Mi D. Study of the characteristics of gastric carcinoma in Wuwei City of Gansu province. Chinese Journal of General Surgery. 2004;13:667-669.
20. Lee JY, Kim HY, Kim KH, Jang HJ, Kim JB, et al. No Changing Trend in Incidence of Gastric cardia carcer in Korea. J Korean Med Sci. 2003;18(1):53-57.
21. Chang SS, Lu CL, Chao JY, et al. Unchanging trend of adenocarcinoma of the esophagus and gastric cardia in Taiwan a 15-year experience in a singe center. Dig dis sci. 2002;47(4):735-740.
22. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med. 1999;340(11):825-831.
23. Li Z, Wang W, Xu G, Yu F, Zou D, Sun Z. Clinical analysis of 1,827 patients with reflux esophagitis (in Chinese). Zhonghua Nei Ke Za Zhi. 2001;40(1):9-12.
24. Chang CS, Poon SK, Lien HC, Chen GH. The incidence of reflux esophagitis among the Chinese. Am J Gastroenterol. 1997;92(4):668-671.
25. Yeh C, Hsu CT, Ho AS, Sampliner RE, Fass R. Erosive esophagitis and Barrett's esophagus in Taiwan: a higher frequency than expected. Dig Dis Sci. 1999;42:702-706.
26. Mold JW, Reed LE, Davis AB, Allen ML, Decktor DL, RobinsonM. Prevalence of gastroesophageal reflux in elderly patientsin a primary care setting. Am J Gastroenterol. 1991;86(8):965-970.
27. Tokudome S, Soeripto, Triningsih FX, Ananta I, Suzuki S, et al. Rare Helicobacter pylori infection as a factor for the very low stomach cancer incidence in Yogyakarta, Indonesia. Cancer Lett. 2005;219(1):57-61.
28. Parsonnet J, Friedman GD, Vandersteen DP, Chang Y, Vogelman JH, et al. Helicobacter pylori infection and the risk of gastric carcinoma. N Engl J Med. 1991; 325(16): 1127-1131.
29. Konturek SJ, Starzynska T, Konturek PC, Karczewska E, Marlicz K, et al. Helicobacter pylori and CagA status, serum gastrin, interleukin-8 and gastric acid secretion in gastric cancer. Scand J Gastroenterol. 2002; 37(8): 891-898.
30. Chen YY, Antonioli DA, Spechler SJ, Zeroogian JM, Goyal RK, Wang HH. Gastroesophageal reflux disease versus Helicobacter pylori infection as the cause of gastric carditis. Mod Pathol. 1998;11(10):950-956.
31. Wang K, Wang R. Meta2analysis on the epidemiology of Helicobacter pylori infection in China. Chin J Epidemiol. 2003;24:443-446.???
32. Taylor D, Blaser MJ. The epidemiology of Helicobacter pylori infection. Epidemiol Rev. 1991; 13: 42–59. GGG
33. Wu AH, Wan P, Bernstein L. A multiethnic population-based study of smoking, alcohol and body size and risk of adenocarcinomas of the stomach and esophagus (United States). Cancer Causes Control. 2001; 12(8): 721-732.
34. Ji BT, Chow WH, Yang G, McLaughlin JK, Gao RN, et al. Body mass index and the risk of cancers of the gastric cardia and distal stomach in Shanghai, China. Cancer Epidemiol Biomarkers Prev. 1997;6(7):481-485.
35. Tran GD, Sun XD, Abnet CC, Fan JH, Dawsey SM, et al. Prospective study of risk factors for esophageal and gastric cancers in the Linxian general population trial cohort in China. Int J Cancer. 2005;113(3):456-463.
36. Deurenberg P, Yap M, van Staveren WA. Body mass index and percent body fat: A meta-analysis among different ethnic groups. Int J Obes. 1998;22(12):1164-1171.
37. Zhang J, Su XQ, Wu XJ, et al. Effect of body mass index on adenocarcinoma of gastric cardia. World J Gastroenterol. 2003;9(12):2658-2661.