

Randomized controlled trial comparing gastric cancer screening by gastrointestinal X-ray with serology for *Helicobacter pylori* and pepsinogens followed by gastrointestinal endoscopy

Takuji Gotoda · Hideki Ishikawa · Hirohide Ohnishi ·
Kentaro Sugano · Chika Kusano · Chizu Yokoi ·
Yutaka Matsuyama · Fuminori Moriyasu

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Abstract

Background Based on the results of several case–control and cohort studies gastrointestinal X-ray (GI X-ray) has been recommended for use in the nationwide screening program for gastric cancer. Although this was the only effective screening program when almost all of the Japanese population were *Helicobacter pylori* (*H. pylori*) positive, there has been concern whether an alternative effective screening system should be established for the

future *H. pylori*-negative generation. We therefore conducted the first randomized controlled trial (RCT) comparing GI X-ray and gastrointestinal endoscopy (GIE) scheduled according to results of serological testing (ST); this was done to determine the potential for an alternative screening method.

Methods Subjects who fulfilled the inclusion criteria were residents between the ages of 30 and 74 and who were able to receive gastric cancer screening in the Yurihonjo area. Participants were assigned to the GI X-ray group or the GIE-ST group by computer randomization. Subjects in each group were further subdivided into 4 categories according to their different risks for gastric cancer. The feasibility of stratified randomization was serologically assessed and detection rates of gastric cancer at entry by the different screening methods were also compared.

Results Of the 2,962 subjects invited, 1,206 individuals (41 percent) were included in the first stage of this stratified RCT, and 604 and 602 individuals were assigned to the GI X-ray group and the GIE-ST group, respectively. There were no statistically significant differences in sex, age, height, body weight, smoking, alcohol intake and family history of cancer between the 2 groups. During ST the GI X-ray group showed a distribution that was not statistically different from that of the GIE-ST group. Although 3 cases of gastric cancer were detected in the GIE-ST group, there was no statistically significant difference between the 2 groups. One complication found was barium aspiration during the examination in the X-ray group.

Conclusion We confirmed that baseline demographic features of the 2 groups were well balanced. We are now organizing the first RCT to compare the existing screening method and the alternative method (Clinical trial registration number: UMIN000005962).

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T. Gotoda (✉) · C. Kusano · F. Moriyasu
Department of Gastroenterology and Hepatology, Tokyo
Medical University, 6-7-1 Nishishinjuku, Shinjuku-ku,
Tokyo 160-0023, Japan
e-mail: takujigotoda@yahoo.co.jp

H. Ishikawa
Department of Molecular-Targeting Cancer Prevention, Kyoto
Prefectural University of Medicine, Osaka, Japan

H. Ohnishi
Department of Gastroenterology, Akita University Graduate
School of Medicine, Akita, Japan

K. Sugano
Division of Gastroenterology, Department of Internal Medicine,
Jichi Medical University, Shimotsuke, Japan

C. Yokoi
Gastroenterology and Hepatology Division, National Center for
Global Health and Medicine, Tokyo, Japan

Y. Matsuyama
Department of Biostatistics, School of Public Health, Graduate
School of Medicine, The University of Tokyo, Tokyo, Japan

Keywords Gastric cancer · Gastrointestinal X-ray · Serological testing · Gastrointestinal endoscopy · Randomized controlled trial

Abbreviations

GI X-ray Gastrointestinal X-ray
 ST Serological testing
 GIE Gastrointestinal endoscopy
 RCT Randomized controlled trial
H. pylori *Helicobacter pylori*

Introduction

Gastric cancer is the second most common cause of death from cancer worldwide [1], and especially in Eastern Asia countries such as China, Japan and Korea [2]. The need for efficient, cost-effective and practical nationwide mass screening systems for gastric cancer in Eastern Asia remains controversial, although the incidence of gastric cancer remains high [3]. It is well known that early detection and treatment are essential in reducing gastric cancer death rates. In Japan, there were 50,136 deaths from gastric cancer in 2010, which accounts for 14.2 percent of all cancer deaths [4]. Japanese population screening using gastrointestinal X-ray (GI X-ray) with a double-contrast barium meal began in 1964 [5–7]. More than 6 million individuals are currently screened annually in this program.

A meta-analysis of 3 case–control studies showed that screening by GI X-ray results in reduced mortality from gastric cancer [8]. Thus, Japanese guidelines established in 2006 recommended the population undergo gastric cancer screening using GI X-ray [9, 10]. However, these guidelines did not recommend gastrointestinal endoscopy (GIE) as a population screening system instead of GI X-ray since no satisfactory evidence of decreased mortality from gastric cancer upon GIE screening was in the literature.

The pathogenic role of *Helicobacter pylori* (*H. pylori*) in gastric cancer has been reported both in epidemiological and basic research studies [11–13]. Gastric atrophy, corpus-predominant gastritis or intestinal metaplasia caused by long-time *H. pylori* infection were indicated as increased risk factors for gastric cancer [14, 15]. Infection with *H. pylori* plays an important role in gastric cancer development, even in high-risk geographical regions [16]. It is well known that gastritis is more prevalent and severe when there is more corpus-predominant atrophy and intestinal metaplasia, which may partially explain the higher incidence of gastric cancer in Japan [17].

Serum pepsinogen was recently found to be a promising biomarker for predicting the status of the gastric

mucosa [18]. Thus, the use of serum pepsinogen I concentration and pepsinogen I/II ratio for the detection of gastric atrophy was proposed. Consequently, serum pepsinogen may be useful in gastric cancer screening [19]. Recently, the combination of serum pepsinogen concentration and presence of the *H. pylori* antibody has been recommended and used in some cases as a useful marker for gastric cancer screening [20, 21]. Although a change to more efficient and cost-effective population screening methods is necessary, serological risk-testing methods for population screening are still in question because satisfactory evidence showing decreased mortality rates from gastric cancer using these methods has not yet been demonstrated.

We are therefore conducting the first randomized controlled trial (RCT) to study gastric cancer screening by GI X-ray with serology for *H. pylori* and pepsinogens followed by GIE scheduled according to the results of serological testing (ST); GI X-ray is the currently employed intervention in Japan. The first stage of this RCT evaluates the feasibility of stratification of this RCT at the time of recruitment and the detection rate of gastric cancer during the first stage.

Subjects and methods

Subjects and participants of this study

This RCT has been named “gastric cancer screening labeled by serum examination” in place of aged gastric cancer organized screening system (GALAPAGOSS) and is now ongoing in the Yurihonjo area (Yurihonjo city and Nikaho city, Akita prefecture, Japan). Subjects included in the study were 30- to 74-year old residents with access to screening in the Yurihonjo area; they were recruited between June 2011 to March 2013. Candidates were excluded if they had any history of malignant disease, gastrectomy or severe co-morbidities with less than 5 years of life expectancy. Candidates whose informed consent could not be obtained and those whom the doctors considered would have difficulty participating in the study were also excluded. Participants were defined as those who provided written informed consent. All information of the subjects was anonymously processed at the data center.

The study protocol was approved by the ethics review board of the Tokyo Medical University and written informed consent was obtained from each individual according to the Declaration of Helsinki. This trial is registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry, number UMIN000005962.

Study design

Participants of this study were assigned to the GI X-ray group or the GIE-ST group by computer randomization, and thus were screened according to the protocol shown in Fig. 1. Gender and age (30–59 and 60–74 years) were adopted as stratified factors for randomization.

GI X-ray, which is the currently employed intervention for gastric cancer in Japan, was annually scheduled for the subjects assigned to the GI X-ray group. GI X-ray was performed according to the standard methods proposed by the Japanese Society of Gastroenterology Cancer Screening [22] and double checks were performed in a blind manner. For the individuals of this group who showed abnormalities in their GI X-ray results a high definition video GIE was performed by experienced endoscopists with certification from the Japanese Society of Gastrointestinal Endoscopy (JSGE). The video was conducted after a pre-endoscopic drink of 100 ml of water, 2 ml of Gascon (Kissei Pharmaceutical Co., Ltd., Nagano, Japan) and 20,000 units of Pronase (Kaken Pharmaceutical Co., Ltd., Tokyo, Japan) [23] according to the nationwide gastric cancer-screening program. A gastric biopsy was performed if necessary. Serological assessment was also carried out in both groups to assess the validity of the stratified randomization of this study at enrolment.

GIE-ST subjects were subdivided into 4 categories with different risks of gastric cancer, according to the combination of *H. pylori* status and serum pepsinogen concentration. The groups were scheduled for high definition video GIE (GIF-Q260, Olympus, Tokyo, Japan) with 25

images taken as follows (Fig. 1): no screening in A, GIE every 3 years in B, GIE every 2 years in C and annual GIE in D [24]. Biopsies that were taken from any gastric mucosal abnormality were histologically diagnosed. GIE was performed at the first stage in all individuals allocated to the GIE-ST group to confirm the absence of any abnormalities of the stomach; this was done in order to avoid disadvantaging subjects, especially those who were serologically assessed as group A. Furthermore, GIE is planned at the end of this RCT for all subjects, including those allocated to the GI X-ray group, to evaluate any lesions overlooked.

Serological examinations

H. pylori status was evaluated by the detection of a specific *H. pylori* IgG antibody using a commercial enzyme immunoassay kit (E-plate; Eiken Kagaku, Tokyo, Japan). The levels of pepsinogen I (PG I) and pepsinogen II (PG II) were also measured by radioimmunoassay (pepsinogen kit; BML Inc., Akita, Japan). The results were considered indicative of atrophic gastritis when the PG I level was <70 ng/L and the PG I/II ratio was <3.0 (atrophic pepsinogen), as proposed by Miki et al. [25]. All other cases were considered to be non-atrophic [26]. According to the results of the serological examination, subjects were subdivided into 4 groups: Group A: negative for *H. pylori* and non-atrophic pepsinogen; Group B: positive for *H. pylori* and non-atrophic pepsinogen; Group C: positive for *H. pylori* and atrophic pepsinogen; and, Group D: negative for *H. pylori* and atrophic pepsinogen.

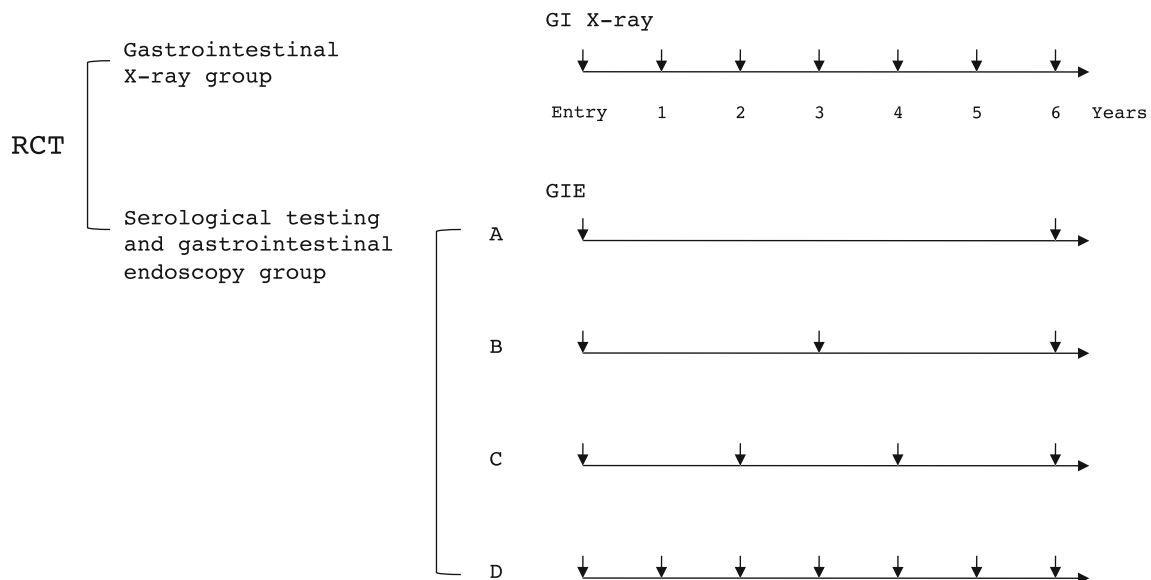


Fig. 1 RCT protocol comparing GI X-ray with GIE scheduled according to the results of serological testing, as a new detection method for gastric cancer

Endpoints

The aim of this RCT is to compare GI X-ray by barium meal, which is the nationwide screening program for gastric cancer, with the new method of screening using GIE scheduled according to the results of ST of *H. pylori* antibody and pepsinogen status. The primary endpoint of this study is to calculate the mean medical fee per examination and the mean medical expense required to detect a single gastric cancer case, enabling assessment of the total medical cost in the GI X-ray group and the GIE-ST group.

This study will assess the detection rate of gastric cancer between GI X-ray and ST with GIE at the first stage, the rate of gastric cancer and tumor stage detected during the observation period, the overlooked rate of gastric cancer and tumor stage by the final GIE at the end of the study, complications during the study and the reduction in the mortality rate from gastric cancer. This assessment will provide a means of comparing the GI X-ray group and the GIE-ST group as the secondary endpoint. This paper evaluated as the first report of the study the feasibility of stratification of this RCT at the time of recruitment and the detection rate of gastric cancer at the first stage.

Sample size and statistical analyses

We calculated the required sample size from the average medical expense of each individual under the Japanese medical insurance system, with a statistical power of 0.8 using an α error of 0.05, and the number of subjects required was determined to be 254 in each group, which we then increased to 1,000 subjects in total in expectation of a significant drop-out rate. Medical fees calculated for this sample size were the following: 4,500 Japanese yen/time/person for the GI X-ray, 11,140 yen/time/person for the GIE, 5,000 yen/time/person for endoscopic biopsy and 2,000 yen/time/person for the *H. pylori* antibody + pepsinogen ST.

Statistical significance of the differences was assessed using the Chi square test. A value of $p < 0.05$ was regarded as indicating a statistically significant difference between groups. All statistical evaluations were performed using SPSS version 20.0 J software (IBM).

Results

Feasibility of stratification

Of the 2,962 subjects enrolled, 1,206 participants were registered in this RCT (Fig. 2) and 604 and 602

participants were assigned to the GI X-ray group and the GIE-ST group by computer randomization, respectively (Table 1).

There were no statistically significant differences in sex, age, height, body weight, smoking, alcohol intake and family history of cancer between the 2 groups. Serologically, the 2 groups also showed no statistically significant differences.

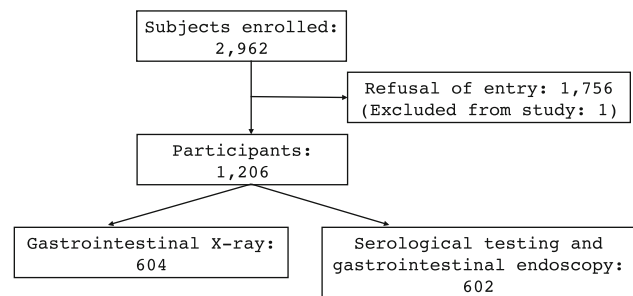


Fig. 2 Trial profile

Table 1 Characteristics of study participants and serological data on the presence of a specific *Helicobacter Pylori* IgG antibody and pepsinogen

	Gastrointestinal X-ray	Gastrointestinal endoscopy scheduled according to the results of serological testing	<i>p</i> value
<i>n</i>	604	602	
Sex			
Male	304	304	0.95
Female	300	298	
Age (mean \pm SD)	61.5 \pm 7.9	61.3 \pm 7.8	0.71
Height (mean \pm SD)	158.9 \pm 8.2	158.6 \pm 8.4	0.49
Body weight (mean \pm SD)	59.6 \pm 10.0	59.3 \pm 10.3	0.64
Smoking			
Non-smoker	520	519	0.95
Smoker	84	83	
Alcohol			
Non-drinker	269	258	0.56
Drinker	335	344	
Family history of cancer			
No	416	393	0.18
Yes	188	209	
Serological testing			
Group A	197 (33.1 %)	198 (32.9 %)	0.97
Group B	147 (24.3 %)	150 (24.9 %)	
Group C	222 (36.8 %)	215 (35.7 %)	
Group D	41 (6.8 %)	39 (6.5 %)	

Refusal reasons

More than half of the eligible individuals refused to register in the study because they did not wish to be tested by GIE (Table 2). The individuals who did not wish to be tested by GIE tended to be younger in age. On the other hand, there was a higher tendency to refuse randomization in the elderly compared with the younger people.

Rate of secondary examination in the GI X-ray group

A total of 100 individuals (16.7 percent) were recommended to undergo secondary examination using a high definition video GIE. The rate of secondary examination is shown according to the serological results in Table 3. Of the 100 individuals, 21 (10.8 percent) were serologically subdivided into Group A.

Detection rate of gastric cancer and complications at entry

The rate of complications and gastric cancer detection rate was not statistically different between the 2 groups (Table 4). Three cases of gastric cancer were detected from Group C of the GIE-ST group, compared to 0 in the GI X-ray group. All

Table 2 Reasons eligible subjects refused to register in the study

Sex	Male		Female		Total (1,755)
	30–59	60–75	30–59	60–75	
Age group (years)	30–59	60–75	30–59	60–75	
<i>n</i>	210	493	328	724	
Dislike of gastrointestinal endoscopy	127	223	219	356	925 (52.7 %)
Dislike of gastrointestinal X-ray using barium meal	4	16	9	27	56 (3.2 %)
Refusal of randomized controlled trial	63	199	69	233	564 (32.1 %)
Long restriction	13	49	24	93	179 (10.2 %)
Others	3	6	7	15	31 (1.8 %)

Table 3 Number of participants chosen for secondary examination using gastrointestinal endoscopy in the gastrointestinal X-ray group

Serological testing	Primary gastrointestinal X-ray	Secondary gastrointestinal endoscopy	%
Group A	194	21	10.8
Group B	147	26	17.7
Group C	222	42	18.9
Group D	41	11	26.8

Table 4 Number of gastric cancers detected and complications encountered upon screening by gastrointestinal X-ray, or upon gastrointestinal endoscopy scheduled according to the results of serological testing

	Gastrointestinal X-ray	Gastrointestinal endoscopy scheduled according to the results of serological testing	p value
<i>n</i>	604	602	
Number of gastric cancers	0	3	0.25
Number of complications	1	0	1.00

gastric cancer cases were treated by endoscopic resection. One complication found was barium aspiration during examination in the GI X-ray group. However, no therapeutic procedures were required for this case.

Discussion

Early detection and treatment is an important way to reduce deaths from gastric cancer. To the best of our knowledge, mass screening for gastric cancer has not been assessed in an RCT and more data should be collected to support the current screening program [27]. Thus, this paper assessed the feasibility of an RCT comparing gastric cancer screening by GI X-ray with serology for *H. pylori* and pepsinogens followed by GIE scheduled according to the results of ST, with the final aim of the study being to assess the cost-effectiveness of the 2 methods. We confirmed that the participants were randomly assigned by the following 2 stratified factors: gender and age (30–59 and 60–74 years). The risk of gastric cancer is generally higher in men; most studies have reported a 1.8–2.0 times higher risk of gastric cancer in men compared with women [28]. Of the 2,962 subjects invited, 1,206 individuals were recruited at the first stage of the study. Furthermore, the GI X-ray group showed a serological distribution equal to the GIE-ST group. Although there was no statistically significant difference in the gastric cancer detection rate between the 2 groups, all 3 gastric cancer cases were detected in the GIE-ST group.

Although comprehensive data are not available, the acceptance rate in this study (41 percent) was much higher compared to the general rate, which is known to be 10–30 percent[29]. Reasons for refusal indicated, consistent with previous data, that GIE is still a feared medical procedure, and thus should be improved for comfort. Although the rate of the population subdivided into serological Group A (around 30 percent) was higher

than recent average rates in urban areas, this is probably because this RCT is being conducted in a rural area of Japan with a large aging population. Furthermore, there were no statistical differences in refusal rate between each of the categories (data not shown). The rate of secondary examination in the GI X-ray group was slightly higher than the average rate reported by the Japanese Society of Gastroenterology Cancer Screening. However, considering the mean age of the subjects in this RCT, the rate may not be so high compared to the number of Japanese citizens in their 60's.

In Japan GI X-ray using a barium meal is the method for mass gastric cancer screening and is available to asymptomatic individuals older than 40; this is the established nationwide program [8]. Upon positive findings in the barium meal examination [30] further investigation with GIE is recommended. However, the actual participation rate among eligible individuals is only around 20 percent [31]. In Japan, an individual pays no more than 30 percent of the total medical fee associated with such an examination; government insurance covers the rest. This means that asymptomatic individuals can readily receive GIE as an opportunistic screening at an outpatient clinic or even at a hospital under the Japanese health insurance system. Consequently, many endoscopic examinations outside the mass-screening program contribute to the high detection rate of early gastric cancers in Japan [32]. A study from Niigata, Japan reported that the detection rate of gastric cancers by GIE is about 2.7 to 4.6 times higher than the detection rate using barium [33].

Whether cost-effective mass screening for gastric cancer should be performed remains controversial, especially in countries with a low or moderate incidence of gastric cancer. A study from Singapore suggested that endoscopy screening every 2 years for a moderate- to high-risk population (e.g., Chinese men aged 50–70 years) was highly cost effective in the health-care system [34]. Therefore, endoscopy screening in targeted high-risk populations might be more cost effective than mass screening in countries with intermediate to low risk of gastric cancer. Cost-effectiveness is affected by the cost of the GIE and the gastric-cancer incidence rate among the screened population [35]. The cost of GIE is therefore the major modifiable factor that affects the ultimate cost-effectiveness of such a screening program.

In Korea the National Cancer Screening Program recommends biennial stomach-cancer screening for men and women older than 40 years of age by GI X-ray and/or GIE. According to the 2005 National Cancer Screening Program report, the expected frequency of gastric-cancer detection is 0.12 percent (i.e., detection of 1,381 gastric cancers in the 1.15 million people screened) [36]. GIE seems to be the

most cost-effective screening method in Korea given the relatively low cost of this technique (about the same as GI X-ray) and the high incidence of gastric cancer. However, considering the decline in the incidence of gastric cancer in the near future in Japan and Korea mass screening for gastric cancer, particularly by only GIE, may not be the most practical approach because of reasons such as acceptance, availability and cost. Multistage screening by serum-PG testing or *H. pylori* serology, or both, might help identify at-risk individuals for further invasive screening.

In multiracial countries, such as Malaysia and Singapore, gastric cancer is more common in the Chinese people than in those of Malay and Indian origin [37]. Therefore, screening of high-risk populations rather than mass population screening might be more cost effective. A study from Singapore reported that the age-standardized rate of gastric cancer is 21.4 per 100,000 per year in Chinese males and 10.8 per 100,000 per year in Chinese females [38]. There is no nationwide population-screening program. A cost-benefit analysis of screening for gastric cancer showed that screening by endoscopy was cost effective in a moderate-to high-risk population (e.g., Chinese men infected with *H. pylori*) [34].

To identify individuals at high risk in countries with moderate to low incidence rate for gastric cancer a stepwise approach starting from demographic factors and *H. pylori* status seems feasible. For the younger Japanese generation the cost-effective screening of epidemiological factors, genetic or hereditary risks and status of *H. pylori* infection might be the method adopted within the next 2 decades. Thus, we conducted the first RCT with feasible stratification comparing the existing screening method and an alternative method that may be useful for the next generation.

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References

- Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin*. 2005;55:74–108.
- Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002. Cancer incidence, mortality and prevalence worldwide. IARC Cancer Base No. 5, version 2.0. Lyon: IARC Press, 2004.
- International Agency for Research on Cancer. GLOBOCAN 2008. <http://globocan.iarc.fr/>.
- National Cancer Center, Center for Cancer Control and Information Services. <http://ganjoho.ncc.go.jp/professional/statistics/index.html>.
- Hisamichi Y, Nishino Y, Hisamichi S. Screening for gastric cancer. *World J Surg*. 1989;13:31–7.
- Tsubono Y, Nishino Y, Hisamichi S. Screening for gastric cancer in Miyagi, Japan: evaluation with a population-based cancer registry. *Asian Pac J Cancer Prev*. 2000;1:57–60.
- Shiratori Y, Nakagawa S, Kikuchi A, Ishii M, Ueno M, Miyashita T, et al. Significance of a gastric mass screening survey. *Am J Gastroenterol*. 1985;80:831–4.
- Tsubono Y, Nishino Y, Hisamichi S. Screening for gastric cancer in Japan. *Gastric Cancer*. 2000;3:9–18.
- Hamashima C, Shibuya D, Yamazaki H, Inoue K, Fukao A, Saito H, et al. The Japanese guideline for gastric cancer screening. *Jpn J Clin Oncol*. 2008;38:259–67.
- Sobue T, Fukao A, Tsuji I, Ohnuki K, Sagawa M, Aoki D, et al. The Japanese Research Group for Development of Cancer Screening Guideline. Japanese guideline for gastric (stomach) cancer screening. (In Japanese). Tokyo: The Japanese Ministry of Health, Labour and Welfare; 2006.
- Personnet J, Friedman GD, Vandersteen DP, Chang Y, Vogelstein JH, Orentreich N, et al. *Helicobacter pylori* infection and the risk of gastric carcinoma. *N Engl J Med*. 1991;325:1127–31.
- Nomura A, Stemmermann GN, Chyou PH, Kato I, Perez-Perez GI, Blaser MJ. *Helicobacter pylori* infection and gastric carcinoma among Japanese American in Hawaii. *N Engl J Med*. 1991;325:1132–6.
- Hirata Y, Maeda S, Mitsuno Y, Takeishi K, Yanai A, Akanuma M, et al. *Helicobacter pylori* CagA protein activates serum response element-driven transcription independently of tyrosine phosphorylation. *Gastroenterology*. 2002;123:1962–71.
- Correa P. Human gastric carcinogenesis: a multistep and multifactorial process—First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res*. 1992;52:6735–40.
- Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, et al. *Helicobacter pylori* infection and the development of gastric cancer. *N Engl J Med*. 2001;345:784–9.
- Huang JQ, Scridhar S, Chen Y, Hung RH. Meta-analysis of the relationship between *elicobacter pylori* seropositivity and gastric cancer. *Gastroenterology*. 1998;114:1169–79.
- Naylor GM, Gotoda T, Dixon M, Shimoda T, Gatta L, Owen R, et al. Why does Japan have a high incidence of gastric cancer? Comparison of gastritis between UK and Japanese patients. *Gut*. 2006;55:1545–52.
- Samloff IM, Varis K, Ihamaki T, Siurala M, Rotter JJ. Relationships among serum pepsinogen I, serum pepsinogen II, and gastric mucosal histology. A study in relatives of patients with pernicious anemia. *Gastroenterology*. 1982;83:204–9.
- Yoshihara M, Hiyama T, Yoshida S, Ito M, Tanaka S, Watanabe Y, et al. Reduction in gastric cancer mortality by screening based on serum pepsinogen concentration: a case-control study. *Scand J Gastroenterol*. 2007;42:760–4.
- Yamaji Y, Mitsushima T, Ikuma H, Okamoto M, Yoshida H, Kawabe T, et al. Inverse background of *Helicobacter pylori* antibody and pepsinogen in reflux oesophagitis compared with gastric cancer: analysis of 5732 Japanese subjects. *Gut*. 2001;49:335–40.
- Watabe H, Mitsushima T, Yamaji Y, Okamoto M, Wada R, Kokubo T, et al. Predicting the development of gastric cancer from combining *Helicobacter pylori* antibodies and serum pepsinogen status: a prospective endoscopic cohort study. *Gut*. 2005;54:764–8.
- Guidelines for standard method of stomach radiography (in Japanese). *J Gastroenterol Mass Surv*. 2002;40:437–447.
- Bhandari P, Green S, Hamanaka H, Nakajima T, Matsuda T, Saito Y, et al. Use of Gascon and Pronase either as apre-endoscopic drink or as targeted endoscopic flushes to improve visibility during gastroscopy: a prospective, randomized, controlled, blinded trial. *Scand J Gastroenterol*. 2010;45:357–61.
- Asaka M, Kato M, Graham DY. Strategy for eliminating gastric cancer in Japan. *Helicobacter*. 2010;15:486–90.
- Miki K, Ichinose M, Kakei N, Yahagi N, Matsushima M, Tsukada S, et al. The clinical application of the serum pepsinogen I and II levels as a mass screening method for gastric cancer. *Adv Exp Med Biol*. 1995;362:139–43.
- Watanabe Y, Kurata JH, Mizuno S, Mukai M, Inokuchi H, Miki K, et al. *Helicobacter pylori* infection and gastric cancer. A nested case-control study in a rural area of Japan. *Dig Dis Sci*. 1997;42:1383–7.
- Leung WK, Wu MS, Kakugawa Y, Kim JJ, Yeoh KG, Goh KL, et al. Screening for gastric cancer in Asia: current evidence and practice. *Lancet Oncol*. 2008;9:279–87.
- Yang L. Incidence and mortality of gastric cancer in China. *World J Gastroenterol*. 2006;12:17–20.
- Wittes RE, Friedman MA. Accrual to clinical trials. *J Natl Cancer Inst*. 1988;80:884–5.
- Kunisaki C, Ishino J, Nakajima S, Motohashi H, Akiyama H, Nomura M, et al. Outcomes of mass screening for gastric carcinoma. *Ann Surg Oncol*. 2006;13:221–8.
- Foundation for Promotion of Cancer Research. Cancer statistics in Japan—2012. Tokyo, Japan.
- Suzuki H, Gotoda T, Sasako M, Saito D. Detection of early gastric cancer: misunderstanding the role of mass screening. *Gastric Cancer*. 2006;9:315–9.
- Tashiro A, Sano M, Kinameri K, Fujita K, Takeuchi Y. Comparing mass screening techniques for gastric cancer in Japan. *World J Gastroenterol*. 2006;12:4874–5.
- Dan YY, So JB, Yeoh KG. Endoscopic screening for gastric cancer. *Clin Gastroenterol Hepatol*. 2006;4:709–16.
- Riecken B, Pfeiffer R, Ma JL, Jin ML, Li JY, Liu WD, et al. No impact of repeated endoscopic screening on gastric cancer mortality in a prospectively followed Chinese population at high risk. *Prev Med*. 2002;34:22–8.
- Choi JJ. Screening and surveillance of gastric cancer. *Korean J Gastroenterol*. 2007;49(suppl):15–22.
- Goh KL, Cheah PL, Md N, Quek KF, Parasakthi N. Ethnicity and *H. pylori* as risk factors for gastric cancer in Malaysia: a prospective case control study. *Am J Gastroenterol*. 2007;102:40–5.
- National Registry of Diseases Office. Singapore Cancer Registry Interim Report. Trends in cancer incidence in Singapore 2001–2005. http://www.hpb.gov.sg/nrdo/files/Cancer%20reports/Cancer%20interim%20report%20v3%2001-05_for%20web.pdf. Accessed 5 Feb 2008.