

The Japanese Guidelines for Gastric Cancer Screening

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Background: Gastric cancer is the leading cause of death from cancer in Japan. In 2004, there were 50 562 deaths from gastric cancer; they accounted for 15.8% of the total number of cancer deaths. Since 1983, under the Health Service Law for the Aged, gastric cancer screening has been conducted nationwide for all residents aged 40 years and over.

Methods: On the basis of the standardized method developed for the Japanese Guidelines for Cancer Screening, the efficacies of various methods for gastric cancer screening were evaluated and the guideline was developed.

Results: Four methods for gastric cancer screening were evaluated: photofluorography, endoscopy, serum pepsinogen testing and *Helicobacter pylori* antibody testing. On the basis of the analytic framework involving key questions, 1715 articles, published from January 1985 to February 2005, were selected using MEDLINE, the Japanese Medical Research Database and other methods. After the systematic literature review, 10 articles were identified as direct evidence and 49 articles as indirect evidence. The studies that evaluated mortality reduction from gastric cancer included five case–control and two cohort studies for radiographic screening. On the basis of the balance of benefits and harms, the recommendations for population-based and opportunistic screening were formulated. Gastric cancer screening using photofluorography was recommended for both screening programs. The other methods were not recommended for population-based screening due to insufficient evidence.

Conclusions: The guideline for gastric cancer screening guideline was developed based on the previously established method. Gastric cancer screening using photofluorography is recommended for population-based and opportunistic screening in Japan.

Key words: gastric cancer – cancer screening – guideline – recommendation – photofluorography

INTRODUCTION

Gastric cancer is the leading cause of death from cancer in Japan. However, between 1980 and 2003, the age-adjusted mortality has decreased from 69.9 to 34.5 per 100 000 in males and from 34.1 to 13.2 per 100 000 in females (1). There were 50 562 deaths from gastric cancer in 2004; they accounted for 15.8% of all cancer deaths (2). Gastric cancer is the third cause of death from cancer in males and the second cause of death from cancer in females. Around 1960, gastric cancer screening using photofluorography was started

in Miyagi prefecture, and this approach has been adopted nationwide. In 1983, under the Health Service Law for the Aged, gastric cancer screening was introduced for all residents aged 40 years and over. In 2004, 4.4 million inhabitants participated in gastric cancer screening; the screening rate has been around 13% (3).

In Japan, the research group for cancer screening recommended six cancer screening programs in 2001 (4). Photofluorography was recommended for gastric cancer screening based on the results of several case–control and cohort studies. Although photofluorography screening has been mandated in population-based screening as public policy, other methods including endoscopy, serum pepsinogen testing and *Helicobacter pylori* antibody testing have been used mainly in the clinical setting for opportunistic

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screening. However, based on previous reports, the efficacy of these methods remains unclear.

A new research group established a standardized method for developing the Japanese Guidelines for Cancer Screening (5). On the basis of this methodology, we evaluated the efficacy of various methods for gastric cancer screening and developed the new guidelines.

METHODS

The target audience for the gastric cancer screening guideline includes the public, health professionals working in cancer screening programs, providers of cancer screening programs and policy makers. The gastric cancer screening guideline was developed using the standardized methods (4). The members of the guideline development group for gastric cancer screening (Panel) were selected from various specialties, including gastroenterologists, endoscopists, epidemiologists and researchers involved in public health and the gastric cancer screening program. A systematic literature review was conducted by the members of the review committees for gastric cancer screening, including the Panel members. The recommendations were assessed in conjunction with the board members of the Japanese Research Group for Cancer Screening Guidelines.

ANALYTIC FRAMEWORK

The target population for gastric cancer screening was defined to be asymptomatic people with an average risk of gastric cancer. Four methods were evaluated: photofluorography, endoscopy, serum pepsinogen testing and *H. pylori* antibody testing. To select appropriate evidence, an analytic framework for gastric cancer screening was developed (Fig. 1). For each stage of the analytic framework, key questions based on the PICO (population, intervention, comparison and outcome) format were prepared. Direct evidence was defined as evidence provided by a study that evaluated the efficacy of cancer screening in reducing gastric cancer mortality (Fig. 1, arrow 1). Other studies that provided indirect evidences were selected based on the key questions related to other stages of the analytic framework (Fig. 1, arrows 2–9). *Helicobacter pylori* antibody screening is not intended to detect gastric cancer directly, but it is done to identify a high-risk group. It is possible to prevent gastric cancer by eradication of *H. pylori*. Thus, another route was prepared to evaluate the efficacy of *H. pylori* antibody screening (Fig. 1, arrows 10–12).

SYSTEMATIC LITERATURE REVIEW

A search of literature published from January 1985 to February 2005 was performed using MEDLINE, CINHAI and the Japanese Medical Research Database (Igaku-Cyuo-Zasshi). Key journals were searched

manually, including the *Journal of Gastroenterological Cancer Screening* and the *Journal of the Japanese Association for Cancer Detection and Diagnosis*. In addition, the reference lists of the NCI-PDQ (6) and the previous report (4) dealing with the evaluation of gastric cancer screening were checked, and appropriate articles were included. To select appropriate evidence, a systematic review of the retrieved articles was conducted using the standardized method (5).

TRANSLATION INTO RECOMMENDATIONS

The body of evidences for each screening method was summarized in an evidence table based on the analytic framework's key questions. The benefit of each screening modality was determined based on the level of evidence (5). The evidence is divided into eight levels based on study design and quality. The harms, including the false-negative rate, the false-positive rate and the burden of screening, were compared among the methods. Considering the balance of the benefits and harms, five grades of recommendations were determined for population-based and opportunistic screening (5).

FORMULATING THE GUIDELINE

After the consultations were completed, three types of guidelines were published and posted on two websites: Promoting Evidence-based Cancer Screening (<http://canscreen.ncc.go.jp/>) and the Research Center for Cancer Prevention and Screening, National Cancer Center (<http://ganjoho.ncc.go.jp/pro/index.html>).

RESULTS

SYSTEMATIC LITERATURE REVIEW

On the basis of the literature search using MEDLINE and other databases, 1715 articles published from January 1985 to February 2005 were identified. The abstracts were reviewed, and 149 articles were selected for full text review. After the full text review, 10 articles were identified as providing direct evidence and 49 articles were identified as providing indirect evidence. To facilitate judging the evidence provided by the selected articles, an evidence table for each stage of the analytic framework was created for the screening methods. The numbers of articles selected as providing evidence for each screening method is shown in Table 1.

LEVEL OF EVIDENCE

PHOTOFLUOROGRAPHY (LEVEL OF EVIDENCE: 2++)

No RCT dealing with the use of photofluorography in gastric cancer screening has been published. Five case-control

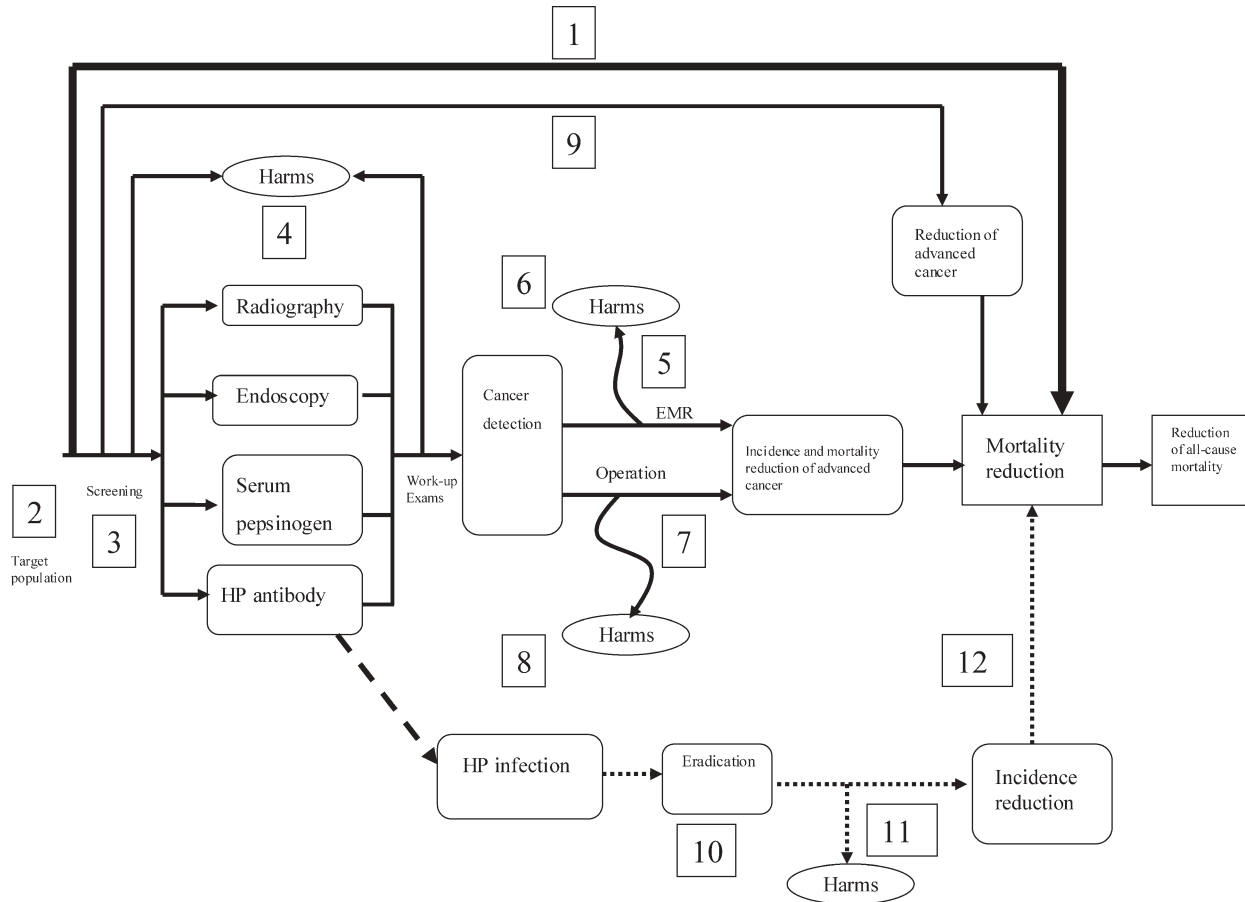


Figure 1. Analytic framework and key question. HP, *Helicobacter pylori*.

studies and two cohort studies dealing with photofluorography were identified (Table 2) (7–13). Although as observational studies these studies had limitations, the main potential confounders were identified and taken into account during the evaluation of most the studies. Therefore, these studies were graded as providing a 2++ level of evidence. One of the case–control studies was conducted in

Venezuela, and the others were conducted in Japan. Most of the case–control studies suggested a 40–60% decrease in gastric cancer mortality with photofluorography screening. Tsubono et al. performed a meta-analysis of three case–control studies conducted in Japan. Their results showed that gastric cancer screening using photofluorography resulted in a mortality reduction from gastric cancer (male OR: 0.47,

Table 1. Evidence for gastric cancer screening

Methods	Level of evidence	Direct evidence (AF)		Indirect evidence (AF2-12)					
		All Effective (significant)	Others	All Target AF2	Accuracy AF3	Harms AF4	Survival rate AF7.8	HP eradication AF10.11.12	Target age/Interval others
Gastroglurography	2++	8 7	1 (effective—not significant)	24 0	8	9	4	0	3
Gastroendoscopy	2–	1 0	1 (low quality)	4 0	3	2 ^a	0	0	0
Serum pepsinogen	2–	1 0	1 (low quality)	13 0	7	9 ^b	0	0	0
<i>Helicobacter pylori</i> antibody	2–	0 0	0	6 1 ^c	1	0	0	4	0

^aOne article provides evidence of test accuracy.

^bThree articles provide evidence of test accuracy.

^cOne article provides evidence of test accuracy for serum pepsinogen and *Helicobacter pylori* antibody.

HP, *Helicobacter pylori*.

Table 2. Observational studies dealing with gastric cancer screening

Author	Year reported	Study design	Study population	Age (year)	No of subjects	Follow-up	Results
Oshima et al.	1986	Case-control	Osaka, Japan	40 +	Males: 54 cases/156 controls Females: 37 cases/105 controls	—	Odds ratio (95% CI) Males: 0.595 (0.338–1.045) ^a Females: 0.382 (0.185–0.785) ^a
Pisani et al.	1994	Case-control	Tachira, Venezuela	35 +	All: 241 cases/2410 controls	—	Odds ratio (95% CI) Males: 1.52 (0.94–2.47) Females: 0.77 (0.33–1.91)
				35 +	All: 85 cases/375 controls	—	Odds ratio (95% CI) All: 0.47 (0.24–0.98) ^b All: 0.25 (0.12–0.51) ^c
Fukao et al.	1995	Case-control	Miyagi, Japan	50 +	Males: 126 cases/364 controls Females: 72 cases/213 controls	—	Odds ratio (95% CI) Males: 0.32 (0.19–0.53) Females: 0.63 (0.34–1.16)
Abe et al.	1995	Case-control	Chiba, Japan	30–89	Males: 527 cases/1552 controls Females: 293 cases/861 controls	—	Odds ratio (99% CI) Males: 0.371 (0.242–0.568) ^d Females: 0.458 (0.263–0.797) ^d
Tsubono et al.	1999	Case-control	Miyagi, Japan	40–64	All: 27 cases/270 controls	—	Odds ratio (95% CI) All: 0.20 (0.04–0.96) ^e
Inaba et al.	1999	Cohort	Gifu, Japan	35 +	Screened: male 4934, female 4208 Unscreened: male 6536, female 8456	40 months	Relative risk (95% CI) Males: 0.72 (0.31–1.66) Females: 1.46 (0.4–4.90)
Mizoue et al.	2003	Cohort	Japan Collaborative Cohort Study	40–79	Screened: male 12 999, female 17 772 Unscreened: male 23 156; female 33 385	8 years	Relative risk (95% CI) Males: 0.54 (0.41–0.70) Females: 0.74 (0.51–1.07)
Tsubono et al.	1999	Meta-analysis (3 Japanese CCS)	Osaka, Miyagi Chiba	—	Males: 706 cases/2072 controls Females: 402 cases/1179 controls	1 year	Odds ratio (95% CI) Males: 0.39 (0.29–0.52) Females: 0.50 (0.34–0.71)

^a90% confidence interval.^bExcluded cases within one month before diagnosis.^cExcluded cases within six months before diagnosis.^d99% confidence interval.^eObservation period was limited within 1 year.

95% CI: 0.29–0.52; female OR: 0.50, 95% CI: 0.34–0.72) (10). One of the cohort studies lacked power and did not show a significant difference for the relative risk of mortality (12). The other cohort study showed a significantly decreased mortality in males (RR: 0.54, 95% CI: 0.41–0.70); the reduction in mortality was not significant in females (RR: 0.74, 95% CI: 0.52–1.04) (13). However, in this study, there was selection bias, since both all-causes and gastric cancer mortalities were reduced.

Sensitivity was estimated based mainly on the data obtained from the cancer registry (Table 3) (14–28). The sensitivity of photofluorography ranged from 60% to 80%, whereas the specificity ranged from 80% to 90%. The survival rate of the screened group was compared with that of a

non-screened group in whom cancer was detected in the clinical setting. The 5-year survival rate was 74–80% for the screened group and 46–56% for the non-screened group (29–32).

ENDOSCOPY (LEVEL OF EVIDENCE: 2 –)

Although no published studies have evaluated the efficacy of endoscopic screening in terms of mortality reduction in Japan, one cohort study was conducted in an area with a high incidence of gastric cancer in Linqu County, China (33). From 1989 to 1999, endoscopic screening was conducted for 4394 residents. Both the incidence and mortality of gastric cancer were monitored until 2000. In this period,

Table 3. Test accuracy of photofluorography for gastric cancer screening

Author	Reported year	Follow-up strategy	Follow-up period (year)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)
Murakami et al.	1989	Cancer registry	1	88.5	92.0	1.40
Sugahara N et al.	1991	Cancer registry	1	70.4	90.1	1.60
Fukao A et al.	1992	Cancer registry	1	69.3	88.8	2.00
Ishida T et al.	1994	Cancer registry	1	84.1	81.3	0.78
Ishida T et al.	1994	Cancer registry	2	70.1	81.3	0.90
Hattori M et al.	1998	Cancer registry	1	68.6–72.5	?	?
Abe S et al	2000	Cancer registry	1	56.8	90.7	2.00

85 gastric cancers were detected, of which 29 cases were early cancers. However, compared with the overall mortality for Linq County, the standard mortality ratio was 1.01 (95% CI: 0.32–1.37).

Only two studies related to the use of endoscopy as a diagnostic test reported the accuracy of endoscopy (34,35). In the first study, the sensitivity of endoscopy was found to be 77.8% based on 3-year follow-up using the cancer registry system in Fukui prefecture (34). However, the target population of this study was patients who had symptoms. In addition, the specificity was not reported. In another study based on a follow-up survey of individual participants, Otsuji et al. (35) reported that the sensitivity of endoscopy was 84.0%. No studies that have compared the survival of patients with gastric cancer between screened and non-screened group.

Adverse effects related to endoscopy are reported every 5 years by the Japanese Association of Gastroenterological Endoscopy (36). However, these results are not separately reported and classified by the purpose of endoscopy (screening, diagnostic test and treatment). The details of the adverse effects associated with endoscopic screening are unclear.

SERUM PEPSINOGEN TEST (LEVEL OF EVIDENCE: 2 –)

A one-arm cohort study was conducted in a small distinct of Tokyo (37). On the basis of death certificates, three gastric cancer deaths were identified. Compared with gastric cancer deaths nationwide, the relative risk for the screening group was 0.34 (95% CI: 0.07–0.98). However, there are several limitations to this study related to target selection, lack of an appropriate comparator within the same population, lack of previous screening history and the short follow-up period. These issues were not discussed in the published paper.

Several studies reported the sensitivity of serum pepsinogen testing compared with the results of endoscopy done at the same time (38–45). The sensitivity of the serum pepsinogen test ranged from 40% to 80%, but the specificity was below 80%. Several studies reported that, compared with the results of endoscopy, the sensitivity of the serum pepsinogen test was higher than that of radiography. When the accuracy of a new method is compared with that of

photofluorography, it is important to recognize that gastric cancer screening using radiography is popular in Japan, and that most participants have been previously screened by radiography. Although the detection rate of radiographic screening is low because it is being used as an incidence screen, it was the first time that most participants had been screened using serum pepsinogen testing; thus, the serum pepsinogen screen was a prevalence screen. The sojourn time of the serum pepsinogen testing, which is diagnostic test for atrophic gastritis, is probably longer than that of radiography. If one wishes to compare the two methods, they must be analysed under the same conditions.

HELICOBACTER PYLORI ANTIBODY (LEVEL OF EVIDENCE: 2 –)

A high-risk group of patients could be identified using a combination of the *H. pylori* antibody and serum pepsinogen tests. Watabe et al. (46) followed 9293 participants who were screened using both *H. pylori* antibody and serum pepsinogen tests for 4.7 years. Compared with gastric cancer cases detected in the group that had a negative serum pepsinogen test and a negative *H. pylori* antibody ($n = 3324$), the hazard ratios were higher in the following groups: the positive serum pepsinogen test and negative *H. pylori* antibody group ($n = 2134$), 1.1 (95% CI 0.4–3.4); the normal serum pepsinogen test and positive *H. pylori* antibody group ($n = 1082$), 6.0 (95% CI 2.4–14.5) and the positive serum pepsinogen test and positive *H. pylori* antibody ($n = 443$), 8.2 (95% CI 3.2–21.5). Yamanoi et al. (43) reported that the sensitivity of *H. pylori* antibody testing was 87.1% and the specificity was 40.8%.

An RCT dealing with the prevention of gastric cancer using *H. pylori* eradication therapy was reported from China (47). The incidence of gastric cancer was similar between participants receiving *H. pylori* eradication therapy and those receiving placebo over a 7.5-year period (hazard ratio 1.10, 95% CI 1.05–1.15).

RECOMMENDATIONS

On the basis of the balance of benefits and harms, recommendations were formulated for population-based and opportunistic screening. Benefits were defined as evidence that mortality from a specific cancer was reduced by a cancer screening

program. As well, the harms of various methods were compared (Table 4) (15–28,34–36,38–45,48–57).

Gastric cancer screening using photofluorography was a grade B recommendation for population-based and opportunistic screening (Table 5). The other methods were not recommended as population-based screening due to insufficient evidence. In opportunistic screening, if individuals request screening they should be given appropriate information, and decision-making should be made at the individual level.

DISCUSSION

A guideline for gastric cancer screening was developed using a standardized method. The details of the guideline development

method have been provided elsewhere, and the differences in the guideline development method have also been described elsewhere. Although the efficacy of gastric cancer screening has been evaluated in previous reports without providing recommendations (4), in our guideline, recommendations have been clearly defined based on the evidences. In the previous guideline, photofluorography was recommended for population-based gastric cancer screening. However, *H. pylori* antibody screening was not recommended, and the evidence for serum pepsinogen testing was insufficient to be able to make a recommendation either for or against its use. In addition, endoscopic screening was not targeted for evaluation.

Over the years, there have been four reports that have made suggestions about gastric cancer screening. In 1990, the UICC report concluded that screening programs should continue in regions with a high incidence of gastric cancer

Table 4. Harms of gastric cancer screening

Harms	Radiography	Gastroendoscopy	Serum pepsinogen	<i>Helicobacter pylori</i> antibody
False negative rate	20–30%	16%	16–50%	17.9%
	>10%	No report	20–30%	59.2%
	No	No	No (may be affected by nutrition)	No
False positive rate	No	Anticoagulant	Affected by use of proton pump inhibitor	No
Nutrition restriction	Photofluorography: No	Pharynx anesthetic sedation	No	No
Adverse effects of premedication	Direct radiography: possible (antispasmodic agent) shock, blood pressure failure, respiratory failure	Antispasmodic agent shock, hypotension, respiratory failure	—	—
Adverse effects of premedication (Death)	Possible	0.0001% (14/12,844,551)*	—	—
Adverse effects of screening test	False swallowing of barium meal constipation ileus	Bleeding, perforation, etc.	—	—
Frequency of adverse effects	False swallowing of barium meal 0.08–0.17%	0.012% (997/826,313)	No	No
	Defecation delay: 4–11%			
Adverse effects of screening test	False swallowing of barium meal constipation ileus	Bleeding, perforation, etc.	—	—
Death due to adverse effect	Cases reported	0.00076% (63/826,313)	—	—
Infection	No	Possible	No	No
Radiation exposure (effective dose)	Direct radiography	No	No	No
	Males: 4.9 mSv			
	Females: 3.7 mSv			
	Photofluorography			
	Males: 0.6 mSv			
	Females: 0.6 mSv			
Others	—	—	May be affected by stomach resection, renal failure and HP eradication	Antibiotic resistance, diarrhoea, soft stool

*Included in colonoscopy and laparoscopy.

Table 5. Recommendation for gastric cancer screening

Screening methods	Recommendation grade	Recommendations (language)	
		Population-based screening	Opportunistic screening
Gastrogastrography	B	Recommend	Recommend
Gastroendoscopy	I	Not recommend ^a	Decision making at individual ^b
Serum pepsinogen	I	Not recommend ^a	Decision making at individual ^b
<i>Helicobacter pylori</i> antibody	I	Not recommend ^a	Decision making at individual ^b

^aThere is insufficient evidence to recommend.

^bIf required, the health professional should explain that the evidence regarding mortality reduction by cancer screening is unclear. In addition, information about the harms is required. In such situations, the decision regarding cancer screening should be made on the individual level.

where they were already under way, but that gastric cancer screening could not be recommended as public health policy in other countries (58). The NCI-PDQ concluded that there was insufficient evidence to suggest that gastric cancer screening, including endoscopy, reduced mortality from gastric cancer (6). The European Code against Cancer (3rd edition) stated that there were no evidences to support gastric cancer screening using radiography, endoscopy or *H. pylori* antibody testing (59). The Medical Screening Association stated that the efficacy of radiographic screening was uncertain (60). The evaluations of endoscopy and *H. pylori* antibody testing reached the same conclusion that we reached. It is possible that serum pepsinogen testing may be effective due to its high test accuracy, as reported by Kitahara et al. (42). In all of the previous reports, no methods were recommended for gastric cancer screening.

The requirements of cancer screening programs differ among countries due to differences in cancer incidence and mortality. In Japan, although the incidence and mortality of gastric cancer have decreased in the last decade, gastric cancer screening is a major issue because the incidence and mortality remain high (1). The screening rate for gastric cancer has flattened, and the effectiveness of gastric cancer screening has been limited. However, endoscopic screening is expected to be an alternative strategy to radiography. No studies have evaluated whether endoscopic screening reduces gastric cancer mortality. Although most people consider that endoscopy has a high detection rate, its sensitivity compared with that of radiography is unclear. To prevent premature death from gastric cancer, evidence-based screening should be promoted. To achieve this aim, it is necessary to determine the mortality reduction that is associated with endoscopic screening. An RCT would be the most preferred strategy, but it would be difficult for gastric cancer screening to be conducted in Japan due to widespread of the screening

programs nationwide. A case-control or cohort studies may be expected as alternative methods for evaluating mortality reduction by endoscopic screening.

After the publication of our guidelines, two cohort studies dealing with radiographic screening were reported (61,62). The results of these studies with respect to the mortality reduction of photofluorography screening are similar. Therefore, we did not need to change our recommendations. In addition, Yoshihara et al. (63) reported the results of a case-control study of serum pepsinogen testing. In this study, although mortality reduction by serum pepsinogen testing was suggested, there were several serious issues that could affect the interpretation of the result. More than half of the cases were over 70 years of age (mean age 71.9 years, ranged up to 92 years). Since the reference date was not clearly defined, the history of exposure to serum pepsinogen testing was not reliable. Therefore, it is difficult to judge the efficacy of serum pepsinogen screening based on this low-quality study. However, both serum pepsinogen testing and *H. pylori* antibody testing are expected to be used to identify individuals at high risk of gastric cancer. A recent study by You et al. (64) reported that *H. pylori* eradication reduced the prevalence of precancerous gastric lesions. Gastric cancer prevention may become possible if the efficacy of *H. pylori* eradication were to be proven. Furthermore, a new screening method involving endoscopy may be expected in the near future. Therefore, we are planning to revise the guideline within 5 years, given that new evidence may become available.

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Conflict of interest statement

None declared.

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Appendix:

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