

No Changing Trends in Incidence of Gastric Cardia Cancer in Korea

Although there is a controversy, several reports have shown that gastric cardia cancer has tended upwards in recent years. The aim of this study was to investigate the changing trend of stomach cancer according to the location of cancer and histologic type in Korea, where is known to be one of the most prevalent areas for gastric cancer. All the patients newly diagnosed as gastric cancer from 1991 through 2000 were recruited in Hallym University Medical Center. The periods were divided into the first (1991 through 1995) and the second (1996 through 2000) period. We analyzed the characteristics of cancer in the aspects of age, sex, tumor locations (cardia and non-cardia), and tumor grade of differentiation (well, moderate, and poor differentiated type). The number of cases was 2,395 and that of cardia cancer was 158 (6.6%). There was no evidence about the changes in the incidence of cardia cancer and histologic differentiation between two periods. The development of cardia cancer was not associated with the factors of age and sex with having no difference in the point of tumor grade. We could not find an upward tendency of cardia cancer development in recent 10 yr in Korea.

Key Words : Cardia; Stomach Neoplasms; Korea

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INTRODUCTION

Gastric cancer is the second leading cause of cancer-related death throughout the world (1). Incidence and mortality rate of gastric cancer have been declined steadily in most countries, especially in the developed countries such as the United States and Europe, while those of adenocarcinoma arising from gastric cardia and esophagus have been stable or increased, especially among white males (2-4). Most clinical and epidemiological observations have strongly suggested the rising incidence of adenocarcinoma of gastric cardia and esophagus (5-10). In contrast, recent international study involving 50 countries from 5 continents about the incidence of gastric cardia cancer (11) was inconsistent in part with the findings of most previous studies. Although this study provided the increase in age-specific incidence rate with advanced age for esophageal and gastric cardia adenocarcinoma, there was a marked variation in global incidence between countries and ethnicities. And this global variation was even more marked than that previously reported in North America and Europe (7, 8, 10).

Until now, most of the previous epidemiologic studies about

the incidence of gastric cardia cancer have been confined to the areas with low-risk for gastric cancer such as the United States, Europe and New Zealand (2-4, 10). On the contrary, the study about the cardia cancer in high-risk area has been very rare, while Japanese epidemiologic study with 30 yr-period showed no change of gastric cancer location (12). In general, Korea has been classified as one of the high-risk countries for development of gastric cancer, along with Central and South America, and most countries in the East Asia (13).

With this in mind, we conducted present study to determine the changing trend in the development of gastric cancer in Korea, an area with a high incidence of gastric cancer, during the recent 10 yr.

MATERIALS AND METHODS

Subjects

The subjects were collected from the 4 hospitals of Hallym University Medical Center including Kangdong, Kangnam,

Hankang, and Chuncheon Sacred Heart Hospital from 1991 through 2000. We reviewed all cases of gastric adenocarcinoma with gastroduodenoscopic and histologic findings for the recent 10 yr. All the subjects with newly diagnosed gastric adenocarcinoma during the study period were enrolled. All the enrolled subjects were confirmed histologically as gastric adenocarcinoma, using endoscopic biopsy without considering whether they had gastric operation or not. If gastric cancer had been suspected on radiographic studies like upper gastrointestinal series, we performed gastroduodenoscopy and confirmed histologically as gastric adenocarcinoma by endoscopic biopsy.

The specimens were fixed in a formaldehyde solution and embedded in paraffin. The sections were then routinely stained with hematoxylin-eosin and PAS. After the confirmation of adenocarcinoma, each case was classified according to tumor site (cardia and non-cardia) and grade of differentiation (well, moderate, or poorly differentiated type).

Clinical data, including sex, age, and location of tumor were analyzed through a special report form completed by clinicians. All the participated hospitals have used the report in same format on endoscopy, tumor grade, and description of tumor locations.

Gastric cardia cancer was defined as the tumorous lesion with its center located within 1 cm proximal and 2 cm distal to gastro-esophageal junction. Tumors distal to this area were classified as non-cardia gastric cancers, while tumors locating above this area were classified as esophageal cancer (14). All cases were classified as well, moderate, and poorly differentiated type by the classification of grade of differentiation.

The data from 1991 to 1995 (the first period) and those from 1996 to 2000 (the second period) were compared according to the location of cancer and their grade of differentiation. Age was expressed by mean \pm standard deviation (SD).

Analysis

The demographic and clinical characteristics were analyzed statistically using Pearson's χ^2 test, Student t-test, and univariate analysis as appropriate. A value of $p < 0.05$ was considered to be statistically significant. Statistical calculation was made with the help of SPSS statistical package for windows version 10.0 (SPSS Inc. Chicago, IL, U.S.A.).

RESULTS

From 1991 through 2000, there were 2,476 cases confirmed as gastric adenocarcinoma. Among them, 2,395 cases were analyzed and 81 cases were excluded, because clinical data were unavailable. The numbers of males and females were 1,588 (66.3%) and 807 (33.7%), respectively with the ratio of 1.97:1. The mean age at diagnosis was 59.6 ± 13.1 yr old. Among the enrolled 2,395 cases of gastric adenocarcinoma, 158 (6.6%) were found to be cardia cancer and 2,237 (93.4%) were non-

Table 1. The age and sex of patients with gastric cancer according to the location for ten years

Location	Male	Female	M/F	Mean age (yr)
Cardia	113 (71.5%)	45 (28.5%)	2.51*	60.9 ± 13.3^1
Non-cardia	1,475 (65.9%)	762 (34.1%)	1.94	59.5 ± 13.1
Total	1,588 (66.3%)	807 (33.7%)	1.97	59.6 ± 13.1

*Comparison of male to female ratio between cardia and non-cardia cancers ($p=0.09$); ¹Comparison of mean age at diagnosis between cardia and non-cardia cancer ($p=0.19$).

Table 2. No sexual difference according to the location and the year of diagnosis

Location	Year of diagnosis		<i>p</i> value
	1st period (1991-1995) (n=1,039)	2nd period (1996-2000) (n=1,356)	
Cardia	64 (6.2%)	94 (6.9%)	NS*
Male	45	68	
Female	19	26	
Non-cardia	975 (93.8%)	1,262 (93.1%)	NS
Male	646	829	
Female	329	433	

* $p > 0.05$ for the comparison of the rates for cardia cancer between two periods. Odds ratio for the cardia cancer in 2nd period is 1.14 (95% CI, 0.82-1.53).

Table 3. The grade of differentiation of gastric cancer according to location of gastric cancer

Grade of differentiation	Location	
	Cardia (n=158)	Non-cardia (n=2,237)
Well	22 (13.9%)	489 (21.9%)
Moderate	48 (30.4%)	653 (29.2%)
Poorly	86 (54.4%)	1,089 (48.7%)
Undefined	2 (1.3%)	6 (0.3%)

cardia cancer. The numbers of cases by sex and anatomical sites are shown in Table 1. Tumor grades are distributed as follows: 511 (21.3%) in well differentiated, 701 (29.3%) in moderate differentiated, and 1,175 (49.1%) in poorly differentiated type.

Changes in the incidence of cardia and non-cardia cancer

Sixty-four (6.2%) out of 1,039 cases from the first period and 94 (6.9%) out of 1,356 cases from the second period were confirmed to be cardia cancer. There was no statistically significant change in the incidence of cardia and non-cardia cancer between the two periods (Table 2). Age and sex were not associated with the development of cardia cancer (Table 1). Even after adjusting these two factors by univariate analysis, the increasing tendency of cardia cancer was not observed in the second period compared with that in the first period. In cardia cancer, the increasing tendency in male to female ratio was observed with no statistical significance (Table 1).

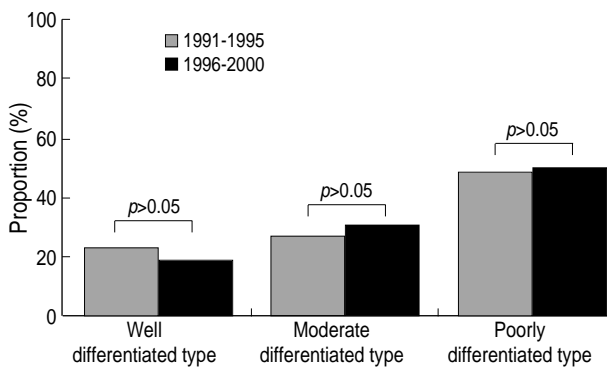


Fig. 1. The grade of differentiation of gastric cancer according to diagnosed period.

Histological changes in the grade of differentiation

Table 3 presents the numbers of gastric adenocarcinoma according to tumor grade and location. Poorly differentiated type cancer was more common, but there was no significant difference between cardia and non-cardia cancer ($p > 0.05$). Each proportion of gastric cancer according to tumor grade from the first and second period was 23.6% and 19.6% in well differentiated type, 27.5% and 30.6% in moderate differentiated type, and 48.8% and 49.3% in poorly differentiated type, respectively (Fig. 1). Although the number of cases of well-differentiated type was decreased and that of moderate differentiated type was increased in the second period, there was no statistical significant difference ($p > 0.05$, Fig. 1).

DISCUSSION

The increasing trend of adenocarcinoma arising from gastric cardia was not observed in Korea from 1991 through 2000. Gastric cancer has been the most common malignant neoplasm among both male and female cancer patients in Korea, one of the most prevalent areas of gastric cancer in the world. The incidence of stomach cancer in Korea is estimated to be 36.2 per 100,000 males and 25.1 per 100,000 in females (15). Although the incidence has been decreased in Korea, gastric cancer is still the most prevalent malignancy with a portion of 21% of all the cancers with an estimated annual death rate of 24 per 100,000 deaths (16, 17).

Our study has not only several methodological advantages but also some limitations. First, our study used the same definition for location of gastric cardia cancer. Until a recent date, gastric non-cardia cancer might be misclassified as cardia cancer in some studies because there had been no consensus on the definition for cardia cancer (18). The main concern regarding most previous studies of the incidence of gastric cardia cancer has been the potential for misclassification of cardia cancer. According to the analysis of Swedish cancer registry data that has been known as one of the most exact population-based

studies, the positive predictive value of the diagnosis of cardia cancer was reported at 82%. It is possible that such a misclassification may make the incidence of cardia cancer to be inflated (6, 19). Secondly, we had almost no losing data with analysis of 2,295 of 2,476 cases (97%) of gastric cancer in current study. Previous population-based studies had high portion of undefined location because they collected data using ICD code from cancer registry (3, 7, 8), and the rate of undefined location was as high as 45% (3).

One of the limitations is that our study was not a population-based study. However, we believe that our results could overcome selection bias, because of the stable incidence of gastric cancer in each hospital and each year (data not shown) throughout the studied period.

Little is known about the etiology and pathogenesis of adenocarcinoma from gastric cardia and esophagus. Recent analytic studies, however, have revealed various risk factors of the adenocarcinoma of esophagus and gastric cardia. Increased risk has been reported to be associated with gastroesophageal reflux disease, Barrett's esophagus, smoking, and alcohol (18, 20, 21). *Helicobacter pylori* infection has been known as a risk factor of gastric adenocarcinoma and the association is accentuated with tumors located distal to the gastric cardia (22, 23). Moreover, the reasons for the increase in gastric cardia and esophageal adenocarcinoma remain uncertain, but the interesting epidemiological results have been surfaced in the previous studies of cardia cancer. First of all, in cardia cancer, the male to female ratio has been more markedly accentuated than that of the distal carcinomas with the ratio as high as 5 to 1 (7, 13). And there is even a racial difference in the same area. For instance, the proximal cancer is more common and more rapidly increasing in the white race in the United States (7, 8, 13). The precise reasons for such gender and racial differences are still unknown.

Although our results contradict those of most population-based studies that observed the increasing incidence of adenocarcinoma from gastric cardia in western countries with low-risk of gastric cancer, our findings are in favor with the results from the international and Japanese studies (11, 12). We suggest some explanations for no increasing trend of gastric cardia cancer in Korea. First, 10 yr may be relatively short to confirm the trend of cardia cancer. Duration of other studies varies from 6 to 30 yr (3, 6, 7, 9, 10). We believe that 10 yr can be enough to observe the trend; the Swedish study with 6 yr-period showed definite decrease in gastric cancer, although the Japanese study with longer 30 yr-period showed no change in tumor location (12). In addition, the proportion of cardia cancer in each year has not been changed in this study. Secondly, risk factors such as race, geographic area, or environmental factors should be considered to conclude that the development of cardia cancer is generally increasing worldwide. The results of the previous epidemiologic studies have provided a question about the recent increasing trends in gastric cardia cancer. In other words, because most studies about the

incidence of gastric cardia cancer were performed in the low-risk area of gastric cancer, such as in the United States and Europe (4, 8, 10), the observed increasing trend in adenocarcinoma from gastric cardia may have been inflated by selecting studied population. For example, most studies have shown the definitely increasing trend of cardia cancer among males rather than among females, especially in the white (13). But, there was no significant difference in the development of cardia cancer between males and females in the present study. On the basis of data from previous studies and current study, we suggested that many factors such as gender, racial differences and environmental factors were associated with the development of cardia cancer, which had separate etiologies for non-cardia cancer. It is an interesting finding, therefore, that there is no increasing tendency of cardia cancer in high-risk area of gastric cancer.

The prevalence of *H. pylori* infection that is known to be one of the important etiologic factors for gastric cancer is higher in Korea, with approximately 47% of healthy population (24), than in developed countries (25, 26). Most reports have suggested that gastric cardia and non-cardia cancer may have different etiologic and pathologic events, and *H. pylori* infection has been known to cause non-cardia cancer rather than cardia cancer (13, 23, 27). However, we could not obtain the information on the presence or absence of a history of infection and could not investigate the association of cancer location with *H. pylori* infection. The large-scale study about their association will be warranted.

Our results show that the grade of differentiation of gastric cancer had no significant change over 10 yr and that there was no correlation between tumor grade and location. Recently, a Japanese study showed the decrease in differentiated gastric cancer during the last 30 yr (12) and the retrospective study in the United States during the last 10 yr showed the small decrease in well differentiated carcinoma (28). In the latter study, poorly differentiated gastric adenocarcinoma represented 60% of total gastric cancer (28), compared with 50% of that in our study. Our study also showed small decreasing proportion of well-differentiated adenocarcinoma, but this did not reach statistical significance. The reason of this result could be due to short duration. More study using standard pathologic criteria will be needed to investigate the precise relation among histologic subtype, tumor location and risk factors.

In conclusion, the increasing trend of gastric cardia cancer, that is shown in the countries with low risk of gastric cancer, is not observed in Korea with high risk of gastric cancer. The prospective and long-term studies for this phenomenon are warranted.

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