Gastric Cancer (2000) 3: 123–127

Original article

Time trends for small gastric cancer in Japan

Naoko Tsuji[1,3], Shingo Ishiguro[1], Masayuki Mano[1], Tsutomu Kasugai[1], Yasuko Nishizawa[1], Kuninori Nose[1], Isao Miyashiro[2], Masahiro Hiratsuka[2], and Hiroshi Furukawa[2]

[1] Department of Pathology, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3 Nakamichi, Higashinari-ku, Osaka 537-8511, Japan
[2] Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan
[3] Department of Gastroenterology, Yuseikai Midorigaoka Hospital, Osaka, Japan

Abstract

Background. **Gastric cancer rates in Japan have been declining since the 1970s. The rate of differentiated carcinomas has decreased and that of undifferentiated carcinomas has increased. However, little is known about the time trends of small gastric cancer. The aim of this study was to investigate the trends of small gastric cancer over time in Japan.**

Methods. **We reviewed cases of small gastric cancer (less than 20 mm in diameter) in two groups of patients who entered the age range of 55-to-67 years 14 years apart: patients in cohort 1 ($n = 66$) were born between 1899 and 1912, and those in cohort 2 ($n = 66$) were born between 1926 and 1936. Between-group comparisons were made for macroscopic, microscopic, and histochemical findings. Mucin histochemical analysis was used to investigate gastric and nongastric phenotypes. *Helicobacter pylori* was also investigated by immunohistochemistry.**

Results. **There were significant decreases in the incidence of elevated carcinoma (20% in cohort 1 vs 6% in cohort 2; $P < 0.05$) and papillary adenocarcinoma (11% vs 2%; $P < 0.05$). The incidence of flat carcinomas was significantly increased (3% vs 15%; $P < 0.05$). The incidence of tumors surrounded by fundic gland mucosa increased (20% vs 29%), whereas that of tumors surrounded by intestinal metaplastic mucosa decreased (52% vs 41%). The rate of *H. pylori* infection in mucosa surrounding tumors was the same in both groups (35%). The incidence of tubular adenocarcinoma with gastric-type mucin was higher in cohort 2 (64%) than in cohort 1 (51%).**

Conclusion. **The rate of tubular adenocarcinomas containing gastric type mucin has increased over time. These tumors had a tendency to develop in the fundic gland mucosa and to show less intestinal metaplasia. The *H. pylori* infection rate was unrelated to this time trend. In advanced gastric cancer, the differentiated carcinoma rate has decreased; however, in small gastric cancer, the rate of tubular adenocarcinoma containing gastric type mucin has increased. This suggests that tubular adenocarcinoma with gastric type mucin changes into poorly differentiated adenocarcinoma as tumors grow to advanced stages.**

Key words Small gastric cancer · Time trends · Mucin phenotype

Introduction

Gastric cancer is a common disease in Japan, with incidence and mortality rates declining since the 1970s [1]. Intestinal-type adenocarcinoma, which is believed to an environmental carcinoma, has been declining in Japan and other countries [2]. Trends in small gastric cancer have not been well investigated. The relation between the histologic type of gastric cancer and the property of the background mucosa has been well investigated [3]. Differentiated carcinomas are believed to be intestinal type, developing in intestinal metaplastic mucosa, and undifferentiated carcinomas are believed to develop in the gastric mucosa proper. Recent advances in mucin histochemistry reveal that some differentiated adenocarcinomas and intestinal type carcinomas have gastric type mucins [4]. Etiological factors of intestinal type cancer are related to diet and infection. *Helicobacter pylori* is thought to be related to gastric carcinogenesis [5,6].

We investigated the time trends of small gastric cancer only, because small gastric cancer does not exist for a long time after carcinogenesis and the background mucosa is well preserved. We can see not only the characteristics of the tumor itself but also that of background mucosa. In the present study, two groups with birth ranges beginning 14 years apart were selected, and the trends in small gastric cancer were investigated with respect to the macroscopic and microscopic findings of the cancer and background mucosa, the phenotypic expression of mucin, and infection of *H. pylori*.

Offprint requests to: N. Tsuji
Received: April 24, 2000 / Accepted: August 1, 2000

Patients and methods

This study was based on a retrospective review of unselected cases that fulfilled the criteria of two cohorts. We studied gastrectomy specimens from 66 consecutive patients born between 1899 and 1912 and from 66 consecutive patients born between 1926 and 1936. The tumors were surgically resected between 1962 and 1978 in cohort 1 and between 1990 and 1994 in cohort 2, at Osaka Medical Center for Cancer and Cardiovascular Diseases. All tumors were smaller than 20 mm in diameter and patient ages at the time of surgery ranged from 55 to 67 years (Table 1). All specimens were fixed in 10% formalin, cut serially into 5-mm slices parallel with the lesser curvature, and embedded in paraffin. Tissue sections were stained with hematoxylin and eosin. Samples of each tumor, representing its maximum diameter, were selected for mucin histochemistry and immunohistochemistry (*H. pylori*). Comparisons were made between the two groups (cohort 1 vs cohort 2) based on tumor location within the stomach, gross appearance, depth of invasion, and histologic type of neoplasm.

For mucin histochemistry, galactose oxidase Schiff (GOS; mucin of surface mucus cell) and paradoxical concanavalin A class III (PCS; mucin of the mucus neck cells/pyloric gland cells) were used [7]. GOS-and/or-PCS positive cancer cells were classified as gastric-type cells, and cells negative for GOS and PCS were classified as nongastric-type cells. Carcinomas consisting of over 80% gastric-type cells were designated as gastric phenotype and those consisting of 20%–80% gastric-type cells were designated as intermediate-type. Other carcinomas were classified as nongastric cell type. The surrounding non-neoplasitic gastric mucosa, up to 20 mm from the margin of each carcinoma, was also examined. The status of the gastric glands, intestinal metaplasia, and *H. pylori* infection were investigated. *H. pylori* bacteria were detected with immunohistochemical staining, using the avidin-biotin complex method (Vectastain ABC kit, Vector, Burlingame, CA, USA). Anti-*Helicobacter pylori* polyclonal antibody (Dako, Copenhagen, Denmark) diluted (×5) with phosphate-buffered saline (pH 7.4) was used as the primary antibody. Deparaffinized sections were treated sequentially with 0.1% trypsin (37 °C; 30 min), normal goat serum, anti-*Helicobacter pylori* antibody (4 °C; overnight), biotin-labeled anti-rabbit IgG (room temperature; 30 min), and avidin-biotin-peroxidase complexes. The peroxidase binding sites were identified by staining with 20% 3,3′-diaminobenzidine and 0.03% hydrogen peroxide.

Table 1. Patients' characteristics

	Cohort 1 (n = 66)	Cohort 2 (n = 66)
Birth year range	1899–1912	1926–1936
Male/Female	53/13	50/16
Time of operation	1962–1978	1990–1994
Age at operation (years)	55–67	55–67
Tumor size (mm)	2–20	2–20

Results

Tumor characteristics over time

When the tumors of the two cohorts were compared, significant differences as well as interesting similarities were observed to have occurred over time. The specific percentages of characteristics in both groups are presented in Tables 2 through 5. The number of tumors in the middle-third of the stomach increased over time, whereas numbers in the upper- and lower-thirds decreased (Table 2). The number of elevated-type tumors was significantly lower and that of flat type was significantly higher in the more recently treated group (cohort 2) than in the group treated earlier (cohort 1 ; $P < 0.05$; Table 2). Intramucosal carcinomas increased over time, whereas submucosal and muscularis propria carcinomas had decreased a little; however, none of these changes were significant (Table 2). Papillary adenocarcinomas

Table 2. Time trend of tumor characteristics

	Cohort 1 (n = 66)	Cohort 2 (n = 66)
	No. of patients (%)	No. of patients (%)
Location		
Upper-third	9 (14)	5 (8)
Middle-third	19 (19)	26 (39)
Lower-third	38 (58)	35 (53)
Gross type		
Elevated	13 (20)	4 (6)*
Depressed	51 (77)	52 (79)
Flat	2 (3)	10 (15)**
Depth of invasion		
Mucosa	37 (56)	44 (67)
Submucosa	26 (39)	20 (30)
Muscularis propria	3 (5)	2 (3)
Histologic type		
Papillary	7 (11)	1 (2)***
Tubular	51 (77)	55 (83)
Poorly[a]/Signet	8 (12)	10 (15)

*; **; *** $P < 0.05$, Fisher's exact test
Cohort 1, Patients born between 1899 and 1912; cohort 2, patients born between 1926 and 1936
[a] Poorly differentiated

were the only type that showed a significant decrease in number across time ($P < 0.05$).

Surrounding mucosa

Tumors surrounded by fundic gland mucosa were increased, while those surrounded by intestinal metaplasia were decreased. *H. pylori* bacteria were found in the surface GOS-positive mucin within the foveola and on the surface of foveolar epithelium, but not in the tumors. Tumors surrounded by *H. pylori* were found equally in both groups. No significant differences in any surrounding mucosal specimens were observed between the two groups (Table 3).

Mucin histochemistry (Fig. 1)

The number of gastric phenotype tumors increased and that of nongastric phenotype tumors decreased across time (Table 4). The phenotypic expressions in each histological category and the time trends are summarized in Table 5. In both groups, most papillary adenocarcinomas were intermediate phenotype, and most poorly differentiated adenocarcinomas and/or signet-ring cell carcinomas were gastric phenotype. Tubular adenocarcinomas were the most frequent type in both cohorts. The incidence of tubular adenocarcinoma containing gastric-type mucin (gastric and intermediate) was higher, and that with nongastric mucin was lower in cohort 2 than in cohort 1.

Table 3. Time trend of properties of the mucosa surrounding the tumors

	Cohort 1 ($n = 66$)	Cohort 2 ($n = 66$)
	No. of patients (%)	No. of patients (%)
Gastric gland		
Fundic gland	13 (20)	19 (29)
Nonfundic gland	53 (80)	47 (71)
Intestinal metaplasia		
−	32 (48)	39 (59)
+	34 (52)	27 (41)
Helicobacter pylori		
−	43 (65)	43 (65)
+	23 (35)	23 (35)

Cohort 1, Patients born between 1899 and 1912; cohort 2, patients born between 1926 and 1936

Discussion

Gastric cancer has been divided into two categories: the intestinal type and the diffuse type [8]. The intestinal type, or well-differentiated adenocarcinoma, is more common in high-risk populations from certain regions of the world, and is more frequent in men than in women and in older than in younger adults [9]. Risk factors for stomach cancer are also related to diet, including high intake of salty foods, and to *H. pylori* infection. The intestinal metaplasia of gastric mucosa and well-differentiated adenocarcinomas are closely related [3].

In countries where the rate of gastric cancer has been decreasing, the frequency of intestinal-type cancers has been decreasing [10]. Gastric cancer remains common for men and women in Japan, but the incidence has been declining in recent decades [1]. Ishiguro et al. [11] reported a decline in well-differentiated gastric cancer in Japan, from a study of 1104 age-matched 50- to 59-year-old gastric cancer patients during three time periods. The incidences of intestinal metaplasia in mu-

Table 4. Time trend of phenotypic expression of small gastric cancer

	Cohort 1 ($n = 66$)	Cohort 2 ($n = 66$)
	No. of patients (%)	No. of patients (%)
Gastric	7 (11)	13 (20)
Intermediate	31 (47)	31 (47)
Nongastric	28 (42)	22 (33)

Cohort 1, Patients born between 1899 and 1912; cohort 2, patients born between 1926 and 1936

Table 5. Time trend of phenotypic expression of small gastric cancer in each histological category

	Papillary		Tubular		Poorly/Signet	
	Cohort 1 ($n = 7$) (%)	Cohort 2 ($n = 1$) (%)	Cohort 1 ($n = 51$) (%)	Cohort 2 ($n = 55$) (%)	Cohort 1 ($n = 8$) (%)	Cohort 2 ($n = 10$) (%)
Gastric	0 (0)	0 (0)	2 (4)	5 (9)	5 (63)	8 (80)
Intermediate	6 (86)	1 (100)	24 (47)	30 (55)	1 (13)	0 (0)
Nongastric	1 (14)	0 (0)	25 (49)	20 (36)	2 (25)	2 (20)

Cohort 1, Patients born between 1899 and 1912; cohort 2, patients born between 1926 and 1936

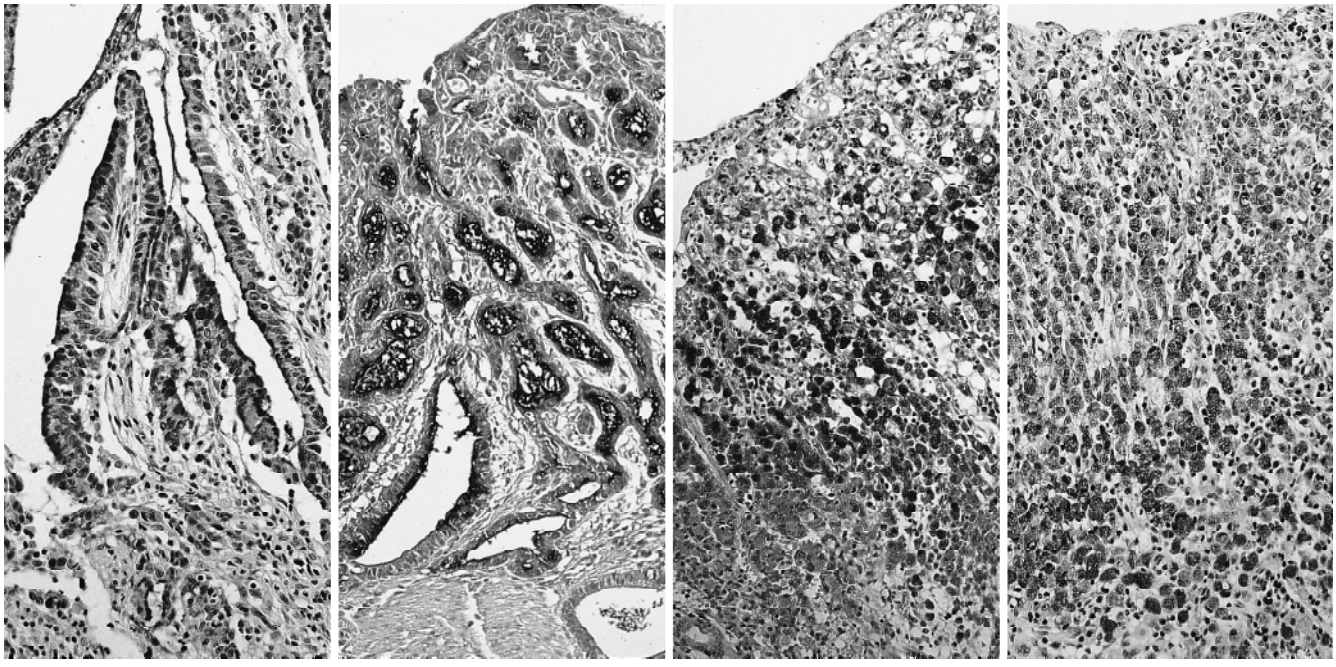

Fig. 1a–d. Gastric adenocarcinoma with gastric mucin. **a** Tubular adenocarcinoma stained with galactose oxidase Schiff (GOS). **b** Tubular adenocarcinoma stained with paradoxical concanavalin A class III (PCS). Mainly, the surface areas of cancer cells in the upper part of the mucosa contain GOS-positive mucin, while those in the lower part contain PCS-positive mucin. **c** Signet-ring cell carcinoma stained with GOS. **d** Signet-ring cell carcinoma stained with PCS. Cancer cells in the upper part of the mucosa were strongly GOS-positive, while those in the lower part were PCS-positive. ×20

cosa surrounding tumors and macroscopically localized carcinomas have also declined. In this study, we analyzed two cohorts of patients with small gastric cancer who were between the ages of 55 and 67 years at the time of their surgeries. When investigating time trends in gastric cancer, the matching of patient ages is important because histological type is closely related to age.

Advances in mucin histochemistry enable us to determine the phenotypic expression of gastric cancer cells [7]. GOS staining has been shown to specifically stain the mucin of surface mucus cells, and PCS staining targets the class III mucin of mucus neck cells and pyloric gland cells. These staining techniques confirm the existence of differentiated carcinomas with well-preserved gastric-type mucin [4]. Tatematsu et al. [4] has reported that 27% of differentiated carcinomas are gastric-type adenocarcinomas. In our study, 4% of tubular adenocarcinomas in cohort 1 and 9% of tubular adenocarcinomas in cohort 2 had pure gastric mucin. Roughly half of the patients in each cohort had tubular adenocarcinomas, with at least some gastric mucin. Many intestinal-type adenocarcinomas, by Lauren's criteria [8], have gastric-type mucin.

In our present series, macroscopically elevated and microscopically papillary adenocarcinoma decreased over time. Papillary adenocarcinoma tends to form an elevated or penetrating type. Most papillary adenocarcinomas in our study were of the intermediate phenotype. In 1981, Hirota et al. [12] reported a decline in the rate of elevated type, early gastric cancer in Japan.

H. pylori has been suggested as a risk factor for gastric carcinogenesis. In Japan, the prevalence of *H. pylori* infection in asymptomatic adults is high (70%–80%) [13]. In the present study, *H. pylori* was found in the mucosa surrounding the cancer in 35% of the patients. The infection rate was low compared with that in biopsy specimens or serological tests in reports of chronic gastritis and gastric and duodenal ulcers. *H. pylori* infection, chronic gastritis, atrophy, and intestinal metaplasia have been considered carcinogenic [14]. *H. pylori* may not be persistent when carcinoma develops, as it did not colonize the metaplastic mucosa in our patients, and was seen only on the surface of the foveolar epithelium, in the gastric pits, and on the surface GOS-positive mucin. Intestinal metaplasia in the mucosa surrounding the cancer was seen in about half of the patients in our series. The prevalence of *H. pylori* infection is thought to have decreased as public hygiene has improved with time. The sewage systems in Japan were better equipped after 1955, and electric refrigerators were more readily available after 1960. Patients in both study groups were born before 1936, and the sanitary conditions in which they lived were probably similar. Asaka et al. [13] reported that, in the asymptomatic Japanese

population, the prevalence of anti-*H. pylori* immunoglobulin G antibody was high for people born before 1950. *H. pylori* was thought to be unrelated to the time trends in our two groups.

We observed that intestinal metaplasia of the gastric mucosa surrounding the primary tumors showed a tendency to decrease over time. This may be due to changes in dietary habits, such as the spread of Western-style foods and the diminished intake of traditional Japanese foods, as many epidemiological studies have suggested [15–18]. In advanced gastric cancer, the well-differentiated type decreased over time. In this study, however, tubular adenocarcinoma showed no tendency to decrease. The incidence of tubular adenocarcinoma with gastric-type mucin increased. This suggests that tubular adenocarcinoma with gastric-type mucin becomes a diffuse type as tumors grow to an advanced stage. Shimoda et al. [19] compared the intramucosal and submucosal or deeper components of the same advanced gastric cancer and reported that many diffuse-type gastric cancers had a well-differentiated component in the mucosa. In intramucosal lesions, Ishiguro [20] showed that gastric-type differentiated adenocarcinoma changed into undifferentiated adenocarcinoma. He showed that undifferentiated carcinomas under 10 mm were quite rare, and that foveolar-type adenocarcinoma almost always contained undifferentiated adenocarcinomas.

In conclusion, our results indicate that, for small gastric cancer in Japan, macroscopically elevated-type and microscopically papillary adenocarcinoma have decreased significantly during the past decades. The incidence of tubular adenocarcinoma containing gastric-type mucin increased. In the more recent cohort, the tumors tended to develop in fundic gland mucosa and to have less surrounding intestinal metaplasia. The infection rate of *H. pylori* was not related to this time trend. In this study, the time interval between the birth years of the two cohorts was only 14 years, and the *H. pylori* infection rate is now decreasing in Japan. In the near future, the characteristics of small gastric cancer in Japan will change even more.

References

1. Health and Welfare Statistics Association. Statistical abstracts on health and welfare in Japan 1999 (in Japanese). Tokyo: Health and Welfare Statistics Association; 1999.
2. Tominaga S. Decreasing trend of stomach cancer in Japan. Gann 1987;78:1–10.
3. Nakamura K, Sugano H, Takagi K. Carcinoma of the stomach in incipient phase: its histogenesis and histological appearances. Gann 1968;59:251–8.
4. Tatematsu M, Ichinose M, Miki K, Hasegawa R, Kato T, Ito N. Gastric and intestinal phenotypic expression of human stomach cancers as revealed by pepsinogen immunohistochemistry and mucin histochemistry. Acta Pathol Jpn 1990;40:494–504.
5. Parsonnett J, Friedman G, Vandersteen DP, Chang Y, Vogelman JH, Orentreich N, et al. *Helicobacter pylori* infection and the risk of gastric carcinoma. N Engl J Med 1991;325:1127–31.
6. The EUROGAST Study Group. An international association between *Helicobacter pylori* infection and gastric cancer. Lancet 1993:341:1359–62.
7. Katsuyama T, Ono K, Nakayama J, Kanai M. Recent advances in mucosubstance histochemistry. In: Kawai K, editor. Gastric mucus secreting cells. Amsterdam: Excerpta Medica; 1985. pp. 3–18.
8. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand 1965;64: 31–49.
9. Muñoz N, Correa P, Cuello C, Duque E. Histological types of gastric carcinoma in high and low-risk areas. Int J Cancer 1968;3:809–18.
10. Muñoz N, Asvall J. Time trends of intestinal and diffuse types of gastric cancer in Norway. Int J Cancer 1971;8:144–57.
11. Ishiguro S, Tsuji N, Hiyama T, Kinoshita N, Furukawa H. Changes in pathological observation of gastric carcinoma during 1961–1985. Stomach Intestine 1993;28:59–63.
12. Hirota T, Itabashi M, Unagami M, Kitaoka H, Oguro Y, et al. Chronological trend in morphological features of early stomach cancer. Recent changes especially of macroscopic findings. Stomach Intestine 1981;16:13–26.
13. Asaka M, Kimura T, Kudo M, Takeda H, Mitani S, Miyazaki T, et al. Relationship of *Helicobacter pylori* to serum pepsinogens in an asymptomatic Japanese population. Gastroenterology 1992; 102:760–6.
14. Correa P. Human gastric carcinogenesis: multistep and multifactorial process — First American Cancer Society award lecture on cancer epidemiology and prevention. Cancer Res 1992;52:6735–40.
15. Hirayama T. The epidemiology of cancer of the stomach. Stomach Intestine 1968;3:787–96.
16. Kurita H. Clinico-epidemiological study of stomach cancer considering sex and age differences. Jpn J Cancer Clin 1974;20:580–93.
17. Tajima K, Tominaga S. Dietary habits and gastrointestinal cancers, a comparative case-control study of stomach and large intestinal cancers in Nagoya, Japan. Gann 1985;76:705–16.
18. Kato I, Tominaga S, Ito Y, Kobayashi S, Yoshii Y, Matsuura A, et al. A comparative case-control analysis of stomach cancer and atrophic gastritis. Cancer Res 1990;50:6559–64.
19. Shimoda T, Fujisaki J, Kajimura H, Ikegami M, Ishii T, Matsui T, et al. Histological type of gastric carcinoma in relation to the mode of intramural spreading of cancer cells. Stomach Intestine 1991;26:1125–34.
20. Ishiguro S. Histological significance of foveolar type tubular adenocarcinoma of the stomach. Its histogenesis and relationship to undifferentiated carcinoma. Osaka Med J 1987;39:507–15.