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Original article

Trends in the incidence of gastric cancer in Japan and their associations with *Helicobacter pylori* infection and gastric mucosal atrophy

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Abstract

Background. **Although age-adjusted mortality from gastric cancer has been decreasing in Japan, the crude incidence of gastric cancer shows a slight increase.**

Methods. **We have observed trends in the incidence of gastric cancer by sex and 20-year age groups over the past two decades (1976–1996). Source data were obtained from the cancer statistics materials provided by the Research Group for Population-Based Cancer Registration in Japan. Simultaneously, we observed changes in the prevalence of *Helicobacter pylori* infection and in serological atrophy of the gastric mucosa, and compared the results with those involving changes in the incidence of gastric cancer.**

Results. **A slight decline was observed in all age groups over 40 years old, in both men and women, between 1986 and 1996. However, a marked decline in incidence was observed for those aged 20–39 years. The prevalence of *H. pylori* infection declined in both sexes between 1989 and 1998. The frequency of serological atrophy of the gastric mucosa significantly declined in all age groups between 1989 and 1996, with young age groups experiencing a more marked decrease.**

Conclusion. **The marked decline in gastric cancer incidence observed in the young population will also begin to occur in the elderly population in the future.**

Key words Gastric cancer incidence · *Helicobacter pylori* · Pepsinogen · Gastric mucosal atrophy

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Introduction

Despite a marked decline in the incidence of gastric cancer in many industrialized countries, gastric cancer is still the second most common cause of cancer-related deaths in Japan [1–4]. Based on regional cancer registrations, the incidence of gastric cancer in Japan in 1997 was 99318 (male, 66307 and female, 33011), accounting for 20.7% of the total cancer incidence in the same year [5]. The number of gastric cancer deaths in 1997 was 49739 (male, 32218 and female, 17521) based on vital statistics [6]. Age-adjusted mortality has been decreasing in both men and women, although crude mortality has not changed. Gastric cancer mortality is about half of the incidence, due to improved diagnostic and therapeutic techniques.

It is well known that *Helicobacter pylori* infection is one of the major risk factors for gastric cancer, and that low values of the pepsinogen (PG) I-to-II ratio can be a marker for atrophy of the gastric mucosa, as well as a marker for gastric cancer risk [7–10]. Therefore, the prevalence of *H. pylori* infection and the frequency of gastric mucosal atrophy may influence the incidence of gastric cancer.

In this study, we analyzed trends in the incidence of gastric cancer over the past two decades, by sex and 20-year age groups. At the same time, we observed changes in the prevalence of *H. pylori* infection and in serological atrophy of the gastric mucosa, and compared them with changes in the incidence of gastric cancer.

Methods

Cancer incidence figures in Japan are available from the Research Group for Population-Based Cancer Registration of the Ministry of Health, Labour, and Welfare, Japan, which issues annual cancer statistical data. We analyzed trends in the incidence of gastric cancer from 1976 to 1996. The figures from 1985 to 1989 were acquired from the published data [11] that this research group had reported, and the pre-1984 data were from the group's website. The gastric cancer incidence in four 20-year age groups (20–39, 40–59, 60–79, and 80 and over) from 1975 to 1996 was calculated using these data. Mortalities from gastric cancer in 1986 and 1996 were acquired from published data [6] from the Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour, and Welfare, Japan. To observe trends in gastric cancer incidence and its mortality, the 1996/1986 ratios of incidence and mortality were calculated by dividing the value in 1996 by the one in 1986. In order to compare findings with the results for frequency of serological atrophy of the gastric mucosa, the 1996/1989 ratios of the incidence were also calculated.

For our analysis of the frequency of serological atrophy of the gastric mucosa, subjects were recruited from a workplace in the Kanto-shin-etsu area of Japan; 4486 of the subjects had participated in a health checkup program in 1989, and 4506 had participated in 1996. Serum PG I and serum PG II values were measured using residual sera from the health checkup programs in those 2 years. Measurements were carried out by immunoradiometric assay, with Pepsinogen I/II Riabead kits (Dainabot, Tokyo, Japan). When the serum PG I level was 70 ng/ml or less and the PG I/II ratio was 3.0 or less, it was defined as "serological atrophy" of the gastric mucosa [12].

To determine the prevalence of *H. pylori*, the subjects were selected from workers who belonged to a group of companies in the Tokyo area who were aged 50–59. Six hundred and seventy-six (male, 532; female, 144) of them took part in a general health checkup program in 1989, and 1916 (male, 1580; female, 336) took part in 1998. The sera in 1989 had been frozen for 10 years at −30 °C, and those in 1998 had been frozen for 1 year at −30 °C before the measurements. Serum *H. pylori* antibodies were measured using both the 1989 and 1998 sera. The measurements were carried out by enzyme-linked immunosorbent assay (ELISA) with Pilika-Plate G Helicobacter II, produced by Biomerica (Newport Beach, CA, USA).

All statistical analyses were conducted using a commercial program for statistical analysis obtained from Halwin Gendai-Sugakusha (Kyoto, Japan). Our studies were approved by the Ethics Committee, Aichi Medical University School of Medicine.

Results

Figure 1 shows changes in gastric cancer incidence by sex in the 20-year age groups. A gradual decline in incidence was observed in all age groups, in both men and women, and the steepest decline was in the 20–39 age group. No clear change was observed before 1986, and a clear decline was observed only between 1986 and 1996, the trend of which was linear and statistically significant in each age group.

The 1996/1986 ratios of gastric cancer incidence for the age groups (Fig. 2) showed that the decline in younger age groups was more conspicuous than that in older age groups. The 1996/1989 ratios gave similar results, but the effect of age was not so clear in the age groups over 40 years.

On the other hand, the 1996/1986 ratios of gastric cancer mortality were in men, 0.516 for those aged 20–39; 0.667 for those aged 40–59; 0.759 for those aged 60–79; and 0.923 for those aged 80 or more. Similarly, in women, the ratios were 0.445, 0.689, 0.652, and 0.849, respectively. The 1996/1986 ratios of gastric cancer mortality showed a trend of decline that was more conspicuous in younger age groups than in older ones.

Figure 3 shows the frequency of serological atrophy of the gastric mucosa in 1989 and 1996. During the 7-year period, the frequency of serological atrophy of the gastric mucosa significantly declined in all age groups, with young age groups experiencing a more notable decrease.

Figure 4 shows the seroprevalence of *H. pylori* among those aged 50–59, in 1989 and 1998. The prevalence of *H. pylori* infection declined significantly in both sexes over the 9-year period of this study.

Discussion

Because the incidence of gastric cancer is low in people under 40 years of age, and because analysis by 20-year groups can maintain the stability of data, we examined the trends in mortality and incidence by 20-year age groups. A decrease in gastric cancer incidence was revealed, with those aged 20 to 40 showing the most rapid decrease, in both men and women. The decrease was observed only after 1986. Highly salted food intake, smoking, and drinking are enumerated as three major risk factors for gastric cancer, other than *Helicobacter pylori* infection and gastric mucosal atrophy. However, these three risk factors do not seem to explain the decrease sufficiently, for the following reasons. Firstly, although a change in the whole amount of salt intake does not necessarily correlate with a change in the dietary intake of highly salted foods, it is unlikely that the dietary intake of highly salted foods fell rapidly, because it

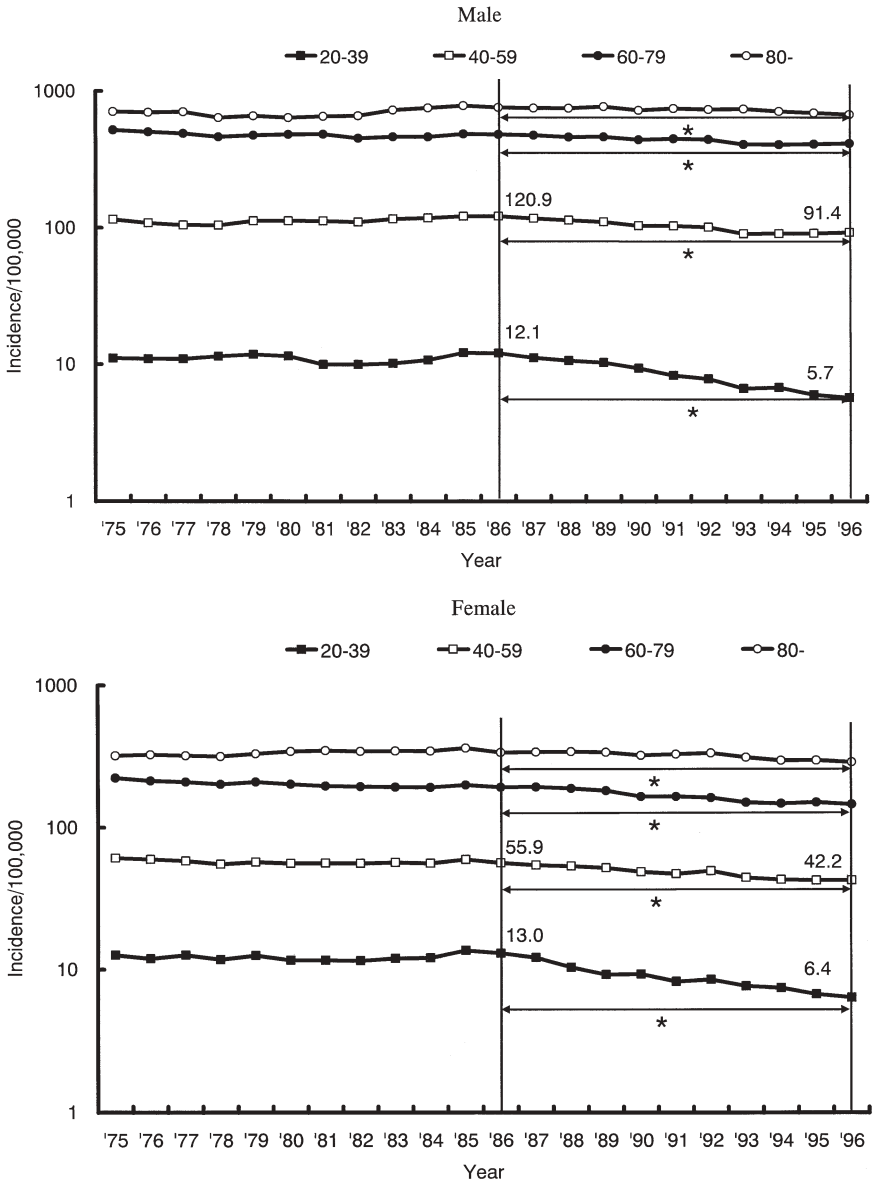

Fig. 1. Changes in gastric cancer incidence according to age are shown. A decline in incidence was observed in all 20-year age groups of both sexes between 1986 and 1996, and the decline in those aged 20–39 years was the steepest. *P*-value for trends, <0.001

has been shown that the amount of salt intake has almost leveled off, according to the National Nutrition Survey in Japan [13]. Secondly, the smoking rate has been decreasing in men and has leveled off in women, but is increasing in young women. The drinking trends have been similar to the smoking trends [14]. Therefore, these three factors do not seem to be major causes of the observed decline in gastric cancer incidence. Thus, among the possible factors contributing to the decrease, two in particular appear to be involved, i.e., changes in the prevalence of *H. pylori* infection, and the diminishing frequency of serological atrophy of the gastric mucosa.

Changes in the prevalence of H. pylori *infection*

Numerous epidemiological and experimental studies using animals have shown that *H. pylori* infection is a causal risk factor for gastric cancer [15,16]. *H. pylori* infection occurs mostly in childhood [17–23] and continues for almost the entire life of the patient. Its overall prevalence is strongly correlated with socioeconomic factors, such as living conditions [24–26], water supply, and sewerage [27,28], which may be especially important in developing countries. In many cross-sectional studies, an increase in the prevalence of *H. pylori* with age has been observed, for which there are two hypotheses: one is that new infections in the aging population increase the gradient of the prevalence; the other is that the gradient is influenced by a cohort effect,

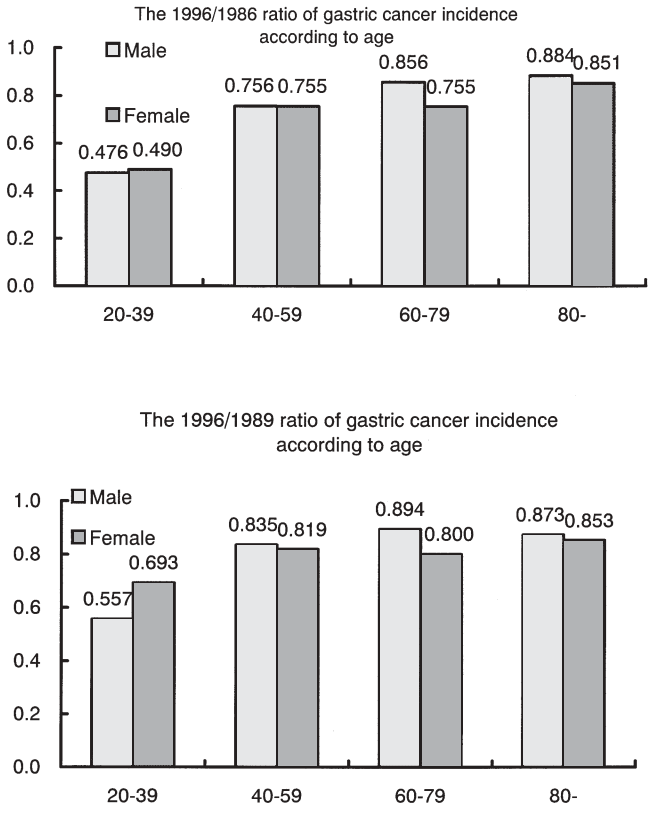

Fig. 2. The 1996/1986 ratios of gastric cancer incidence (over a 10-year period) for each age group showed that the decline was more conspicuous in young age groups than in old age groups. Similar results were observed in the 1996/1989 ratios (over a 7-year period), but the effect of age was not so clear among the age groups aged over 40 years

reflecting more widespread transmission contemporaneous with the childhood years of earlier birth cohorts [19,29,30].

In order to clarify which hypothesis is correct, we compared the prevalence of *H. pylori* between the subjects aged 50–59 years in 1989 and those aged 50–59 years in 1998 in a workers' group and found a decline in seroprevalence over the 9-year period. Although the subjects were only from the Tokyo region, another study with subjects from other areas throughout Japan (Nagano, Niigata, Gunma, Toyama, Shizuoka, Mie, and Miyagi prefectures) has reported the same results [31]. Although these results may not be sufficiently representative of conditions in Japan as a whole, no contradictory results have been found, as far as we can discover, suggesting that the cohort effect of improved hygiene exerts a greater influence on the overall rate of prevalence than new infections with aging [32–34].

Although hygiene conditions in Japan were poor just after World War II, they have gradually improved since about 1950, which seems to support the conclusion mentioned above. If the prevalence of *H. pylori* mainly depends on hygiene conditions in childhood, a decline in *H. pylori* prevalence owing to improved hygiene conditions must occur first in the younger population. These explanations seem to be consistent with the observed decrease in gastric cancer incidence in that young population.

Frequency of serological atrophy of the gastric mucosa

It has been established that people with atrophic gastritis have a high risk for gastric cancer [26,35]. Previous studies have shown that serum PG values were strongly associated with gastric cancer [36]. In people under 40 years of age, the PG II level, as well as the PG I/II ratio, showed a strong association with the risk for gastric cancer [37]. Among those over 40, a strong association was also observed between the gastric cancer risk and serological atrophy of the gastric mucosa [10]. In addition, the relation between atrophic gastritis and gastric cancer has been confirmed by endoscopic studies [38].

Serum PGs are markers for atrophic gastritis and gastric mucosal atrophy. A low serum PG I level and a low PG I/II ratio are related to atrophy of the gastric mucosa, as well as being related to inflammation of the gastric mucosa [39,40]. Therefore, we defined low values for serum PGs (serum PG I level of 70 ng/ml or less and PG I/II ratio of 3.0 or less) as serological atrophy. These low levels are also related to the risk for gastric cancer and are sometimes used in screening programs for gastric cancer [12]. If gastric mucosal atrophy is related to the risk for gastric cancer, a consistent change in the prevalence of gastric mucosal atrophy might be expected in conjunction with the observed decline in the gastric cancer incidence. We observed a change in the frequency of serological atrophy of the gastric mucosa over a 7-year period, and compared it with the change in gastric cancer incidence over the same period.

The frequency of serological atrophy of the gastric mucosa decreased over that 7-year period. The marked decline in frequency of the atrophy cannot be explained without considering the possibility of reversible change in serological atrophy. Indeed, 63% of the subjects experienced an increase or no change in the PG I/II ratio over the 7-year period [39,40], indicating that serological atrophy of the gastric mucosa is reversible.

The decline in young age groups was more conspicuous than that in older groups. Although the subjects did not necessarily represent the Japanese population as a whole, they were, in fact, from relatively wide spread areas: Niigata, Nagano, Gunma, Tochigi, Ibaraki, Saitama, and Tokyo.

So far, many studies have noted the prevalence of gastric mucosal atrophy, but few have examined the

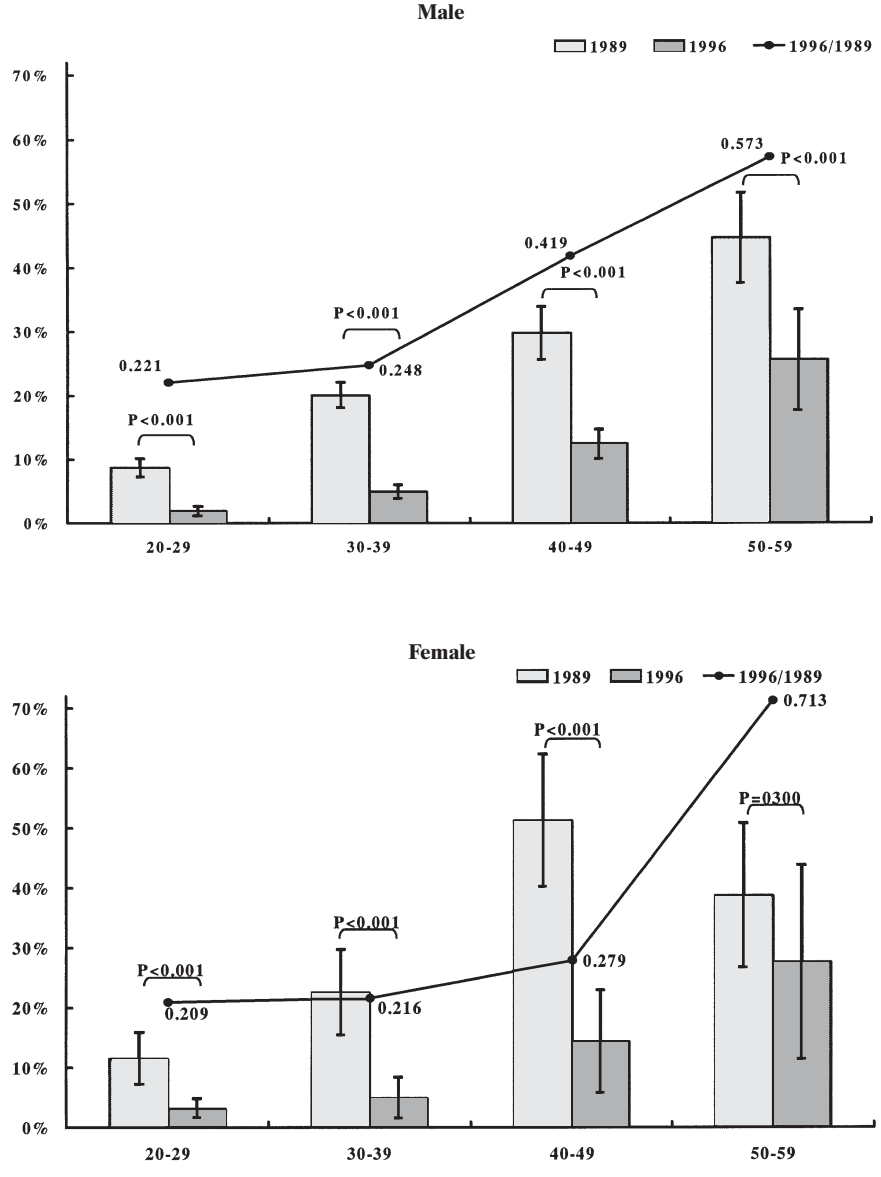

Fig. 3. Frequencies of serological atrophy of the gastric mucosa in 1989 and in 1996. During the 7-year period, the frequency of serological atrophy of the gastric mucosa significantly declined in all age groups, with younger age groups showing a particularly marked decrease

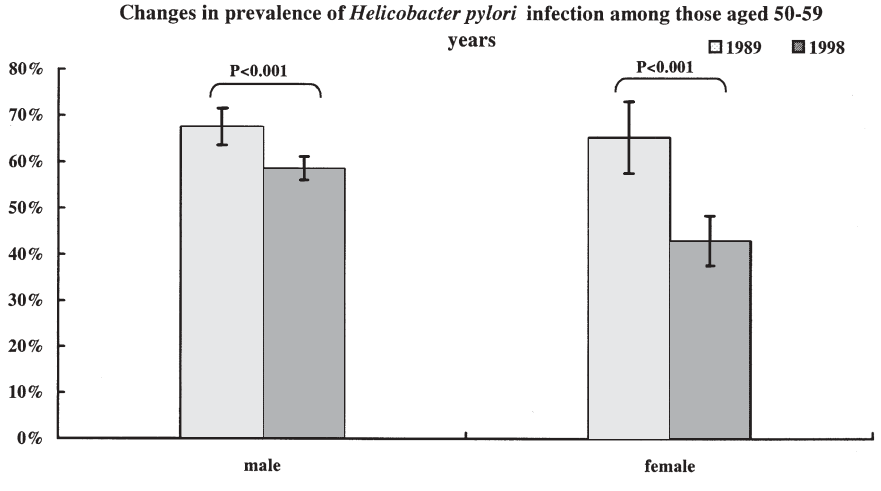

Fig. 4. The prevalence of *Helicobacter pylori* infection declined in both sexes between 1989 and 1998

chronological changes in PG I and II values over a period of several years as our study has. We could find only one study [41] that showed the same trends in serological atrophy as our study did. A large-scale study of Japanese subjects reported that very few cases of atrophy of the gastric mucosa were observed among those without *H. pylori* infection [42], further confirming that a decrease in *H. pylori* prevalence may result in a decrease in gastric mucosal atrophy. Studies reporting a decrease in *H. pylori* prevalence over the years may be considered as indicating a concomitant decrease in gastric mucosal atrophy.

The prevalence of gastric mucosal atrophy seems to have clearly decreased in Japan, along with the prevalence of *H. pylori* infection, with the decrease in the younger population being more conspicuous. Although there may be some limitations to the conclusions discussed above, these findings would seem to explain the decline we observed in gastric cancer incidence. The change in frequency of serological atrophy of the gastric mucosa was more rapid compared with the change in gastric cancer incidence, and this may have occurred because there was a time lag between the beginning of gastric cancer in the atrophic mucosa and the clinical diagnosis of the cancer when it has developed.

Future incidence of gastric cancer

In Japan, there seems to be a decreasing birth cohort effect for *H. pylori* infection, as well as for serological atrophy of the gastric mucosa. The decreasing birth cohort effect is expected to continue in the future. In the observation period of this study, a decline in the incidence of gastric cancer was observed, and it was most marked in those aged 20–39 years. It is expected that the marked decline in the incidence of gastric cancer in the younger population may extend to the older population in the future, as the young population with a low prevalence of *H. pylori* infection gets older.

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