



2016 Gastric Cancer: Global view

## Benefits and harms of endoscopic screening for gastric cancer

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### Abstract

Gastric cancer has remained a serious burden worldwide, particularly in East Asian countries. However, nationwide prevention and screening programs for gastric cancer have not yet been established in most countries except in South Korea and Japan. Although evidence regarding the effectiveness of endoscopic screening for gastric cancer has been increasingly accumulated, such evidence remains weak because it is based on results from studies other than randomized controlled trials. Specifically, evidence was mostly based on the results of cohort and case-control studies mainly conducted in South Korea and Japan. However, the consistent positive results from these studies suggest promising evidence of mortality reduction from gastric cancer by endoscopic screening. The major harms of endoscopic screening include infection, adverse effects, false-positive results, and overdiagnosis. Despite the possible harms of endoscopic screening, information regarding these harms remains insufficient. To provide appropriate cancer screening, a balance of benefits and harms should always be considered when cancer screening is introduced as a public policy. Quality assurance is very important for the implementation of cancer screening to provide high-quality and safe screening and minimize harms. Endoscopic screening for gastric cancer has shown promising results, and thus deserves further evaluation to reliably establish its effectiveness and optimal use.

**Key words:** Gastric cancer; Cancer screening; Upper gastrointestinal endoscopy; Mortality reduction; Cohort study; Case-control study; Harms

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**Core tip:** Although evidence regarding the effectiveness

of endoscopic screening for gastric cancer has been increasingly accumulated based on consistent results, such evidence remains weak because it is based on the results of cohort and case-control studies mainly from South Korea and Japan. However, the consistent positive results suggest promising evidence of mortality reduction from gastric cancer by endoscopic screening. Despite the major harms of endoscopic screening, namely infection, adverse effects, false-positive results, and overdiagnosis, information regarding these harms remains insufficient. To provide appropriate cancer screening, a balance of benefits and harms should always be considered.

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## INTRODUCTION

Gastric cancer has remained a serious burden worldwide, particularly in East Asian countries. In 2012, there was an estimated 1 million new cases of gastric cancer, with half of the world total occurring in Eastern Asia<sup>[1]</sup>. The highest mortality rates are observed in Eastern Asia, occurring at 24.0 per 100000 men and 9.8 per 100000 women. However, prevention and screening programs for gastric cancer particularly at the national level have not yet been established in most countries. The exceptions are South Korea and Japan where gastric cancer screening programs have already been introduced<sup>[2]</sup>. In Japan, gastric cancer screening using upper gastrointestinal series (radiographic screening) has been conducted as a national program since 1983, and it has been attributed to the decrease in gastric cancer mortality<sup>[3]</sup>. After the introduction of radiographic screening for gastric cancer, supporting evidence has been obtained from case-control and cohort studies mainly conducted in Japan<sup>[4]</sup>.

Upper gastrointestinal endoscopy has been performed in clinical practice and is often introduced in opportunistic screening for gastric cancer in Asian countries<sup>[5]</sup>. Therefore, endoscopic screening has been anticipated to be introduced as a screening method in communities. Although South Korea was the first country to introduce endoscopic screening for gastric cancer, there was insufficient evidence of mortality reduction from gastric cancer when it was adopted as a national program<sup>[6]</sup>. Over the last decade, evidence regarding the effectiveness of endoscopic screening for gastric cancer has been increasingly accumulated. Recently in South Korea and Japan, cancer screening guidelines have been revised based on the new research results of endoscopic screening

for gastric cancer<sup>[7,8]</sup>. In both guidelines, endoscopic screening takes an important position in gastric cancer screening. However, evidence regarding the effectiveness of endoscopic screening for gastric cancer remains controversial, and quality assurance needs to be established. Discussion related to its benefits and harms is needed to promote the establishment of endoscopic screening for gastric cancer based on current and reliable evidence.

## EFFECTIVENESS OF ENDOSCOPIC SCREENING FOR GASTRIC CANCER

Evidence regarding the effectiveness of endoscopic screening for gastric cancer has been obtained from cohort and case-control studies mainly conducted in South Korea and Japan. Since these countries have already introduced endoscopic screening for gastric cancer, the study design is limited to observational studies. However, the consistent positive results from these studies suggest promising evidence of mortality reduction from gastric cancer by endoscopic screening.

### Cohort studies

The results from 5 published cohort studies of endoscopic screening for gastric cancer conducted in China and Japan are shown in Table 1. The target population of these studies was limited to asymptomatic individuals in communities. For the first cohort study concluded in China, mortality reduction could not be shown<sup>[9]</sup>. In the area with a high incidence of gastric cancer, endoscopic screening was offered twice with a 5-year screening interval. The standard mortality ratio of participation in endoscopic screening was 1.01 (95%CI: 0.72-1.37) for men and 0.65 (95%CI: 0.26-1.32) for women.

Earlier studies conducted in Japan had several problems in that they included individuals aged over 70 years and ignored the screening history before the defined first screening<sup>[10,11]</sup>. Although the study by Hosokawa *et al*<sup>[11]</sup> had the largest sample size, the sample selection period was different between the radiographic screening group and the endoscopic screening: the radiographic screening group was selected from communities in 1995 whereas the endoscopic screening group was selected from screening center from 1986 to 1999. Therefore, the age distributions and backgrounds of individuals in both groups were different<sup>[11]</sup>.

In Japan, although radiographic screening has been established as the standard method for the national gastric cancer screening program, some municipalities have now individually introduced endoscopic screening for gastric cancer. As an example, Niigata City has provided 3 types of gastric cancer screening since 2005: endoscopy, regular radiography, and photo-fluorography. After a 5-year follow-up period, standard mortality ratios (SMRs) were calculated and were

**Table 1 Comparison of results from cohort studies of endoscopic screening for gastric cancer**

Author	Riecken <i>et al</i> <sup>[9]</sup>	Matsumoto <i>et al</i> <sup>[10]</sup>	Hosokawa <i>et al</i> <sup>[11]</sup>	Hamashima <i>et al</i> <sup>[12]</sup>	Hamashima <i>et al</i> <sup>[13]</sup>
Publication	2002	2007	2011	2015	2015
Country	China	Japan	Japan	Japan	Japan
Target age, yr	35-64	≥ 40	Average: 50.0	40-79	40-79
Follow-up, yr		9	5	5	6
Number of subjects	4364	7178	18011	16373	9950
Comparators	-	-	Radiographic screening	-	Radiographic screening
Number of comparators	-	-	36870	-	4324
Outcome indicators	SMR	SMR	Hazard ratio (HR)	SMR	Relative risk
Main results	1.01 (95%CI: 0.72-1.37)	Male: 0.71 (95%CI: 0.33-1.10) Female: 0.62 (95%CI: 0.19-1.05)	HR = 0.15 (95%CI: 0.05-0.50) Adjusted HR <sup>1</sup> = 0.23 (95%CI: 0.07-0.76)	0.43 (95%CI: 0.30-0.57)	Adjusted RR <sup>2</sup> 0.327 (95%CI: 0.118-0.908)

<sup>1</sup>Adjusted HR by sex and age; <sup>2</sup>Adjusted RR by sex, age group, and resident city. SMR: Standard mortality ratio; CI: Confidence interval; HR: Hazard ratio; RR: Relative risk.

**Table 2 Comparison of results from case-control studies of endoscopic screening for gastric cancer**

Author	Matsumoto <i>et al</i> <sup>[14]</sup>	Hamashima <i>et al</i> <sup>[15]</sup>	Cho <sup>[17]</sup>
Publication	2014	2013	2013
Country	Japan	Japan	South Korea
Target age, yr	54-91	40-79	≥ 40
Number of cases	13	410	35457
Number of control	130	2292	141828
Comparator	Never-screened	Never-screened	Never-screened
Main results	0.206 (95%CI: 0.044-0.965)	0.695 (95%CI: 0.489-0.986)	0.430 (95%CI: 0.40-0.46)

referred to as cancer mortality rate of the population of Niigata City<sup>[12]</sup>. The SMRs of gastric cancer death were 0.43 (95%CI: 0.30-0.57) for the endoscopic screening group, 0.68 (95%CI: 0.55-0.79) for the regular radiographic screening group, and 0.85 (95%CI: 0.71-0.94) for the photofluorography screening group. The mortality reduction from gastric cancer was higher in the endoscopic screening group than in the regular radiographic screening group despite the nearly equal mortality rates of all cancers except gastric cancer. Tottori City and Yonago City have more than 10 years of history of conducting endoscopic screening for gastric cancer. These cities have also provided both endoscopic screening and radiographic screening. After 6 years of follow-up, the subjects screened by endoscopy showed a 67% reduction of gastric cancer compared with the subjects screened by radiography (adjusted relative risk by sex, age group, and resident city: 0.327, 95%CI: 0.118-0.908)<sup>[13]</sup>.

### Case-control studies

The results from case-control studies of endoscopic screening for gastric cancer conducted in South Korea and Japan are shown in Table 2. In previous Japanese guidelines, evidence regarding the effectiveness of radiographic screening for gastric cancer was based on

the results of case-control studies<sup>[4]</sup>. Although these results suggest that gastric cancer mortality could be reduced by endoscopic screening, prudence must be observed in interpreting positive results because these case-control studies may have self-selection bias.

The results of community-based case-control studies of endoscopic screening in Japan have recently been reported by Matsumoto *et al*<sup>[14]</sup> and Hamashima *et al*<sup>[15]</sup>. Results of the larger case-control study of Hamashima *et al*<sup>[15]</sup> conducted in Tottori and Niigata prefectures showed a 30% reduction in gastric cancer mortality by participation in endoscopic screening at least once within 36 mo before the date of diagnosis of gastric cancer compared with never-screened individuals. Although the sample size was small in their Nagasaki study, Matsumoto *et al*<sup>[14]</sup> reported a higher mortality reduction from gastric cancer by 80%.

In South Korea, endoscopic screening has been performed together with radiographic screening, and the recent participation rate has exceeded that of radiographic screening<sup>[16]</sup>. Based on the national database, a nested case-control study from South Korea reported a 57% mortality reduction from gastric cancer by endoscopic screening<sup>[17]</sup>. Mortality reduction from gastric cancer by endoscopic screening was observed in the 40- to 79-year age group when participating in endoscopic screening within 1 year to 3 years before the date of gastric cancer diagnosis.

## INDIRECT EVIDENCE REGARDING THE EFFECTIVENESS OF ENDOSCOPIC SCREENING

Mortality reduction from the target cancer should be evaluated as the most reliable evidence regarding the effectiveness of cancer screening. Sensitivity of the screening test, stage shift, and survival rate of detected cancers by screening are also occasionally considered as possible indicators showing indirect evidence regarding the effectiveness of endoscopic screening for

**Table 3 Sensitivities and specificities of endoscopy and radiography for gastric cancer screening**

Screening round	Method	Sensitivity	Specificity	Sensitivity
		by the detection method	by the detection method	by the incidence method
Prevalence screening	Endoscopic screening	0.955 (95% CI: 0.875-0.991)	0.851 (95% CI: 0.843-0.859)	0.886 (95% CI: 0.698-0.976)
	Radiographic screening	0.893 (95% CI: 0.718-0.977)	0.856 (95% CI: 0.846-0.865)	0.831 (95% CI: 0.586-0.964)
Incidence screening	Endoscopic screening	0.977 (95% CI: 0.919-0.997)	0.888 (95% CI: 0.883-0.892)	0.954 (95% CI: 0.842-0.994)
	Radiographic screening	0.885 (95% CI: 0.664-0.972)	0.891 (95% CI: 0.885-0.896)	0.855 (95% CI: 0.637-0.970)

Adapted from Hamashima *et al*<sup>[19]</sup>.

gastric cancer. However, these three indicators are not valid for revealing evidence regarding the effectiveness of cancer screening because they include biases and require prudent interpretation.

### Sensitivity of endoscopic screening

The sensitivity of endoscopic screening has recently been compared with that of radiographic screenings<sup>[18,19]</sup>. However, since the screening interval and sensitivity calculation method were different between the screening methods, a direct comparison of the results is not suitable. Although the definition of interval cancer was different between South Korea and Japan, the sensitivity of endoscopic screening was always higher than that of radiographic screening. However, there may be an increase in frequency of overdiagnosis by endoscopic screening because it can detect cancer earlier and more than radiographic screening.

In a study conducted in South Korea, the sensitivity of endoscopic screening calculated by 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<sup>[18]</sup>. On the other hand, the sensitivity of radiographic screening was 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<sup>[18]</sup>. In a study conducted in Japan, the sensitivity of prevalence screening for the first round was 0.955 (95%CI: 0.875-0.991) for endoscopic screening and 0.893 (95%CI: 0.718-0.977) for radiographic screening (Table 3)<sup>[19]</sup>. On the other hand, the sensitivity of incidence screening on the subsequent round was 0.977 (95%CI: 0.919-0.997) for endoscopic screening and 0.885 (95%CI: 0.664-0.972) for radiographic screening.

### Stage shifts and survival rates of detected cancer by endoscopic screening

In South Korea, both endoscopic screening and radiographic screening have been provided in the national screening programs<sup>[6]</sup>. Among cancers detected from 2002 to 2007 based on the national cancer registry, localized gastric cancers were more frequently recorded in endoscopic ever-screened patients than in radiographic ever-screened patients and never-screened

patients<sup>[20]</sup>. Compared with never-screened patients, the odds ratio for being diagnosed with localized gastric cancer in endoscopic-screened patients was 2.10 (95%CI: 1.90-2.33). Stage shifts by endoscopic screening could lead to improvement of the survival rate of the detected cancer by endoscopic screening. In a study conducted in Japan, the 5-year survival rates were 91.2% ± 1.5% (95%CI: 87.5%-93.8%) for the endoscopic screening group, 84.3% ± 2.9% (95%CI: 87.5%-93.8%) for the radiographic screening group, and 66.0% ± 1.6% (95%CI: 62.8%-68.9%) for the outpatient group<sup>[21]</sup>.

### HARMS OF ENDOSCOPIC SCREENING

The major harms of endoscopic screening include infection, adverse effects, false-positive results, and overdiagnosis. Infection and adverse effects are original risks of endoscopic screening for gastric cancer, but false-positive results and overdiagnosis are characteristics common in cancer screening.

As everyone is a potential source of infection, all endoscopy procedures can be contaminated<sup>[22]</sup>. Hepatitis B infection caused by endoscopy was reported in the 1980s in Japan<sup>[23,24]</sup>. *Helicobacter pylori* (*H. pylori*) infection was reportedly caused by upper intestinal endoscopy and induced acute gastric mucosal lesions<sup>[25,26]</sup>. The Japan Gastrointestinal Endoscopy Society has published guidelines and manuals for the proper cleaning and disinfection of endoscopes, and had also promoted appropriate methods of cleaning and disinfection of endoscopes according to the standard guidelines set by the World Gastroenterology Organization<sup>[27]</sup>.

Over the last 3 years, the Japanese Association of Gastroenterological Cancer Screening has recorded the number of adverse effects of endoscopic screening for gastric cancer during latest 3 years<sup>[28-30]</sup>. Of the 740245 endoscopic examinations conducted, the rate of adverse effects was 78 per 100000 participants in endoscopic screening for gastric cancer. The most common adverse effects were nasal bleeding and gastric mucosal laceration. The number of bleeding cases after biopsy was 21, with 4 cases requiring admission. However, the association between bleeding and anticoagulant use was unclear. Although endo-



scopic examination is often performed after the temporary stoppage of anticoagulants, there are risks of thrombosis during drug holidays<sup>[31-33]</sup> and bleeding after retaking anticoagulants<sup>[34,35]</sup>. However, regardless of taking anticoagulants, there is always a possibility of bleeding to occur<sup>[36,37]</sup>. Although serious adverse effects including anaphylactic shock and respiratory depression have been reported, there was no case leading to death in any of the reports of the Japanese Association of Gastroenterological Cancer Screening. In a survey conducted by the Japanese Gastrointestinal Endoscopy Society, cases of death caused by sedation for endoscopic examination have been reported<sup>[38]</sup>.

A false-positive result is a common harm in cancer screening and requires further examination to definitively diagnose gastric cancer. In breast cancer screening, it has been suggested that a false-positive result induces psychological anxiety<sup>[39]</sup>. Although the rate of endoscopic screening for gastric cancer has been reported to be 14.9% for prevalence screening and 11.2% for subsequent screening<sup>[19]</sup>, there have been no reports related to psychological burden from endoscopic screening of gastric cancer.

Overdiagnosis is the most serious harm of cancer screening<sup>[40]</sup>. Apparently, there is still no study estimating the number of overdiagnosis of gastric cancer by endoscopic screening. Based on the results of endoscopic screening for gastric cancer, the observed number of detected cancer was twice compared with the expected number in the target group of endoscopic screening for gastric cancer<sup>[41]</sup>. The excess cancers included not only overdiagnosis cases but also early cancers which have the actual possibility of progressing into advanced cancers that lead to death.

Sensitivity is affected by overdiagnosis and it is often overestimated. The detection method is the most common and simplest procedure of calculating sensitivity wherein the number of detected cancers is used as the numerator and the sum of detected cancers and interval cancers is used as the denominator. Although the detection method is commonly used for measuring the sensitivity of the screening method, it cannot exclude cases of overdiagnosis. Notably, the incidence method was developed to avoid cases of overdiagnosis during sensitivity calculations<sup>[42]</sup>. Breast, lung, and colorectal cancer screenings have been evaluated using the incidence method<sup>[43-45]</sup>. In prevalence screening, the sensitivity was reportedly 0.955 (95%CI: 0.875-0.991) by the detection method and 0.886 (95%CI: 0.698-0.976) by the incidence method (Table 3)<sup>[19]</sup>. In incidence screening, the sensitivity was reportedly 0.977 (95%CI: 0.919-0.997) by the detection method and 0.954 (95%CI: 0.842-0.994) by the incidence method<sup>[19]</sup>. The discrepancy between the results calculated by the detection method and the incidence method was small, suggesting the negligible effect of overdiagnosis on endoscopic screening for gastric cancer.

## DISCUSSION

To effectively introduce a new cancer screening method, mortality reduction from the target cancers must be carefully evaluated based on appropriate and reliable studies. However, since randomized controlled trials related to gastric cancer screening are lacking, observational studies have played as a central role in providing evidence regarding mortality reduction from gastric cancer. Importantly, evidence obtained from observational studies has limitations because such evidence cannot exclude serious biases, particularly selection bias. On the other hand, the results of observational studies can show the actual effectiveness in real settings. As South Korea and Japan have already introduced gastric cancer screening, planning a new randomized controlled trial of endoscopic screening for gastric cancer is difficult. Although lines of evidence regarding the effectiveness of endoscopic screening have been accumulated, information on harms remains insufficient. This becomes a barrier for estimating the net benefits of endoscopic screening for gastric cancer.

The adverse effects of endoscopic screening cannot be ignored because the participants of gastric cancer screening are asymptomatic and healthy people who have not yet experienced adverse effects following their participation in cancer screening. However, as upper gastrointestinal endoscopy is an invasive technology, adverse effects cannot be avoided. Bleeding is a common adverse effect and it can occur regardless of whether a patient is taking anticoagulants or not<sup>[36,37]</sup>. Moreover, respiration depression can lead to death when sedation is used in endoscopic examination<sup>[38]</sup>. On the other hand, endoscopy-induced infection becomes a serious problem with the widespread use of endoscopic examinations. Also, there is a risk of transmitting any infection *via* endoscopy if endoscope is not properly cleaned and disinfected. These adverse effects and infection can be reduced by appropriate management. This is the basic requirement of quality assurance of cancer screening. In European countries, quality assurance guidelines for cervical, breast, and colorectal cancers have been published and they have become standards for the management of these programs<sup>[46-48]</sup>. Since 2000, South Korea has introduced endoscopic screening for gastric cancer as one of its national cancer screening programs and has developed quality assurance guidelines<sup>[6,49]</sup>. In Japan, an academic society has developed a quality assurance manual for endoscopic screening of gastric cancer and has recommended the appropriate management<sup>[50-52]</sup>.

False-positive result and overdiagnosis are common harms of all cancer screenings. Both harms lead to unnecessary further examinations and additional burden for participants in cancer screenings. When cancer screening starts, these harms cannot be avoided<sup>[53]</sup>. Recently, a value framework has been suggested as a new concept of cancer screening<sup>[53,54]</sup>. In this concept,

providing the appropriate number of cancer screening is recommended to minimize the harms and maximize the screening value. The Korean guidelines for gastric cancer screening defined the target age group from 40 to 69 years<sup>[8]</sup>. The Japanese guidelines for gastric cancer screening set the starting age from 50 years with no upper age limit<sup>[7]</sup>. Both guidelines have recommended a 2-year screening interval. Based on a comparison of the stage distribution of detected cancers by endoscopic screening, a 2-year screening interval was suggested in a Korean study<sup>[55]</sup>. However, in a Korean case-control study, mortality reduction was shown even if the screening interval was extended until 3 years<sup>[17]</sup>. To minimize harms, additional studies are needed to determine the appropriate target age group and screening interval.

Although the burden of gastric cancer has not been ignored worldwide, gastric cancer screening programs using endoscopy are currently limited to South Korea and Japan. *H. pylori* is one of the main causes of gastric cancer, and 78% of all gastric cancer cases are estimated to be attributed to chronic *H. pylori* infection<sup>[56]</sup>. IARC has recommended *H. pylori* screening and treatment strategies considering the disease burden and local context<sup>[56]</sup>. Although risk stratification can be carried out using *H. pylori* antibody and serum pepsinogen tests<sup>[57]</sup>, it is difficult to predict individuals who will not have gastric cancer in the future because of low predictive specificity of these tests. On the other hand, it is possible to diagnose *H. pylori* infection by endoscopy based on a specific feature in the gastric mucosa<sup>[58]</sup>. Although the discrimination ability to predict the development of gastric cancer by biomarkers and endoscopy is insufficient, considerations should be given on how to use biomarkers in combination with endoscopic screening, for example, adaptation to expand the screening interval. Further study is needed regarding the combination of endoscopic screening with these biomarkers.

## CONCLUSION

Lines of evidence regarding the effectiveness of endoscopic screening have been steadily accumulated showing consistent results. However, these lines of evidence remain weak because they are based on the results of studies other than randomized controlled trials. Moreover, even if possible harms of endoscopic screening can be ascertained, specific information regarding these harms is still insufficient. To provide appropriate cancer screening, a balance of benefits and harms should always be considered when cancer screening is introduced as a public policy. Quality assurance is very important for the implementation of cancer screening to provide high-quality and safe screening and minimize harms. Endoscopic screening for gastric cancer has clearly shown promising results, and thus warrants confirmatory evaluation to reliably

establish its effectiveness and optimal use.

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