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ABOUT COVER

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ORIGINAL ARTICLE

Retrospective Study

Gastric cancer mortality related to direct radiographic and endoscopic screening: A retrospective study

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Author contributions: Hagiwara H designed the study, collected data, and wrote the paper; Moki F performed the follow-up survey and conducted the statistical analysis; Yamashita Y, Saji K, Iesaki K, and Suda H provided clinical advice.

Institutional review board statement: This study was reviewed and approved by the Gunma Prefecture Health and Welfare Department and Maebashi Medical Association.

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Abstract

BACKGROUND

Despite its decreased incidence in Japan, gastric cancer continues among the leading causes of cancer-related deaths in both men and women. Accordingly, efforts are still required to lower the mortality rate of gastric cancer in Japan. Maebashi City introduced endoscopic gastric cancer screening in 2004, and participants are able to choose between direct radiography and endoscopy. Hence, we expected to see a decrease in mortality rate from gastric cancer after introducing endoscopic screening and a difference in mortality rate reduction between screening methods.

AIM

To evaluate the impact on gastric cancer mortality rate of two types of gastric cancer screening in Maebashi City, Japan.

METHODS

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Participants aged 40 to 79 years of the Maebashi City gastric cancer screening program in 2006 who were screened by direct radiography (n = 11155) or endoscopy (n = 10747) were included. Participants were followed until March 31, 2012, by cross-referencing their data against the Gunma Prefecture cancer registry data. We compared the detection rate of gastric cancers. Then, we compared the mortality rate between the two groups. The Cox proportional hazards model was used to estimate the hazard ratio (HR) of gastric cancer death. Finally, the reduction in gastric cancer mortality rate associated with each screening method was evaluated.

RESULTS

Gastric cancer was detected in 22 participants undergoing direct radiography (detection rate, 0.20%) and in 52 participants undergoing endoscopy (detection rate, 0.48%). However, most gastric cancers detected by endoscopic screening were early cancers that may not have resulted in death. We found no significant difference in gastric cancer mortality rate between participants receiving annual screening and those who do not. When the number of gastric cancer deaths in the direct radiography group was set as 1 in the Cox proportional hazard analysis, the HR of gastric cancer death was 1.368 (95%CI: 0.7308–2.562) in the overall group of participants. The results showed no significant difference between the two screening methods in any of the analysis groups.

CONCLUSION

Although endoscopic screening detected more gastric cancer than direct radiographic screening, no significant difference in the reduction of gastric cancer mortality rate between the two screening methods was found.

Key Words: Gastric cancer; Radiography; Endoscopy; Population-based cancer screening; Mortality reduction

Core Tip: Although the incidence rate has declined in Japan, gastric cancer is still the leading cause of cancer-related deaths in men and women. Therefore, Japan still needs to work hard to reduce the death rate of gastric cancer. Maebashi City introduced endoscopic gastric cancer screening in 2004. Endoscopic screening detects more gastric cancer than direct radiographic screening does, but both screening methods have similar effects on reducing the mortality rate from gastric cancer.

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INTRODUCTION

In 2017, 24.5 million patients globally had a cancer diagnosis, and 9.6 million patients died of cancer. Of these deaths, 861000 were due to gastric cancer (men, n = 542000; women, n = 319000). Furthermore, gastric cancer was the third-highest cause of death among men dying from cancer and the fourth-highest in women dying from cancer[1].

In Japan, the prevalence of *Helicobacter pylori* (*Hp*) infection—a known cause of gastric cancer—has decreased, and the incidence of gastric cancer and the age-adjusted mortality rate from gastric cancer have also been decreasing. Nonetheless, in 2018 gastric cancer was the second-highest cause of death among Japanese men dying from any cancer and the fourth-highest among Japanese women dying from any cancer[2]. Accordingly, further efforts are still required to lower the mortality rate of gastric cancer in Japan.

In Japan, for many years, gastric cancer mass screening programs conducted by municipal governments were performed by using indirect radiography to examine large numbers of people, and direct radiography was used to examine individual patients at medical institutions. However, in 2015 the Gastric Cancer Screening Guidelines were revised to recommend endoscopy for organized gastric cancer screening[3]. Accordingly, many municipal governments subsequently started using endoscopy rather than indirect radiography for gastric cancer screening.

In Maebashi City, endoscopic gastric cancer screening was introduced in 2004, and subsequently, participants were able to choose between direct radiography and endoscopy[4]. Therefore, we examined clinical data from participants in the Maebashi City gastric cancer screening program in 2006 to assess whether the mortality rate from gastric cancer decreased after the introduction of endoscopic screening.

MATERIALS AND METHODS

Study design and participants

Citizens aged 40 years and older are eligible to participate in the Maebashi City gastric cancer screening as part of their personal health check, and participants can choose between direct radiography and endoscopy every year. Gastric cancer screening is conducted at practitioner clinics or at hospitals in Maebashi City that have elected to participate in the screening program, and institutions do not have to fulfill any eligibility criteria to participate. In 2006, 23963 citizens participated in gastric cancer screening, accounting for 20.5% of the overall eligible population. A total of 12014 participants underwent direct radiographic screening and 11949 endoscopic screening.

The present study included participants aged 40 to 79 years; 79 years was chosen as the upper age limit because, in Japan, the average lifespan is 79.00 years in men and 85.81 years in women[5]. A total of 21802 participants were included, comprising 11155 individuals who underwent direct radiography and 10747 who underwent endoscopy.

First, we investigated the number of gastric cancers detected and the cancer stage at detection. Next, we compared the detection rate between the two participant groups undergoing direct radiography or endoscopy. Then, we compared the mortality rate between the two groups. The clinical data of the present study cohort, including the name, sex, date of birth, and history of participation in gastric cancer screening, were extracted from the Maebashi Medical Association cancer screening database. The participants were followed up until March 31, 2012, using the Gunma Prefectural Cancer Registry data. The 2006 Maebashi City gastric cancer screening was conducted from May 2006 until the end of February 2007, and participants could choose to be screened by either of the two imaging methods. The follow-up period ranged from 5 years, 1 mo, to 5 years, 11 mo.

The two screening methods are offered by at least 80 institutions each year. Direct radiographic examination is performed by the standard imaging method (8-image method). For endoscopic gastric cancer screening, 30 to 40 images are taken that cover the esophagus and duodenum. Screening physicians are required to submit the images to the Maebashi Medical Association, where they are reviewed by two other physicians commissioned by the Maebashi Medical Association; these physicians check the quality and look for missed lesions (secondary review). Generally, endoscopic images are reviewed by physicians who are board-certified by the Japan Gastroenterological Endoscopy Society.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Outcomes

The primary outcome was death from gastric cancer. We compared the incidence rate of the primary outcome between the two screening methods in the whole group of participants and between those participants who had also participated in the gastric cancer screening in the previous year and those who had not.

The secondary outcome was the incidence rate of death from any cancer except gastric cancer, and the same comparisons were performed for the secondary outcome as for the primary outcome.

To obtain additional information on causes of death, we compared the data in the Gunma Prefectural Cancer Registry with the death certificates.

The accuracy of the 2006 Gunma Prefectural Cancer Registry was low with 40.5% of incidence cancer rate registered as death certified only; however, the data of death was perfectly obtained.

Statistical analysis

We compared the participants' background factors between the two groups using Fisher's exact test and Student's *t*-test. The Cox proportional hazards model was used to estimate the hazard ratio (HR) of gastric cancer death, and death from any cancer other than gastric cancer, in the overall group of participants and the subsets of participants who had or had not participated in gastric cancer screening in the previous year. HRs were adjusted for sex and age group. Finally, the average covariate method was used to estimate and plot the survival curve adjusted for sex and age groups[6,7]. All test statistics were 2-tailed, and a *P* value less than 0.05 was considered to indicate a statistically significant difference. Analyses were performed with EZR (easy-R)[8]. The use of Gunma Cancer Registry data was approved by Gunma Prefecture. The statistical review of the study was performed by Moki F from Gunma Health Foundation.

RESULTS

Participants and gastric cancer detection rates

The percentages of male participants and participants aged 60 years or older were slightly higher in the endoscopic screening group (Table 1). Similar results were found in the subsets of participants who had also participated in the screening in the previous year (Table 2) and those who had not (Table 3).

Among all screening program participants, gastric cancer was detected in 25 participants undergoing direct radiography (detection rate, 0.21%) and in 72 participants undergoing endoscopy (detection rate, 0.60%). Thus, the gastric cancer detection rate with endoscopy was triple that of direct radiography. In the participants aged from 40 to 79 years, gastric cancer was detected in 22 individuals undergoing direct radiography (detection rate, 0.20%) and in 52 individuals undergoing endoscopy (detection rate, 0.48%). Thus, endoscopic screening detected gastric cancer in participants aged 80 years or over more frequently than direct radiographic screening.

In the participants aged from 40 to 79 years, the categories of gastric cancer lesions detected by direct radiographic screening and respective numbers and percentages of participants were as follows: Stage IA, n = 6 (27.2%); stage IB, n = 2 (9.1%); stage II, n = 3 (13.6%); stage IIIA, n = 1 (4.5%); stage IIIB, n = 4 (18.2%); stage IV, n = 5 (22.7%); and unspecified stage, n = 1 (4.5%). The respective data for gastric cancer detected by endoscopic screening were as follows: Stage IA, n = 30 (57.7%); stage IB, n = 3 individuals (5.8%); stage II, n = 6 (11.5%); stage IIIA, n = 1 (1.9%); stage IIIB, n = 2 (3.8%); stage IV, n = 7 (13.5%); and unspecified stage, n = 3 (5.8%)[9]. The stage IA gastric cancer lesions detected by endoscopic screening were treated by endoscopic submucosal dissection (ESD) in 21 of the 30 individuals, and all 6 of the stage IA lesions detected by direct radiographic screening were treated by gastrectomy.

Gastric cancer mortality rates

Gastric cancer deaths were detected in 17 of the 11 155 individuals who underwent direct radiography and in 23 of the 10 747 individuals who underwent endoscopy. The five-year survival by the Kaplan-Meier method was 0.998 (95%CI: 0.998–0.999) in individuals who underwent direct radiography and 0.998 (95%CI: 0.997–0.999) in individuals who underwent endoscopy. Overall, no significant difference was observed between the two screening methods (P = 0.285) (Figure 1). Among participants who had not participated in screening in the previous year, gastric cancer deaths were detected in 10 of 4 382 individuals who underwent direct radiography and in 16 of 6 915 individuals who underwent endoscopy. The five-year survival rate was 0.998 (95%CI: 0.996–0.999) in individuals who underwent direct radiography and 0.998 (95%CI: 0.996–0.999) in individuals who underwent endoscopy. No significant difference was observed between the two screening methods (P = 0.971) (Figure 2). Among participants who had also undergone screening in the previous year, gastric cancer deaths were detected in 7 of 6 773 individuals who underwent direct radiography and 7 of 3832 individuals who underwent endoscopy. The five-year survival rate was 0.999 (95%CI: 0.998–1.000) in individuals who underwent direct radiography and 0.998 (95%CI: 0.996–0.999) in individuals who underwent endoscopy. Again, no significant difference was observed between the two methods (P = 0.280) (Figure 3).

Table 1 Characteristics of individuals aged 40 to 79 years who participated in gastric cancer screening in Maebashi City, Japan, in 2006

		Screening method		
		Endoscopy	Radiography	*P* value
Participants, *n*		10747	11155	
Sex, *n* (%)	Male	4323 (40.2)	4103 (36.8)	< 0.001
	Female	6424 (59.8)	7052 (63.2)	
Age group, *n* (%)	40–49 yr	952 (8.9)	1005 (9.0)	NA
	50–59 yr	2043 (19.0)	2264 (20.3)	
	60–69 yr	3667 (34.1)	3986 (35.7)	
	70–79 yr	4085 (38.0)	3900 (35.0)	
Age group, *n* (%)	40–59 yr	2995 (27.9)	3269 (29.3)	0.019
	60–79 yr	7752 (72.1)	7886 (70.7)	
Age, mean (SD), yr		64.75 (9.69)	64.30 (9.57)	< 0.001

NA: No significant.

Table 2 Characteristics of individuals aged 40 to 79 years who participated in gastric cancer screening in Maebashi City, Japan, in 2006 and did not subsequently receive annual screening

		Screening method		
		Endoscopy	Radiography	*P* value
Participants, *n*		6915	4382	
Sex, *n* (%)	Male	2680 (38.8)	1570 (35.8)	0.002
	Female	4235 (61.2)	2812 (64.2)	
Age group, *n* (%)	40–49 yr	764 (11.0)	552 (12.6)	NA
	50–59 yr	1483 (21.4)	1032 (23.6)	
	60–69 yr	2372 (34.3)	1528 (34.9)	
	70–79 yr	2296 (33.2)	1270 (29.0)	
Age group, *n* (%)	40–59 yr	2247 (32.5)	1584 (36.1)	< 0.001
	60–79 yr	4668 (67.5)	2798 (63.9)	
Age, mean (SD), yr		63.54 (9.99)	62.51 (10.08)	< 0.001

NA: No significant.

A Cox hazard analysis was conducted. Because the proportional hazard was not maintained for participants who had not participated in the previous year, the HR was estimated for participants who had also participated in the screening in the previous year and those who did not. When the number of gastric cancer deaths in the direct radiography group was set as 1 in the Cox proportional hazard analysis, the adjusted HR of gastric cancer death was 1.368 (95%CI: 0.7308–2.562) in the overall group of participants and 1.600 (95%CI: 0.5604–4.569) in the subset of participants who had also participated in gastric cancer screening in the previous year. These results showed no significant difference between the two screening methods in any of the analysis groups (Table 4).

Mortality rates for any cancer

Deaths from any cancer other than gastric cancer occurred in 163 of 11 155 individuals who underwent direct radiography and 178 of 10 747 individuals who underwent endoscopy. The five-year survival rate was 0.987 (95%CI: 0.985–0.989) in individuals who underwent direct radiography and 0.986 (95%CI: 0.984–0.988) in individuals who

Table 3 Characteristics of individuals aged 40 to 79 years who participated in gastric cancer screening in Maebashi City, Japan, in 2006 and subsequently received annual screening

		Screening method		
		Endoscopy	Radiography	*P* value
Participants, *n*		3832	6773	
Sex, *n* (%)	Male	1643 (42.9)	2533 (37.4)	< 0.001
	Female	2189 (57.1)	4240 (62.6)	
Age group, *n* (%)	40–49 yr	188 (4.9)	453 (6.7)	NA
	50–59 yr	560 (14.6)	1232 (18.2)	
	60–69 yr	1295 (33.8)	2458 (36.3)	
	70–79 yr	1789 (46.7)	2630 (38.8)	
Age group, *n* (%)	40–59 yr	748 (19.5)	1685 (24.9)	< 0.001
	60–79 yr	3084 (80.5)	5088 (75.1)	
Age, mean (SD), b		66.95 (8.71)	65.46 (9.03)	< 0.001

NA: No significant.

Table 4 Cox proportional hazards analyses of gastric cancer deaths in individuals aged 40 to 79 years who participated in gastric cancer screening in Maebashi City, Japan, in 2006

	Screening method	Participants, *n* (%)	Gastric cancer deaths, *n* (%)	Adjusted reduction rate[1]	95%CI
All participants	Radiography	11155	17	1.000	
	Endoscopy	10747	23	1.368	0.7308–2.562
Participants receiving annual screening after 2006	Radiography	6773	7	1.000	
	Endoscopy	3832	7	1.600	0.5604–4.569

[1]Adjusted for sex and age group (40–59 years and 60–79 years).

underwent endoscopy. No significant difference between the two screening methods was observed in the overall population (P = 0.249) (Figure 4A).

Among participants who had not participated in screening in the previous year, gastric cancer deaths were detected in 77 of 4 382 individuals who underwent direct radiography and 110 of 6 915 individuals who underwent endoscopy. The five-year survival rate was 0.985 (95%CI: 0.981–0.988) in individuals who underwent direct radiography and 0.986 (95%CI: 0.983–0.989) in individuals who underwent endoscopy. No significant difference was observed between the two screening methods (P = 0.509) (Figure 4B).

Among participants who had also participated in screening in the previous year, gastric cancer deaths were detected in 86 of 6 773 individuals who underwent direct radiography and 68 of 3 832 individuals who underwent endoscopy. The five-year survival rate was 0.988 (95%CI: 0.985–0.990) in individuals who underwent direct radiography and 0.985 (95%CI: 0.981–0.989) in individuals who underwent endoscopy. A significant difference was observed between the two screening methods (P = 0.038) (Figure 4C). The Cox proportional hazard test was conducted. For participants who had not participated in the previous year, the Cox hazard was not maintained. Accordingly, the HR was estimated for the overall population and participants who had also participated in the screening in the previous year.

When the number of deaths from any cancer other than gastric cancer in the participants who received direct radiographic screening was set as 1 in the Cox proportional hazard analysis, the adjusted HR of deaths from any cancer other than gastric cancer was 1.090 (95%CI: 0.8813-1.3480) in the overall group, 1.284 (95%CI: 0.9334–1.7650) in the participants who had also participated in the screening in the previous year. Again, no significant difference was found between the two screening

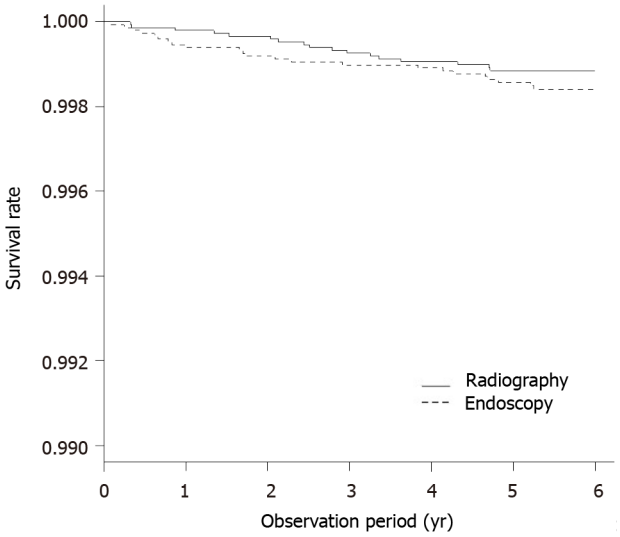

Figure 1 Survival curves of gastric cancer deaths in all individuals aged 40 to 79 years old who participated in gastric cancer screening in Maebashi City, Japan, in 2006. Survival curves are adjusted for sex and age group (40–59 years and 60–79 years). No significant difference was observed in the 5-year survival rate between the direct radiography and the endoscopy groups (P = 0.285).

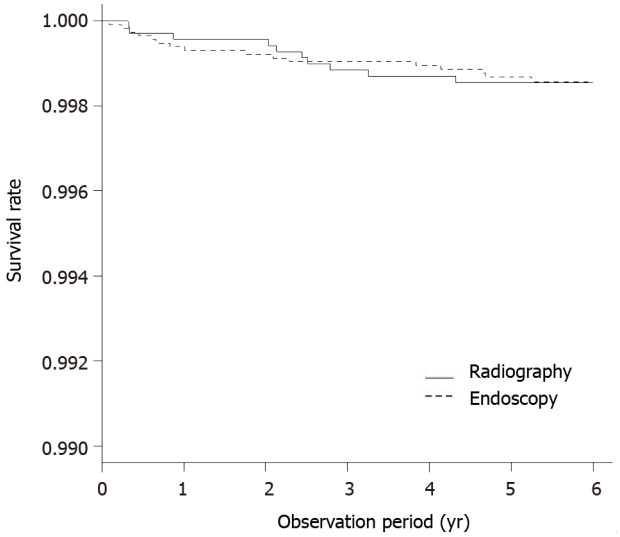

Figure 2 Survival curves of gastric cancer deaths in individuals aged 40 to 79 years old who participated in gastric cancer screening in Maebashi City, Japan, in 2006 and did not subsequently receive annual screening. Survival curves are adjusted for sex and age group (40–59 years and 60–79 years). No significant difference was observed in the 5-year survival rate between the direct radiography and the endoscopy groups (P = 0.971).

methods in terms of death from any cancer except gastric cancer (Table 5).

DISCUSSION

In this study, we examined clinical data from participants in the Maebashi City gastric cancer screening program in 2006 to assess whether the mortality rate from gastric cancer decreased after endoscopy was introduced as an additional screening method in addition to direct radiography. We found that although endoscopy detected more gastric cancers than direct radiography, the mortality rate from gastric cancer showed no difference between the two screening methods. Hence, endoscopy likely detected relatively slowly progressing gastric cancer (mainly differentiated gastric cancer common in older adults), whereas failed to detect gastric cancer that rapidly progresses in the early stage.

Hamashima *et al*[10] performed a study, the Tottori Cohort Study, on data from gastric cancer screening by radiography and endoscopy conducted in Yonago City and

Table 5 Cox proportional hazards analyses of all cancer deaths, without gastric cancer, in individuals aged 40 to 79 years who participated in gastric cancer screening in Maebashi City, Japan, in 2006

	Screening method	Participants, *n* (%)	Cancer deaths[1], *n* (%)	Adjusted reduction rate[2]	95%CI
All participants	Radiography	11155	163	1.000	
	Endoscopy	10747	178	1.090	0.8813–1.3480
Participants receiving annual screening after 2006	Radiography	6773	86	1.000	
	Endoscopy	3832	68	1.284	0.9334–1.7650

[1]Gastric cancer deaths are not included.
[2]Adjusted for sex and age group (40–59 years and 60–79 years).

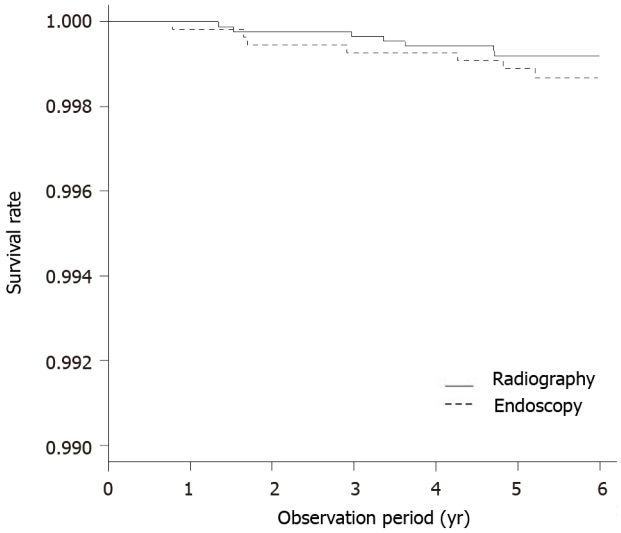

Figure 3 Survival curves of gastric cancer deaths in individuals aged 40 to 79 years old who participated in gastric cancer screening in Maebashi City, Japan, in 2006 and subsequently received annual screening. Survival curves are adjusted for sex and age group (40–59 years and 60–79 years). No significant difference was observed in the 5-year survival rate between the direct radiography and the endoscopy groups (P = 0.280).

Tottori City in 2007 and 2008[10]. This study included people aged 40 to 79 years who had not participated in gastric cancer screening in the previous year and followed them until the end of 2013 by using data from the Tottori Prefectural cancer registry. The authors reported that endoscopic screening reduced the gastric cancer mortality rate by 67% compared with radiographic screening[10]. In contrast, our study results found that the introduction of endoscopy in an organized gastric cancer screening program did not significantly reduce the gastric cancer mortality rate compared with direct radiographic screening. In Tottori Prefecture, institutions are allowed to conduct endoscopic screening if they perform at least 50 endoscopies annually, submit arbitrary endoscopic films, and attend seminars specified by the Tottori Prefecture Health Promoting Council[11]. In Maebashi City, institutions do not have to fulfill any particular eligibility criteria, and all of the institutions wishing to conduct endoscopic screening are allowed to participate in the gastric cancer screening program. Accordingly, the institutions conducting endoscopic screening in Yonago City and Tottori City may have achieved higher accuracy than those in Maebashi City, which may explain the inconsistent findings between the Tottori Cohort Study and our study.

Endoscopy of the upper gastrointestinal tract has become the more common evaluation method in routine clinical care in Japan. In 2014, endoscopies were performed in 527086 patients *per* month at hospitals and in 378195 patients *per* month at general clinics; and in 2017, in 572409 and 500447 patients *per* month, respectively. Thus, the use of endoscopy has increased markedly in recent years, especially at general clinics[12].

In Japan, endoscopies are not always performed by endoscopists with specialized training in the procedure, particularly at general clinics, and most of the general clinics in Maebashi City that routinely perform endoscopies participated in the 2006 gastric

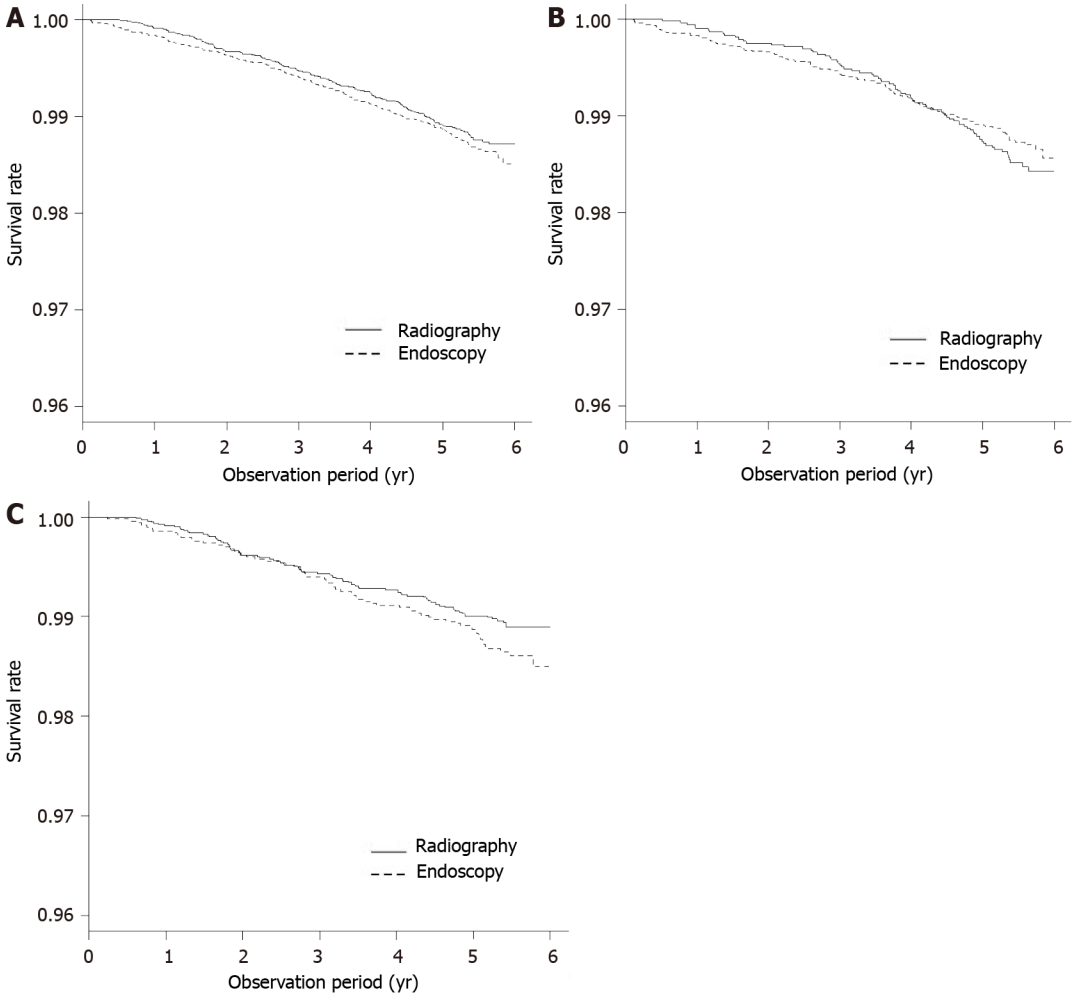

Figure 4 Survival curves of all cancer deaths, other than gastric cancer, in individuals aged 40 to 79 years old who participated in gastric cancer screening in Maebashi City, Japan, in 2006. Survival curves are adjusted for sex and age group (40–59 years and 60–79 years). A: All participants; B: Participants not receiving annual screening; C: Participants receiving annual screening. No significant differences were observed in the 5-year survival rate between the direct radiography and the endoscopy groups in both A and B (A: $P = 0.249$, B: $P = 0.509$). A significant difference was observed between the direct radiography and the endoscopy groups in C ($P = 0.038$).

cancer screening. In this study, endoscopies were performed by endoscopy experts only at 22 of the 82 participating clinics. Shimodate *et al*[13] reported that expert physicians certified by the Japan Gastroenterological Endoscopy Society detected gastric cancer in 1462 patients and that the gastric cancer lesions had been missed in the previous endoscopies in 157 of these patients; in 13 of the 157 patients, the lesion had progressed to advanced gastric cancer at the time of detection. Hosokawa *et al*[14] evaluated the precision of endoscopy for cancer detection and found a false-negative rate during the three years after endoscopy of 22.2%. They also reported that the false-negative rate was higher when the screening doctors had less experience. However, false-negative results were observed in 19.6% of patients even when the endoscopy was performed by trained doctors certified by the Japan Gastroenterological Endoscopy Society. In recent years, the quality of endoscopy devices and their images has increased substantially, but to our knowledge, no study has clarified whether the false-negative rate of diagnosing cancer has decreased.

Physicians of varying skill levels participate in endoscopic gastric cancer screening. Therefore, secondary review of endoscopic images by physicians who are board-certified by the Japan Gastroenterological Endoscopy Society is considered mandatory to compensate for any skill gaps among physicians and to standardize image interpretation[11]. Secondary review of endoscopic images was reported to decrease failures in identifying cancer and reduce the number of unnecessary biopsies[15,16]. Nevertheless, double-checking of images cannot achieve its mission if the inside of the stomach has not been thoroughly and systematically investigated and photographed and if a lesion site is missed during photography or the lesion image is unclear. A study that examined previously taken images to find reasons for false-negative cases

found that the physician had failed to take an image of the lesion site in 16.4% of the cases, even at institutions where a trained doctor certified by the Japan Gastroenterological Endoscopy Society was available[14]. An earlier study we performed also found that no endoscopic image was taken of the lesion site in 39.5% of the false-negative cases among participants in the 2006 to 2007 gastric cancer screening[17].

The "Manual for Organized Gastric Endoscopic Screening" published by the Japanese Society of Gastrointestinal Cancer Screening specifies that physicians who are qualified to perform endoscopic gastric cancer screening include expert physicians certified by Japanese endoscopy-related medical societies, physicians who have been performing endoscopies in at least 100 individuals annually, and physicians who have at least the equivalent ability to investigate the stomach and take endoscopic images [11]. This level of experience and skill in performing endoscopies is necessary to completely monitor and photograph the inside of the stomach so that the number of false-negative results of gastric cancer screening can be reduced as far as possible.

The efficacy of radiographic screening in reducing mortality has been well verified. A recent study found that the efficacy of radiographic screening in reducing gastric cancer mortality rate is equivalent to that of endoscopic screening[18]. In contrast, another study found that radiographic screening did not show efficacy in reducing the gastric cancer mortality rate[19]. The Japan Gastroenterological Endoscopy Society has recommended "a new radiography method" based on a double-contrast examination that uses high-density, low-viscosity barium sulfate[20]. Radiographic screening by this new method was reported to increase the detection rate of early cancer and reduce the requirement rate for detailed examinations when compared with the conventional screening method that uses medium-density barium sulfate[21,22].

The maximum follow-up period in our study was 5 years and 11 mo (*i.e.*, 71 mo). Early cancer was reported to become advanced cancer over 44 mo and to lead to death over 75 mo[23]. The Tottori Cohort Study showed a significant difference in gastric cancer mortality rate from 3 years after the screening. Therefore, the present study may have had a different result if the follow-up period were longer.

In the present study, we were unable to evaluate the difference between the two screening methods based on the number of times participants had previously undergone gastric cancer screening because we did not know how many participants newly received endoscopic screening after receiving direct radiographic screening in the previous year. Participants in the screening program were allowed to choose the screening method freely and could change the screening method from year to year, so we also had difficulties acquiring the history of participation in each screening method. Therefore, in the present study, we divided the participants into three analysis groups: The whole group of participants, participants who had also participated in the screening in the previous year, and participants who had not participated in the previous year. We conducted survival curve analyses for each of these three analysis sets and calculated gastric cancer mortality and the proportional HR for the mortality rate for any cancer other than gastric cancer. For the mortality rate from any cancer other than gastric cancer, among participants who had also participated in the screening in the previous year, survival analysis detected a difference between individuals undergoing direct radiography and individuals undergoing endoscopy. However, no difference was found with the Cox proportional hazard model. This may be due to slight differences in demographic characteristics between the two screening groups for participants who had also participated in screening the year prior. The reason for this may be as follows. When comparing the screening database *vs* the cancer registration, patients diagnosed with cancer prior to the study period were excluded in both groups. However, the quality of the cancer registration was low, and, therefore, cancer patients may have been included in the analysis set, resulting in a bias. Hence, for participants who had also participated in screening the previous year, differences in demographic characteristics between screening groups may exist for those with gastric cancer mortality. However, this effect is considered less significant when restricted to gastric cancer.

The analyses revealed no significant difference between the screening methods in any of the analysis sets, suggesting no noteworthy difference in the history of undergoing either of the two screening methods.

Stage IA gastric cancer detected by endoscopy was treated by ESD in 70% of the participants who were found to have a lesion. Intramucosal gastric cancer was more commonly detected by endoscopic screening. On the other hand, all cases of stage IA cancer detected by direct radiographic screening were treated by gastrectomy. Therefore, introducing direct radiographic screening and endoscopic screening has made it possible to detect gastric cancer in earlier stages. The Maebashi City gastric cancer screening detected higher percentages of stage III and IV gastric cancers than those

reported by other authors. Six of the seven participants who were found by endoscopic screening to have a stage IV lesion, and both of the participants who were found by endoscopic screening to have a stage IIIB lesion, had initially undergone endoscopic screening, and five participants who were found by direct radiography to have stage IV cancer and one of the four participants who were found by direct radiography to have stage IIIB cancer had initially undergone direct radiographic screening. We previously reported that stage III and stage IV cancers were more often detected among participants who reported the presence of stomach pain or appetite loss or both on the medical questionnaire for gastric cancer screening[24]. The Maebashi City gastric cancer screening may have included a larger number of participants with such symptoms, even though people with these symptoms are normally supposed to undergo examination at a clinical practice rather than gastric cancer screening.

Endoscopy is able to detect early gastric cancers more frequently than direct radiography, and endoscopic detection of early cancer may be related to overdiagnosis of gastric cancer. In fact, the number of gastric cancers detected by endoscopic screening has previously been reported to be twice the predicted number[25]. Moreover, endoscopic screening detected gastric cancer in a very large number of participants aged 80 years or over. Therefore, the gastric cancer screening system in Japan should be amended to provide an upper age limit.

Infection with *Hp*, current smoking, and salt and alcohol intake are known risk factors of gastric cancer. A previous study reported odds ratios of 2.56 for *Hp* infection, 1.61 for current smoking, 1.34 for salt intake, and 1.19 for alcohol intake[26]. We did not investigate the presence of *Hp* infection in participants in the 2006 Maebashi City gastric cancer screening because testing for *Hp* infection only began to be covered by health insurance in 2013. We also did not investigate smoking, salt intake, or drinking habits. Smoking and alcohol drinking are also risk factors for other cancers, but the present study found no significant difference between the two screening methods in terms of mortality rate from any cancer, which indicates that our comparison of the two screening methods had no risk factor-related bias.

The number of participants undergoing direct radiographic gastric cancer screening has decreased since its peak of 6.9 million or more in 2012[27]. Therefore, the introduction of endoscopic screening was needed to attain the government's target participation rate of 50%. In Maebashi City, in 2003, a total of 18494 citizens (equivalent to a participation rate of 15.8%) participated in gastric cancer screening by direct radiography alone. In 2015, when endoscopic screening was introduced, the number of participants increased to 33607 (participation rate, 28.8%). Nevertheless, it will be challenging to increase the participation rate further if the current screening system remains as it is now, partly because of the lack of qualified staff to perform the screening procedures. We need to establish a screening system that corresponds to the risk of developing gastric cancer and conduct gastric cancer screening efficiently, taking into account a possible reduction in the incidence rate of gastric cancer associated with a reduction in the incidence rate of *Hp* infection.

The present study had some limitations. First, because of the low reporting rate to the Gunma Prefecture cancer registry in 2006, we were unable to determine whether the gastric cancer incidence rate in screening participants was similar across the two screening methods, even though we were able to collect information on cancer deaths from death certificates. Therefore, the incidences of gastric cancer may not be completely accurate. Second, the group of participants undergoing endoscopic screening was highly likely to include a large number of people who had been instructed to undergo endoscopy because of the result of their previous direct radiographic screening; however, we were not able to collect such data. Third, compliance with the screening operation manual and precision control, including secondary review, were insufficient because the present screening was conducted at an early stage after the introduction of endoscopic screening. Because of these limitations, the usefulness of endoscopic screening should be further evaluated in a larger number of participants. In addition, we expect that future studies will examine this topic in regions where endoscopic screening has been newly introduced.

CONCLUSION

We used the data from the Maebashi City gastric cancer screening program in 2006 to compare the efficacy of direct radiography and endoscopy in reducing the gastric cancer mortality rate. In Maebashi City, a larger number of older adults participated in endoscopic gastric cancer screening than in direct radiographic screening. As a result,

endoscopic screening detected more early gastric cancers than direct radiographic screening; however, the mortality rate showed no significant difference between the two screening methods. For future gastric cancer screening, physicians' technical level gap across screening institutions should be corrected, and physicians' interpretation accuracy in secondary review should also be further supported.

ARTICLE HIGHLIGHTS

Research background

Gastric cancer is among the leading causes of cancer mortality worldwide, including in Japan. Initiatives have been implemented to lower the mortality rate of gastric cancer in Japan, including mass screening programs. In 2015, guidelines were revised to recommend endoscopy.

Research motivation

In Maebashi City, endoscopic gastric cancer screening was introduced in 2004, allowing eligible participants to choose between direct radiography and endoscopy. Comparing outcomes is essential to reduce gastric cancer mortality and ensure an effective and efficient screening program.

Research objectives

This study aimed to assess whether the mortality rate from gastric cancer decreased after the introduction of endoscopic screening in Maebashi City and compare gastric cancer mortality rates between screening methods.

Research methods

A retrospective analysis of the Maebashi City Gastric Cancer Screening Program in 2006 was conducted. Participants aged 40 to 79 were screened by direct radiography (n = 11155) or endoscopy (n = 10747) and followed until March 31, 2012. Data was cross-referenced against the Gunma Prefecture cancer registry data. The detection rate of gastric cancer and gastric cancer mortality rate were compared between the two screening groups.

Research results

Gastric cancer detection rate for direct radiography was 0.20% and 0.48% for endoscopy; however, endoscopic screening detected a higher number of early-stage cancers that may not have resulted in death. No significant difference in gastric cancer mortality rate was found between participants who underwent annual screening and those who did not. In addition, no significant difference was found in gastric cancer mortality rate between direct radiographic screening and endoscopic screening (P = 0.285). The five-year survival by the Kaplan-Meier method was 0.998 (95%CI: 0.998–0.999) in individuals who underwent direct radiography and 0.998 (95%CI: 0.997–0.999) in individuals who underwent endoscopy.

Research conclusions

No significant difference in gastric cancer mortality rate was found between direct radiographic screening and endoscopic screening. Screening programs should address gaps in endoscopists' skill levels across screening institutions to ensure the quality of endoscopic examination. Finally, an efficient gastric cancer screening system should consider gastric cancer risk by combining endoscopic and radiographic screening.

Research perspectives

Further research with a larger number of participants and high-quality cancer incidence data is needed to better clarify the usefulness of population-based endoscopic screening.

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