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Update version of the Japanese Guidelines for Gastric Cancer Screening

Chisato Hamashima*, on behalf of the Systematic Review Group and Guideline Development Group for Gastric Cancer Screening Guidelines

Division of Cancer Screening Assessment and Management, Center for Public Health Science, National Cancer Center, Tokyo, Japan

*For reprints and all correspondence: Chisato Hamashima, Division of Cancer Screening Assessment and Management, Center for Public Health Science, National Cancer Center, 5-1-1 Tsukiji Chuo-ku, Tokyo 104-0045, Japan. E-mail: chamashi@ncc.go.jp

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Abstract

Background: Although the incidence and mortality of gastric cancer have gradually decreased, its burden remains in East Asian countries. Gastric cancer screening has been performed in Japan since 1983, and the introduction of new screening techniques has been eagerly anticipated.
Objective: To promote evidence-based screening, the Japanese guidelines for gastric cancer screening have been revised based on the new studies.
Methods: The guidelines for gastric cancer screening have been developed according to a previously established method. To assess evidence regarding the effectiveness of the screening methods, a systematic review was conducted based on an analytic framework including clinical questions aiming at reducing mortality from gastric cancer. The following methods were assessed for gastric cancer screening: upper gastrointestinal series (radiographic screening), gastrointestinal endoscopy (endoscopic screening), *Helicobacter pylori* antibody test and serum pepsinogen tests. Based on the balance of the benefits and harms of each screening method, recommendations for population-based and opportunistic screenings were formulated.
Findings: After the Japanese guidelines for gastric cancer screening were published in 2005, several observational studies on radiographic and endoscopic screenings have been reported. Three case–control studies have evaluated mortality reduction from gastric cancer by endoscopic screening. Notably, evidence of the *H. pylori* antibody and serum pepsinogen tests was insufficient. Although false-positive results, false-negative results, and complications were observed in endoscopic and radiographic screenings, the complication rates were higher in endoscopic screening than in radiographic screening. Overdiagnosis was not estimated directly in both methods.
Recommendations: Radiographic and endoscopic screenings for gastric cancer are recommended for population-based and opportunistic screenings. The *H. pylori* antibody and serum pepsinogen tests are not recommended for population-based screening because of insufficient evidence.

Key words: gastric cancer, cancer screening, upper gastrointestinal series, gastrointestinal endoscopy, *Helicobacter pylori* antibody, serum pepsinogen test, systematic review, guideline

Introduction

Gastric cancer is the second leading cause of death worldwide. About half of the incidence of stomach cancer has been reported in East Asian countries, with the mortality higher than that in other countries (1). In Japan, the reported mortality rates from gastric cancer adjusted according to the world population are 15.4 for men and 5.8 for women (2). Although the incidence of and mortality from gastric cancer have gradually decreased over the years, its burden has remained in East Asian countries. However, in these countries, only Korea and Japan have a national program for gastric cancer screening (3). Thus, gastric cancer screening has played a significant role in reducing mortality from gastric cancer in both countries (4,5).

In Japan, gastric cancer screening was conducted in local areas around the 1960s, and since 1983, it has expanded nationwide in accordance with the Health Law for the Aged (6). The previous guidelines for gastric cancer screening (Japanese version) were published in 2005, and there were referred to in the establishment of a national program (6). Although the upper gastrointestinal series with barium meal (i.e., radiographic screening) has been performed as the main method for population-based screening, endoscopic examinations have increased in the clinical settings over the last decade and have been adopted as opportunistic screening. In Korea, endoscopic and radiographic screenings have been introduced since 2000 (4). However, in the previous guidelines, it was only radiographic screening that was recommended based on the results of observational studies mainly conducted in Japan (5). Evidence for endoscopic screening was limited to only one study from China whose results were insufficient to suggest mortality reduction from gastric cancer by endoscopic screening (7). Following the publication of these guidelines, primary studies to evaluate the effectiveness of endoscopic screening for gastric cancer have increased.

In the Basic Plan for Cancer Control, the targeted participation rate was 40% (8). However, the participation rate in radiographic screening has seen a decrease to about 10% (9). Therefore, some municipalities have introduced endoscopic screening despite insufficient evidence from the previous guidelines (10,11). As an alternative method for gastric cancer screening, a combined method of the *Helicobacter pylori* antibody and serum pepsinogen tests has been eagerly anticipated (12).

The Japanese guidelines for cancer screening have been developed based on the standardized method since 2003 (6). On the base of the results of new studies that were reported after the publication of the previous guidelines, the effectiveness of new techniques for gastric cancer screening, particularly endoscopic screening, was assessed from the perspective of benefits and harms, and then the guidelines were revised.

Methods

The gastric cancer screening guidelines were revised using the standardized method which was defined as the development method for the Japanese guidelines for cancer screening (13). The target audiences of the gastric cancer screening guidelines included citizens, health professionals working in cancer screening programs, providers of cancer screening programs and policy makers. The guideline development group collaborated with the systematic review group and then developed the guidelines based on their results (14). The members of both groups were selected from various specialties, which included primary care physicians, gastroenterologists, surgeons, endoscopists, epidemiologists and economists. Specialists for systematic review and guideline development were also included. All members of the systematic review and guideline development groups have declared that they have no conflicts of interest associated with the guidelines for gastric cancer screening.

Target screening methods

The upper gastrointestinal series with barium meal (radiographic screening), gastrointestinal endoscopy (endoscopic screening), *H. pylori* antibody test, and serum pepsinogen test were assessed in terms of their effectiveness for gastric cancer screening. Although Korea has provided endoscopic screening for gastric cancer to date, there was insufficient evidence when they first introduced it. In Japan, gastrointestinal endoscopy has been used as a standard examination for gastric diseases and is often used as opportunistic screening. Recently, a combined method of the *H. pylori* antibody and serum pepsinogen test has been rapidly disseminated over the last decade, and the introduction of this combined method as population-based screening has been greatly anticipated (12). Therefore, the primary topic in the updated version is assessment of the effectiveness of endoscopic screening. The secondary topic is the assessment of the effectiveness of cancer screening using the *H. pylori* antibody and serum pepsinogen tests.

Analytic framework

The target population for gastric cancer screening was defined as asymptomatic people with an average risk of gastric cancer. To select appropriate evidence, an analytic framework for gastric cancer screening was developed (Fig. 1). For each stage of the analytic framework, clinical questions (CQs) based on the PICO (population, intervention, comparator and outcome) format were developed. Direct evidence was defined as evidence provided by a study that evaluated the effectiveness of gastric cancer screening for reducing gastric cancer incidence and mortality (Fig. 1, CQ 1). The test accuracy of each screening method was assessed in Fig. 1, CQ 2. Information on harms was obtained in Fig. 1, CQ 3. As the assessment focused on the effectiveness on new screening techniques in the updated version, evaluation studies of diagnostic examinations and treatments were excluded (Fig. 1, CQ 4–7).

Systematic literature review

Members of the systematic review group individually conducted a systematic review according to the CQs on the analytic framework. PubMed, Cochrane Central, Web of Science, and Igaku-Cyuo zasshi were searched from January 2000 to September 2013 (Fig. 2). The searches were limited to English-language or Japanese-language publications. For CQ1 studies, search terms such as 'gastric cancer', 'cancer screening' 'upper gastrointestinal series', 'gastrointestinal endoscopy', '*Helicobacter pylori* antibody', 'serum pepsinogen test' and 'mortality reduction' were used. The keywords 'sensitivity' and 'specificity' were added for CQ2 studies. Articles related to CQ3 studies, which included overdiagnosis, false-positive cases, and complications of radiographic and endoscopic screenings, were also identified using the same search engines. As information on complications was limited, a literature search of related studies conducted in Japan was performed until the end of 2014. Additional references recommended by experts were identified and included as needed.

The inclusion criterion for article selection was basically original articles published after peer review (13). For the updated version, we collected articles with information on primary studies that evaluated mortality reduction from gastric cancer by screening. Although

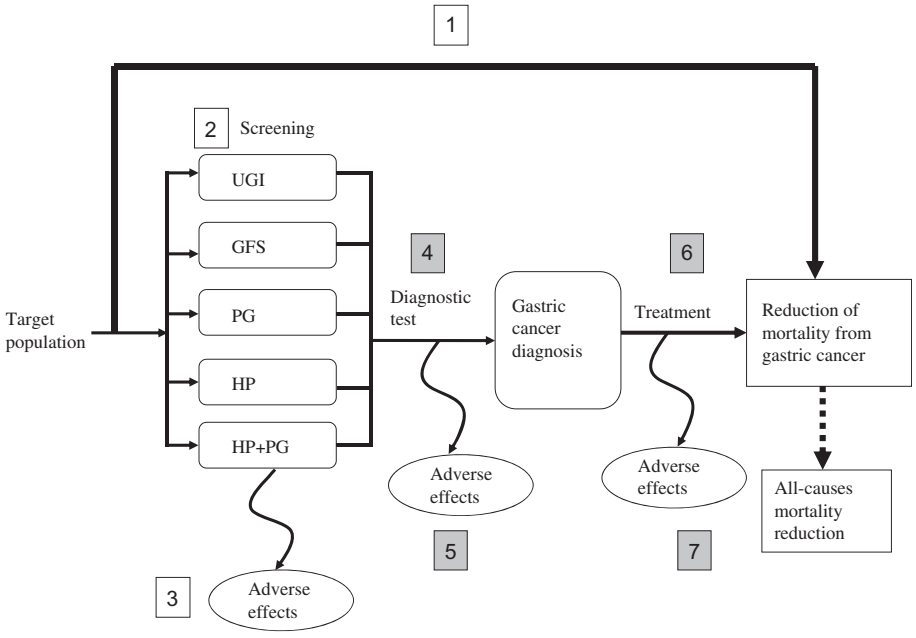

Figure 1. Analytic framework and key questions for gastric cancer screening. The numbers in the analytic framework refer to the following clinical questions. CQ 1. Compared with no screening (or other screening strategies), is there direct evidence that the mortality from gastric cancer is reduced with the following screening methods? (a) Upper gastrointestinal series (UGI), (b) gastrointestinal endoscopy (GFS), (c) serum pepsinogen test (PG) *Helicobacter pylori* antibody (HP), (d) *Helicobacter pylori* antibody (HP), (e) A combined method of *Helicobacter pylori* antibody and serum pepsinogen test (HP + PG). CQ 2. Can the screening test accurately detect gastric cancer? What are the sensitivity and specificity of the screening test? CQ 3. What are the potential harms of the screening tests, and how often do they occur? CQ 4. Can the diagnostic test accurately diagnose gastric cancers? CQ 5. What are the potential harms of the diagnostic examination, and how often do they occur? CQ 6. For gastric cancer patients, how are the efficacy and effectiveness of the treatment? CQ 7. What are the potential harms of gastric cancers treatment, and how often do they occur?.

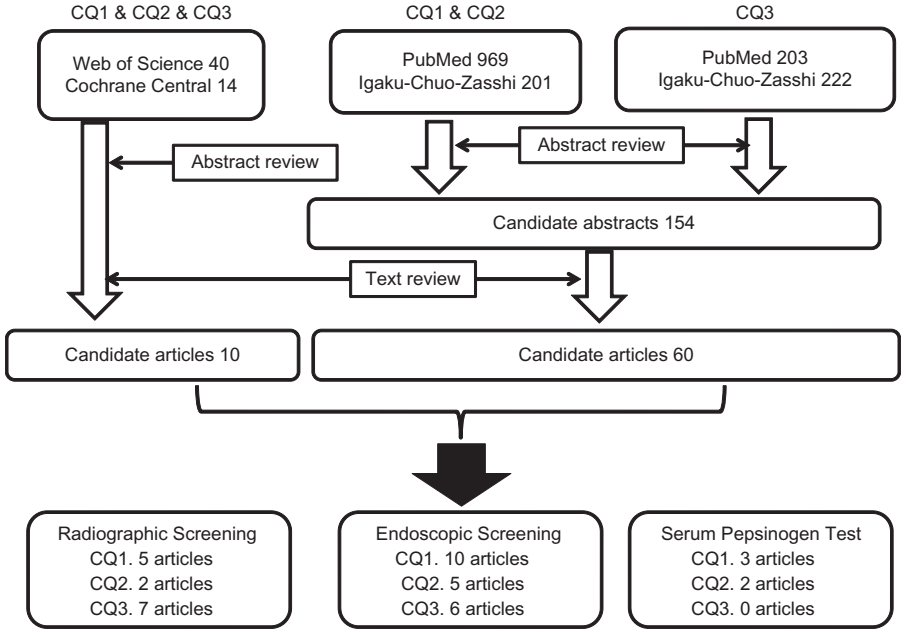

Figure 2. Flowchart of literature search. Members of the systematic review group individually conducted a systematic review according to the clinical questions (CQs) on the analytic framework. PubMed, Cochrane Central, Web of Science and Igaku-Cyuo zasshi were searched from January 2000 to September 2013.

such articles are so-called 'Gray Papers', they were included in the updated version because primary studies related to gastric cancer screening were limited. If the article was not published in a peer-reviewed journal, additional information was directly collected from the authors. If the article was published in a peer-reviewed journal, it was reassessed based on the results.

The study design and outcome were defined differently according to the CQs. The common exclusion criteria among all the screening methods were as follows: (1) no abstract, (2) the target screening group is composed of symptomatic persons (patients), (3) guidelines, evidence reports, or reviews, (4) official statistics, letters and personal communications, and (5) articles which cited in the previous Japanese guidelines for gastric cancer screening. Modeling studies including economic evaluation were excluded for assessment of the studies.

To select appropriate evidence for our clinical questions, a two-stage review process was performed: the title and abstract were initially checked and then potential papers were subsequently reviewed (13). To select appropriate evidence, a systematic review of the retrieved articles was conducted using the standard checklist according to the study design, and the quality of the studies was defined. If the decision regarding the review of full papers was inconsistent, the appropriateness of these studies was carefully discussed. Finally, adequate studies were selected for evaluation of gastric cancer screening.

Evidence for each screening method was summarized in an evidence table based on the CQs. The body of evidence for each screening modality was determined according to the level of evidence, which was defined on the basis of the study design, quality and consistency among study results (13). Finally, the level of evidence for studies evaluating mortality reduction from gastric cancer was decided according to the criteria defined in the guideline development method (13).

Net benefit assessment

To compare the benefits and harms of each screening method, the number needed to screen (NNS) and number needed for recall (NNR) were calculated on the basis of studies for radiographic and endoscopic screenings. NNS refers to the necessary number needed to avoid one gastric cancer death, which suggests the magnitude of mortality reduction as benefits of gastric cancer screening (15). Risk difference was the calculated margin of risk reduction of gastric cancer death in 10 years by gastric cancer screening. The 10 years risk of gastric cancer screening was referred from the cancer statistics of the National Cancer Center in Japan (16), and the magnitude of mortality reduction was referred from the results of a case–control study by Hamashima et al. (17). The magnitude of mortality reduction of radiographic screening was referred from other studies (18,19). Although there are various harms, false positive results are one of the serious harms which increase unnecessary diagnostic examinations and complications. The recall rate for diagnostic examination is a surrogate outcome of a false positive result. Thus, NNR indicates the necessary number needed to avoid one gastric cancer death, which suggests the magnitude of harms (15). Recall rate was referred from annual reports: academic society reports for radiographic screening (20) and annual reports of the Niigata Medical Association (21). The results were compared between radiographic and endoscopic screenings.

Translation into recommendations

Considering the balance of benefits and harms of each screening method, five grades of recommendations were determined for population-based and opportunistic screenings (13). As these grades are supported by sufficient evidence and the benefits outweigh the harms, both Grades A and B recommendations could be conducted as population-based and opportunistic screening programs. However, a screening method with a Grade D recommendation should not be used for either a population-based screening program or an opportunistic screening program because the harms outweigh the benefits. A technique which has no evidence of reducing mortality from the targeted cancer is also included in a Grade D recommendation. A Grade C recommendation implies that the screening method should not be used for population-based screening. Even if there are benefits, a Grade C recommendation is given when the benefits and harms are nearly equal. However, a Grade C recommendation implies that the screening method could be used in clinical settings if both adequate risk management and informed consent with respect to the harms are assured. Screening methods that have insufficient evidence related to mortality reduction from gastric cancer are graded as I. Such methods are not recommended for population-based screening or as routine screening methods in clinical settings. However, the decision to undergo screening could be made at the individual level based on proper information provided by health professionals in clinical settings.

Formulating the screening guidelines

A draft of the screening guidelines has been written and uploaded on the 'Promoting Evidence-based Cancer Screening' website (http://canscreen.ncc.go.jp/). To improve and confirm the guidelines, comments from the public were collected. In addition, major issues identified during the review of the draft were discussed at a guidelines forum open to the public (13). Taking into account the comments received from external reviewers and the guidelines forum, the appropriateness of the recommendation and its language were re-discussed, and the guidelines were refined. After completing the consultations, the guidelines were approved by the National Cancer Center and published on the 'Promoting Evidence-based Cancer Screening' website (http://canscreen.ncc.go.jp/) (6).

Findings

Evidence of the effectiveness of gastric cancer screening methods

From the literature search using PubMed and Igaku-cyuo-zasshi, 1170 articles for CQ1 and CQ2, and 425 articles for CQ3 were identified (Fig. 2). After a two-stage review, 154 articles were selected and then narrowed to 60 articles. By searching the Web of Science and Cochrane Central database, 10 articles were selected. The final number of articles assessed for each screening method were as follows: 14 articles for radiographic screening, 21 articles for endoscopic screening and five articles for the serum pepsinogen test. Evidence of reduction of mortality from gastric cancer could not be found for the *H. pylori* antibody test and the combination method of the *H. pylori* antibody and serum pepsinogen tests.

Body of evidence of gastric cancer screening (CQ1 and CQ2)

Radiographic screening (level of evidence: 2+)

In the previous guidelines, four case–control studies and two cohort studies were cited for mortality reduction from gastric cancer by radiographic screening (5). After the publication the previous guidelines, three cohort studies (Table 1) and two case–control studies (Table 2) were reported (17,22–26). Although case–control studies mainly evaluated the effectiveness of endoscopic screening, the effectiveness of radiographic screening was found to be limited

Table 1. Results of cohort studies for radiographic screening

Authors	Lee KJ	Miyamoto A	Rosero-Bixby L
Publication year	2006	2006	2007
Country	Japan	Japan	Costa Rica
Number of screening group	26 961	24 014	6206
Age of screening group	49.2 ± 5.9 (mean)	Men 52.33 women 53.2 (mean)	64.3 (mean)
Number of no screening group	15 189	17 380	Control 1 20 030 Control 2 11 190 Control 3 11 915 Control 4 11 318
Age of no screening group	50.2 ± 5.8 (mean)	Men 50.33 women 50.4 (mean)	Control 1 57.9 Control 2 64.3 Control 3 58 Control 4 64.6
Follow-up periods	13.1 years (average)	11 years	2–7 years
Relative risk (screened vs not screened)/95% CI			
Gastric cancer incidence	1.06 (0.90–1.25)[a]	0.94 (0.79–1.13)[b]	–
Gastric cancer mortality	0.52 (0.36–0.74)[a]	0.54 (0.38–0.77)[b]	0.42–0.52
All-causes mortality[c]	0.71 (0.65–0.78)[a]	0.83 (0.77–0.90)[b]	–

[a]Adjusted for age at baseline, sex, study area, smoking status, alcohol consumption, educational level, intake of salty food, rice, miso soup, green-yellow vegetables, green tea and family history of gastric cancer.

[b]Adjusted for age in years; family history of gastric cancer, cigarette smoking, alcohol drinking, BMI, the type of health insurance, walk, educational background other screenings (tuberculosis or lung cancer screening, cardiovascular disease screening), consumption frequencies of green tea, coffee, tsukemono, dried fish and salted fish, beef, spinach, carrot, orange, other fruits and milk.

[c]Excluding gastric cancer.

Table 2. Results of case–control studies for radiographic screening and endoscopic screening

Authors	Hamashima C	Matsumoto S	Jun JK
Publication year	2013	2014	2017
Country	Japan	Japan	South Korea
Number of case subjects	410	13	44 095
Age of case subjects	40–79 (range)	72 ± 10 (median)	≥40
Number of control subjects	2292	130	176 380
Age of control subjects	40–79 (range)	69 ± 10 (median)	≥40
Reference	Never screened	Never screened	Never screened
Odds ratio (95% CI)			
Radiographic screening	0.865 (0.631–1.185)[a]	–	0.98 (0.95–1.01)[b]
Endoscopic screening	0.695 (0.489–0.986)[a]	0.206 (0.044–0.965)[b]	0.53 (0.51–0.56)[b]

[a]Screening history within 3 years after the diagnosis date of case subjects.

[b]Screening history within 5 years after the diagnosis date of case subjects.

(17,25,26). These results were inconsistent with the results showing a big impact of radiographic screening from the previous studies.

The results of cohort studies suggested mortality reduction by radiographic screening, which was consistent with the evidence of radiographic screening in the previous version. Although a 40% mortality reduction from gastric cancer was suggested in these studies (22–24), careful interpretation is needed. The Japanese studies were analyzed based on large cohort studies which mainly focused on the association of risk factors for non-communicable diseases including cancers (22,23). However, these were not an incidence-mortality cohort studies and there were no screening opportunities that confirmed the absence of gastric cancer in the study participants during the recruitments. Participation in gastric cancer screening was identified by conducting a questionnaire survey and then dividing the participants into the radiographic screening group and the no screening group. As UGI was a standard method for diagnosing gastric diseases during the first survey in these cohort studies, there was a huge possibility of including symptomatic people in the screening group. In addition, participation in gastric cancer screening was not considered during the follow-up period and depended on individual decision. As positive results were obtained from Japanese studies, mortality reduction might be overestimated.

The sensitivity and specificity of radiographic and endoscopic screenings have been reported in Korea and Japan (27,28). In a study conducted in Korea, the sensitivity of radiographic screening was found to be 38.2% (95% CI: 35.9–40.5) for the first round of screening and 27.3% (95% CI: 22.6–32.0) for the subsequent round (27). In a study conducted in Japan, the sensitivity of endoscopic screening was reported to be 0.893 (95% CI: 0.718–0.977) for prevalence screening (first round) and 0.885 (95% CI: 0.664–0.972) for incidence screening (subsequent round) (Table 3) (28).

Endoscopic screening (level of evidence: 2+)

Although one cohort study was cited as evidence of endoscopic screening in the previous version, six observational studies were published from 2007 to 2012 (29–34). Five articles were cohort studies and the comparators were participants in radiographic screening or no participants in gastric cancer screening. The results of a study conducted in Niigata study were analyzed using an incorrect method, thus the results were subsequently reassessed (34,35). Although these studies attempted to evaluate mortality reduction from gastric cancer, they have serious flaws for adaptation as evidence for endoscopic screening as follows: (1) the sample size and follow-up periods were insufficient; (2) the subjects were not clearly

Table 3. Sensitivity of endoscopic and radiographic screenings for gastric cancer

Screening round	Method	Sensitivity by detection method	Specificity by detection method	Sensitivity by incidence method
Prevalence screening	Endoscopic screening	0.955 (0.875–0.991)	0.851 (0.843–0.859)	0.886 (0.698–0.976)
	Radiographic screening	0.893 (0.718–0.977)	0.856 (0.846–0.865)	0.831 (0.586–0.964)
Incidence screening	Endoscopic screening	0.977 (0.919–0.997)	0.888 (0.883–0.892)	0.954 (0.842–0.994)
	Radiographic screening	0.885 (0.664–0.972)	0.891 (0.885–0.896)	0.855 (0.637–0.970)

(Hamashima et al. Int J Cancer 2013).

limited to asymptomatic patients, and symptomatic people may have been included; (3) there is a possibility that the comparator included symptomatic patients and (4) the radiographic screening history before the start of observation was not considered.

Since 2012, three case–control studies have been published in Korea and Japan (17,25,26,36). Although selection bias was a serious problem, the results were more reliable than the previously reported results. Although one case–control study conducted in Nagasaki prefecture had a small sample size (36), the studies conducted in Niigata and Tottori prefectures had a sufficient sample size for evaluating mortality reduction from gastric cancer by endoscopic screening. Individuals who had at least one history of endoscopic screening within 36 months had the possibility of reducing mortality from gastric cancer by 30% (OR ratio = 0.695, 95%CI: 0.489–0.986) (17). However, a significant reduction in mortality from gastric cancer could not be achieved by individuals who had a radiographic screening history.

When we developed the updated Japanese version of gastric cancer screening, the Korean study we referred to was only described in a Korean report and was not a peer-reviewed article (25). Therefore, additional information was collected from the authors and used in the discussion when the Japanese version was developed. Similar results were obtained in an article published in 2017 and then confirmed as evidence of reduction in mortality from gastric cancer by endoscopic screening. Based on the national database, a nested case–control study from Korea reported a 47% mortality reduction from gastric cancer by endoscopic screening (26). In particular, mortality reduction from gastric cancer by endoscopic screening was observed in the 40- to 74-year age group when participating in endoscopic screening within 1–4 years and over before the date of gastric cancer diagnosis (26).

Although five studies were found to calculate the test accuracy of endoscopic screening (27,28,37–39), the follow-up after obtaining negative results was insufficient in most of the studies. In a study conducted in Korea, the sensitivity of endoscopic screening using the detection method was 69.4% (95% CI: 66.4–72.4) for the first round of screening and 66.9% (95% CI: 59.8–74.0) for the subsequent round (27). In a study performed in Japan, the sensitivity was 0.955 (95% CI: 0.875–0.991) for prevalence screening (first round) and 0.977 (95% CI: 0.919–0.997) for incidence screening (subsequent round) (Table 3) (28).

Serum pepsinogen test (level of evidence: 2−)

In the previous guidelines of gastric cancer screening, one cohort study was cited for reduction in mortality from gastric cancer using the serum pepsinogen test (5). After the publication of the previous guidelines, two case series studies and one case–control study were reported in Japan (40–42). Although these studies suggested positive results, they had serious flaws as follows. First, the sample size and follow-up periods were insufficient. Second, the subjects were not clearly limited to asymptomatic patients. In a previous case–control study, individuals aged 80 years and older were included in the subjects (42). There was a possibility of including symptomatic patients. Third, there was a possibility of including prevalence cases because the diagnosis dates of gastric cancer were unclear in the case-series studies. Finally, radiographic screening history before the start of observation was not considered. Although the results were consistent overall, there is high potential for overestimating the magnitude of mortality reduction from gastric cancer.

Two studies have reported the sensitivity of the serum pepsinogen test referred to the results of UGI at the same time (43,44). Yanaoka reported that the sensitivity of the serum pepsinogen test was 58.7% (95% CI: 45.6–70.8) and its specificity was 73.4% (95% CI: 72.1–74.6) when the cut-off value was defined as PG $I \leq 70$ and PG I/II ≤ 3.0 (44).

***Helicobacter pylori* antibody (level of evidence: 2−)**

There was no study that evaluated reduction in mortality from gastric cancer using the *H. pylori* antibody test.

Combined method of *H. pylori* antibody and serum pepsinogen tests (level of evidence: 2−)

There was no study that evaluated mortality reduction from gastric cancer using the combined method of *H. pylori* antibody and serum pepsinogen tests.

Harms of gastric cancer screening (CQ 3)

The major harms of radiographic and endoscopic screenings are complications, false-positive cases and overdiagnosis (5). The original harms of radiographic screening are radiation exposure and infection from endoscopic screening. Although overdiagnosis in radiographic screening is unclear, other harms have been reported in the previous guidelines. There were no studies related to harms for *H. pylori* antibody and serum pepsinogen tests. Thus, harms were compared between radiographic screening and endoscopic screening.

False-positive and false-negative cases

The false-positive rate is calculated as 1-specificity and the false-negative rate is calculated as 1-senstivity. Based on a Japanese study (Table 3) (28), the false-negative rate in the first round was 10.7% for radiographic screening and 4.5% for endoscopic screening. The false-negative rate in the subsequent round was lower in endoscopic screening than in radiographic screening (2.3% vs 11.5%).

However, the false-positive rates were similar in endoscopic and radiographic screenings. The false-positive rate in the first round was 14.4% for radiographic screening and 14.9% for endoscopic screening. In the subsequent round, the false-positive rate was 10.9% for radiographic screening and 11.2% for endoscopic screening.

Overdiagnosis

When the observed number (O) detected by endoscopic screening was compared with the expected number (E), O/E was around twice in men and women (45). O included cases of overdiagnosis, but all excess number were not equivalent to overdiagnosis. The sensitivities of radiographic screening and endoscopic screenings were calculated using the detection and incidence methods (28). The sensitivities calculated using the detection method were always higher than those calculated using the incidence method in both screenings. The gap between the results calculated using both methods may indicate a proportion of overdiagnosis. The gaps of sensitivity calculated using different methods were small in both screening methods.

Complications

Several studies have reported the complication rates of radiographic screening (46–52). Recently, the incidence of barium meal aspiration has increased with the increase use of high-density barium meal for radiographic screening (46,50–52). Intestinal obstruction was reported as a severe complication of radiographic screening (47). Complications of endoscopic screening were reported in population-based screening and opportunistic screening (34,48,53–55). On the other hand, the main complication of endoscopic screening was nasal bleeding by nasal endoscopy.

The Japanese Association of Gastroenterological Cancer Screening previously compared the complication rates between radiographic screening and endoscopic screening (Table 4) (48). The overall complication rates were 42.8/100 000 for radiographic screening and 87.4/100 000 for endoscopic screening. There was one case of death caused of these by a complication for radiographic screening. Although endoscopic screening was not yet commonly used during the survey period, complication rates were also reported for endoscopic examination. The Japanese Gastrointestinal Endoscopic Association conducts a survey of the complication rates of endoscopic examination every 5 years; however, their results are combined examinations of symptomatic and asymptomatic people (54). In their survey, the complication rate was low at 5.02/100 000, but death cases were reported. In a survey conducted by the Japanese Gastrointestinal Endoscopy Society, cases of death caused by sedation for endoscopic examination have been reported. The different results were based on the definitions of complication and the different subjects of the survey. Therefore, careful interpretation of these results is needed.

Balance of benefits and harms of radiographic and endoscopic screenings

NNS and NNR were calculated for radiographic screening (Table 5) and endoscopic screening (Table 6). To avoid one gastric cancer death, a lower required number of screening participants is preferable. In both screenings, the NNS and NNR were decreased according to age. A huge gap was observed between individuals who were in their 40s and 50s. These results suggest that radiographic and endoscopic screenings could provide higher benefits for women aged 50 years and over. When the magnitudes of mortality reduction from other studies were adapted, similar trends were observed among the different age groups.

Table 4. Complications of radiographic screening and endoscopic screening

Academic association	Japanese Society of Gastrointestinal Cancer Screening	Japanese Gastrointestinal Endoscopy Society
Publication year of reports	2013	2010
Survey year	2010	2003–2007
Radiographic screening		
Total number	3 130 477	–
Number of complications	1340	–
Complication rate (/100 000)	42.8	–
Number of death cases by complications	1	–
Death rate by complications (/100 000)	0.03	–
Endoscopic examination		
Total number	244 899	7 408 688
Number of complications	214	372
Complication rate (/100 000)	87.4	5.02
Number of death cases by complications	0	14
Death rate by complications (/100 000)	0	0.19

Discussion

In the Japanese guidelines of gastric cancer screening, the effectiveness of radiographic and endoscopic screenings was confirmed. Radiographic screening has been the main method for gastric cancer screening in Japan. Photofluorography was developed in Japan and has been used since the 1960s (6). However, the participation rate in gastric cancer screening has gradually decreased to about 10% (9). In the clinical setting, endoscopic examination has already been established as a standard method for examining gastric diseases. Therefore, endoscopic examination has already been introduced as opportunistic screening and population-based screening in several municipalities. However, to the best of our knowledge, there has been no studies evaluating mortality reduction by endoscopic screening in Japan before the publication of the previous guidelines. There was one study from China in the previous guidelines, but the results of the study did not suggest mortality reduction from gastric cancer by endoscopic screening (5,7). In the updated version of the guidelines, endoscopic screening was recommended based on the results of case–control studies in Korea and Japan (17,25,26,36). Although one Korean study was not published in a peer-reviewed journal when the Japanese version of the guidelines was published, evidence was confirmed after its publication in 2017. An English version of the guidelines was subsequently published based on the peer-reviewed article. After the Japanese version was published, one Chinese case–control study (56) and one Japanese cohort study (57) were published. The results were consistent and evidence supported the inclusion of endoscopic screening. Based on the recommendation of the revised guidelines, the Japanese government decided to introduce endoscopic screening for gastric cancer in 2016 (6).

Table 5. Benefits and harms of radiographic screening

	Reference No	Target age (years)							
		40	45	50	55	60	65	70	75
Radiographic screening (Men)									
Risk of gastric cancer death in 10 years (%)	16	0.052	0.111	0.248	0.477	0.770	1.137	1.604	2.124
Relative risk	17	0.865	0.865	0.865	0.865	0.865	0.865	0.865	0.865
Risk of gastric cancer death after introduction of endoscopic screening		0.045	0.096	0.214	0.412	0.666	0.984	1.387	1.837
Risk difference		0.007	0.015	0.033	0.064	0.104	0.154	0.216	0.287
Number needed to screen		14 113	6665	2990	1554	963	651	462	349
Recall rate (%)	20	4.75	6.03	7.94	9.84	11.25	11.91	12.24	12.24
Number needed to recall		670	402	237	153	108	78	57	43
Radiographic screening (Women)									
Risk of gastric cancer death in 10 years (%)	16	0.047	0.074	0.118	0.181	0.248	0.343	0.496	0.727
Relative risk	17	0.865	0.865	0.865	0.865	0.865	0.865	0.865	0.865
Risk of gastric cancer death after introduction of endoscopic screening		0.041	0.064	0.102	0.156	0.215	0.297	0.429	0.629
Risk difference		0.006	0.010	0.016	0.024	0.034	0.046	0.067	0.098
Number needed to screen		15 733	10 036	6303	4097	2981	2157	1494	1019
Recall rate (%)	20	4.14	4.72	5.69	6.54	7.26	7.92	8.46	8.46
Number needed to recall		651	474	359	268	216	171	126	86

Table 6. Benefits and harms of endoscopic screening

	Reference No	Target age (years)							
		40	45	50	55	60	65	70	75
Endoscopic screening (Men)									
Risk of gastric cancer death in 10 years (%)	16	0.052	0.111	0.248	0.477	0.770	1.137	1.604	2.124
Relative risk	17	0.695	0.695	0.695	0.695	0.695	0.695	0.695	0.695
Risk of gastric cancer death after introduction of endoscopic screening		0.036	0.077	0.172	0.331	0.535	0.790	1.115	1.476
Risk difference		0.016	0.034	0.076	0.145	0.235	0.347	0.489	0.648
Number needed to screen		6247	2950	1323	688	426	288	204	154
Recall rate (%)	21	2.86	8.89	11.56	9.71	11.46	10.99	11.21	11.21
Number needed to recall		179	262	153	67	49	32	23	17
Endoscopic screening (Women)									
Risk of gastric cancer death in 10 years (%)	16	0.047	0.074	0.118	0.181	0.248	0.343	0.496	0.727
Relative risk	17	0.695	0.695	0.695	0.695	0.695	0.695	0.695	0.695
Risk of gastric cancer death after introduction of endoscopic screening		0.033	0.051	0.082	0.126	0.173	0.239	0.345	0.505
Risk difference		0.014	0.023	0.036	0.055	0.076	0.105	0.151	0.222
Number needed to screen		6964	4442	2790	1813	1319	955	661	451
Recall rate (%)	21	5.79	5.38	6.40	6.68	7.46	7.30	7.28	7.28
Number needed to recall		403	239	179	121	98	70	48	33

Comparing the net benefit between radiographic screening and endoscopic screening, the impact of endoscopic screening was always higher than that of radiographic screening. Therefore, more benefits can be expected from endoscopic screening. On the other hand, endoscopic screening has also serious harms, namely complications and overdiagnosis. The complication rate of endoscopic screening is high and serious complications may lead to death. Infection control is also necessary by appropriate cleaning of the endoscope. To avoid these complications, appropriate quality assurance is required. To better understand endoscopic screening, an academic society has developed a quality assurance manual that can be referred to when endoscopic screening is introduced in communities (58). It has been reported that sensitivity of endoscopic screening is higher than that of radiographic screening, and that it can easily diagnose early cancer. However, this also suggests that the detected cancers by endoscopic screening may include more overdiagnosis cases than the detected cancers by radiographic screening (59). Although overdiagnosis by endoscopic screening cannot be ignored, studies reporting this harm remain insufficient.

To avoid unnecessary examinations, appropriate screening frequency should be considered (59). Therefore, the target age and screening interval should be clearly defined at the introduction of population-based screening in communities. Since the introduction of gastric cancer screening, the incidence of gastric cancer has decreased. When gastric cancer screening was introduced in the national program in 1983, the incidence of gastric cancer adjusted for the world population was 77.0/100 000 for men and 35.8/100 000 for women (2). The incidence of gastric cancer in individuals who are in their 40s was about twice compared with that in 2015. Therefore, the detection rate of gastric cancer has become lower. In fact, a huge gap in the net benefit was found between individuals who are in their 40s and individuals who are in 50s. Based

on these results, the starting age of screening could be defined as 50 years. However, the stopping age of screening could not be defined from the perspective of net benefit and change of incidence. For the definition of the stopping age, other theories are required, including a modeling approach. The impact of mortality reduction by endoscopic screening was maintained beyond 4 years in a Korean study (26). Mortality reduction achieved in individuals who had at least one screening within 3 years. Thus, the screening interval can be expanded to 2–3 years based on these results. Further research is needed to specifically define the target age group and screening interval.

Helicobacter pylori infection is a major cause of gastric cancer development. IARC recommended *H. pylori* screening based on expert opinions (60), but evidence regarding its effectiveness has remained unclear. Although such evidence is not found in the revised guidelines, screening using *H. pylori* antibody test is still expected. In Japan, the combined method of *H. pylori* antibody and serum pepsinogen tests has become commonly used, and it has been actually adopted as an alternative method for gastric cancer screening. The risk of gastric cancer increases depending on the background condition, namely, *H.* pylori infection and gastric atrophy (61). Although the prediction sensitivity in gastric cancer development was reportedly high, the specificity of predication was low, which led to a high false-positive rate (62). Therefore, the *H.* pylori antibody and serum pepsinogen tests may lead to a mislabeling of gastric cancer risk for individuals and an increase the number of unnecessary endoscopic examinations. As sensitivity and specificity were imbalanced in these methods, it is difficult to adopt them in the primary screening and risk prediction model. However, a combination with endoscopic screening might be another possibility to extend the screening interval for individuals who have a low risk of gastric cancer.

Gastric cancer remains a heavy burden in East Asian countries including Japan (1). Although screening has played a major role in preventing gastric cancer, evidence was weak for cancer screening programs because it was obtained from observational studies. Therefore, primary studies to evaluate reduction in mortality from gastric cancer should be encouraged and accumulated for evidence confirmation. On the other hand, *H. pylori* eradication has been covered by health insurance in Japan since 2015. Although *H. pylori* eradication has been anticipated to prevent gastric cancer development, the efficacy of this procedure remained unclear, and a systematic prevention program has not yet been developed worldwide. To identify and confirm the best available method for gastric cancer screening in Japan, assessment of new techniques is needed to achieve the goal of gastric cancer prevention. After 5 years, a schedule is launched will be set to revise the guidelines of gastric cancer screening based on the results of new studies.

Recommendations

Based on the balance of benefits and harms, recommendations were formulated for population-based and opportunistic screenings (Table 5). Benefits were defined as evidence that mortality from gastric cancer was reduced by cancer screening.

Radiographic screening is recommended for population-based and opportunistic screenings as its benefits outweigh its harms (**Recommendation Grade B**). Endoscopic screening is also recommended for population-based and opportunistic screenings as its benefits outweigh its harms (**Recommendation Grade B**). Both screenings are recommended to individuals aged 50 years and older. As there remains insufficient evidence of mortality reduction from gastric cancer, the *H. pylori* antibody and serum pepsinogen tests used alone or in combination are not recommended for population-based screening (**Recommendation Grade I**). With respect to opportunistic screenings, if individuals request these screenings, they should be given appropriate information with the decision made at the individual level.

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Conflict of interest statement

The author declares that she has no conflicts of interest associated with this study.

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Appendix

Systematic review group of gastric cancer screening guidelines

Chisato Hamashima (Chair, National Cancer Center), Katsuaki Kato (Miyagi Cancer Assciation), Isao Miyashiro (Osaka International Cancer Center), Hiroshi Nishida (AMS New Ohtani Clinic), Reo Takaku (Institute of Health Economics and Policy), Teruhiko Terasawa (Fujita Health University), Takaki Yoshikawa (Kanagawa Cancer Center).

Guideline development group of gastric cancer screening guidelines

Chisato Hamashima (National Cancer Center), Satoshi Honjo (National Hospital Organization Fukuoka National Hospital), Kazuhiko Inoue (Kawasaki Medical University), Takeo Nakayama (Kyoto University), Tomio Nakayama (Osaka International Cancer Center), Rintaro Narisawa (Nigiatta Prefecture Cancer Center Hospital), Motoyasu Sagawa (Tohoku Medical and Pharmaceutical University), Hiroshi Saito (National Cancer Center), Daisuke Shibuya (Miyagi Cancer Assciation), Tomotaka Sobue (Chair, Osaka University).