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Effectiveness of endoscopic screening for gastric cancer: The Japan Public Health Center-based Prospective Study

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Abstract

Upper gastrointestinal endoscopy for gastric cancer screening has been implemented in Japan. However, its effectiveness for gastric cancer prevention has not been fully studied. We aimed to investigate the effectiveness of endoscopic screening to reduce mortality from gastric cancer. In a large prospective population-based cohort study including 80,272 participants, we compared the risk of mortality and incidence of gastric cancer among participants who underwent endoscopic or radiographic screening compared with those who did not undergo any screening using multivariable Cox proportional hazards models. In the 1,023,364 person-year observation period (median; 13.0 years), 1977 cases of gastric cancer were diagnosed, and 783 patients with gastric cancer died. In the endoscopic screening group, the mortality from gastric cancer and incidence of advanced gastric cancer were reduced by 61% (hazard ratio [HR] = 0.39 [95% CI: 0.30–0.51]) and 22% (HR = 0.78 [95% CI: 0.67–0.90]), respectively. The radiographic screening reduced the mortality from gastric cancer (HR = 0.63 [95% CI: 0.54–0.73]), but its effectiveness was lower than that of endoscopic screening. In conclusion, endoscopic screening reduced the incidence of advanced gastric cancer and mortality from gastric cancer in the Japanese population.

KEYWORDS
endoscopic screening, gastric cancer, population-based prospective cohort study, radiographic screening

1 | INTRODUCTION

Gastric cancer remains a cancer of global importance, causing an estimated 769,000 deaths in 2020 with the fourth-highest mortality rate worldwide. It is the most commonly diagnosed cancer, especially in Central and East Asian countries.[1] In Japan, although the gastric cancer-related mortality rate has decreased over past decades, ~45,000 people die annually,[2] emphasizing the importance of the prevention of gastric cancer.

In Japan, the publication of gastric cancer screening guidelines in 2005 led to the initiation of a nationwide program. In a population-based screening, an upper gastrointestinal series with barium meal

Abbreviations: BMI, body mass index; CI, confidence interval; FU, follow-up; HR, hazard ratio; JPHC, Japan Public Health Center-based Prospective Study; METs, metabolic equivalent of tasks; PHC, public health center; Q05, 5-year Questionnaire; Q10, 10-year Questionnaire.

(i.e., radiographic screening) was the mainstream, but in clinical practice, endoscopic examination has been introduced for opportunistic screening and population-based screening in several municipalities.[3] Although a nationwide endoscopic screening program was introduced in 2016, providing biennial endoscopic screening for people aged 50 years and older,[3] the effectiveness of endoscopic screening has not been fully examined in Japan. In a recent meta-analysis including six cohort studies[4–9] and four nested case–control studies[10–13] in Asian countries, endoscopic screening reportedly reduced the mortality from gastric cancer.[14] However, since there have been only two prospective cohort studies[6,9] both of which were small in size, large population-based prospective cohort studies were needed.

The JPHC Study is a large-scale, population-based, prospective study in Japan consisting of 140,420 people living across Japan, which has been tracking disease incidence and mortality for over 20 years. Here, we aimed to evaluate the effectiveness of endoscopic screening in reducing the mortality from gastric cancer in Japan.

2 | MATERIALS AND METHODS

2.1 | Study cohort and participants

The JPHC Study conducted a baseline survey in 140,420 registered residents aged 40–69 years in 11 PHCs (Cohort I: Iwate, Akita, Nagano, Tokyo, Okinawa–Chubu; Cohort II: Niigata, Ibaraki, Osaka, Kochi, Nagasaki, and Okinawa–Miyako) from 1990 to 1993. The 5-year (Questionnaire 05; Q05) and 10-year (Questionnaire 10; Q10) follow-up surveys were conducted in 1995–1998 and 2000–2003, respectively. The details regarding our study design are reported elsewhere.[15] Figure 1 shows the flowchart of participants in this study. We excluded participants registered in Tokyo ($n = 7097$) who did not have any information on cancer incidence, and those who met our exclusion criteria ($n = 288$): foreign nationality ($n = 52$), relocation from the study area before the date of response to the baseline survey ($n = 188$), incorrect date of birth ($n = 7$), loss to follow-up ($n = 29$), and duplicate registration ($n = 12$). After excluding non-respondents for Q05 ($n = 32,040$), 86,243 of 100,995 participants (85.4%) responded to Q10. We further excluded those who had been diagnosed with any type of cancer ($n = 1370$) or had a self-reported history of any cancers ($n = 4124$) before the start of follow-up, who had relocated overseas or died before the start of follow-up ($n = 23$), or who had unknown total energy intake ($n = 454$). The final analysis cohort comprised 80,272 participants.

2.2 | Exposure definition

Participants responded to the self-administered questionnaire with answers of "Yes (received gastric radiography or gastric endoscopy within 1 year of the date of questionnaire response)" or "No" at Q05 and Q10, respectively. Based on each answer, the participants were classified into the radiographic or endoscopic screening groups for Q05 and Q10. At the time of the answers to Q05 and Q10, that is, from 1995 to 2003, in Japan, radiological screening was performed according to the standard method designated by academic societies (photofluorography of the stomach with 10×10 cm miniature films and seven exposures or full-size X-ray test of the stomach),[16] and standard methods for endoscopic screening had not been established. Participants who selected both radiographic and endoscopic screening on the same questionnaire were placed into the radiographic screening group, because endoscopic examination was performed after a positive radiographic screening. The participants who responded that they had not undergone either screening were classified as the unscreened group. The numbers of participants in the unscreened, radiographic screening, and endoscopic screening groups were 44,673 (55.7%), 29,626 (36.9%), and 5973 (7.4%), respectively, at Q05; and 46,548 (58.0%), 24,968 (31.1%), and 8756 (10.9%), respectively, at Q10. In the primary analysis, participants who underwent endoscopic screening at least once on Q05 and/or Q10 were defined as the endoscopic screening group ($n = 12,186$), those who underwent only radiographic screening on Q05 and/or Q10 were defined as the radiographic screening group ($n = 33,770$), and those who were not screened at either Q05 or Q10 were defined as the unscreened group ($n = 34,316$) (Table S1).

2.3 | Follow-up and case identification

The participants were followed-up from the baseline survey until the end of follow-up (December 31, 2012 for Suita, December 31, 2013 for Kochi and Nagasaki, and December 31, 2015 for other PHC areas). In Japan, resident and death registration are required by law, and complete resident registration is performed. The resident registration was checked annually at the resident registry maintained by the municipality in each study area. The participants who relocated from the study area were checked at the municipal office of the new location. We confirmed the information regarding the cause of death with permission from the Ministry of Health, Labour and Welfare. Causes of death were classified based on the International Classification of Diseases 10th edition (ICD-10). Cancer incidence was identified by active patient notification from the major regional hospitals in the study area and data linkage to population-based cancer registries, with the permission of the local government responsible for the cancer registry. Information from death certificates was used as a supplementary source of information. Cancer cases were coded using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3). Gastric cancer cases were identified by codes C16.0–C16.9 of the ICD-O-3. For cancer incidence analysis, carcinoma in situ (high-grade dysplasia or cancer cells only in the top layer of mucosal cells that have not grown into the deeper tissue layers such as the lamina propria) and advanced carcinoma were defined separately. Gastric cancer cases were classified by stage into localized, metastasis to regional lymph nodes, metastasis

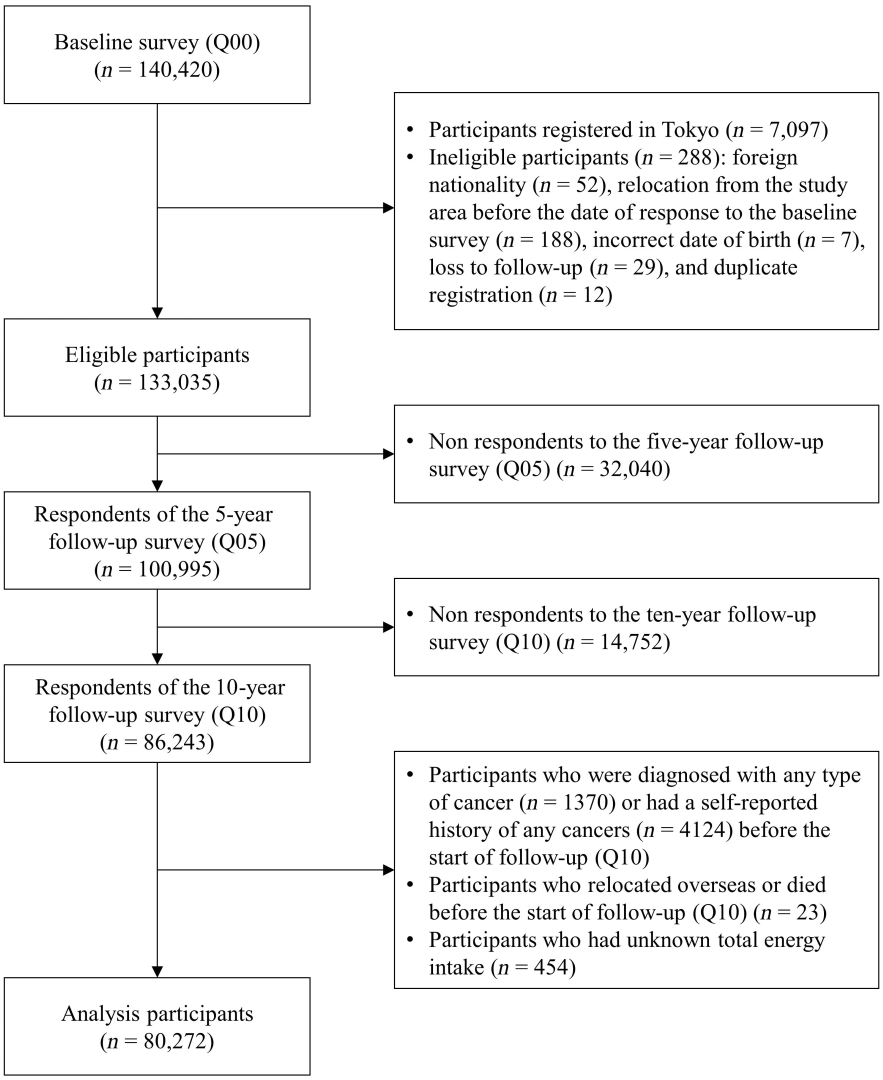

FIGURE 1 Flowchart of study participants

to adjacent organs, metastasis to distant organs, or unknown. If two or more cancers were diagnosed in one participant, the first cancer was used for the analysis.

2.4 | Statistical analysis

Baseline characteristics of study participants according to screening groups were based on information at the start of follow-up (Q10) and compared between groups using the Kruskal–Wallis test or chi-squared test, whichever was appropriate.

The Cox proportional hazards model was used to calculate HRs and 95% CIs to describe the risk of mortality and cancer incidence associated with the radiographic and endoscopic screening groups. For mortality analysis, person-years of follow-up for each participant were calculated from the date of response to Q10 and censored at the date of death, relocation from the study area, or the end of the follow-up, whichever occurred first. For cancer incidence analysis, person-years of follow-up for each participant were calculated from the date of response to Q10 and censored at the date of any cancer diagnosis, death, relocation from the study area, or the end of follow-up, whichever occurred first.

The participants were categorized into three groups (the unscreened group, the radiographic screening group, and the endoscopic screening group) according to their screening status in Q05 and Q10 with the unscreened group as the reference. Moreover, the radiographic screening group and the endoscopic screening group were divided according to the time of the screening (at the beginning of follow-up [Q10] or 5 years before the start of follow-up [Q05]) to evaluate the impact of more recent screening (Table S1).

Model 1 was adjusted for sex, age (<55, 55–60, 60–65, 65–70, or >70), and study area (10 PHC areas). Model 2 was further adjusted for smoking status (never, former, current, or unknown), alcohol drinking status (never, former, current, or unknow), BMI (<18.5, 18.5–25, 25–30, or >30 kg/m^2), history of diabetes mellitus, gastric ulcer, and gastric polyp (yes/no), quintiles of METs (METs hours/day), intake of vegetables, fruits, red meat, fish and salt (quartile of energy-adjusted intake), and coffee and tea intake (<1 cup/week, >1 cup/week, 1–3 cups/day, >4 cups/day, or unknown). Information on the covariates above was defined based

on the responses to Q10. Smoking status was defined by the response to the question, "Do you currently smoke cigarettes?"; "Smoking" as current smoker, "Quit" as former smoker, "Never" as never smoker, and no response as unknown. Drinking status was similarly defined by the responses to the question, "Do you currently drink alcohol?". The intake of food and salt was estimated from a food frequency questionnaire and adjusted for total energy using the residual method.[17] METs hours/day was estimated by multiplying the time score spent at each activity/day by its MET intensity.[18]

A stratified analysis by sex and age categories (<60, 60–70, and >70) was also conducted to examine effect modification by sex and age. Furthermore, a sensitivity analysis was performed by excluding participants who died or were diagnosed with any cancers within 3 years after the beginning of follow-up (date of response to Q10).

All reported *p*-values were two sided, and the significance level was set at $p < 0.05$. All statistical analyses were performed using Stata version 16.0 (Stata Corporation, College Station, TX, USA).

3 | RESULTS

During the 1,023,364 person-years observation period (median; 13.0 years), 18,888 participants died. Of these, 783 (4.2%) died of gastric cancer and 5372 (28.4%) died of other cancers. The other major causes of death were diseases of the circulatory system (5099; 27.0%) and the respiratory system (2435; 12.9%). During the observation period, 12,131 participants were diagnosed with any cancer, of which 1977 participants (16.3%) had gastric cancer.

The baseline characteristics of study participants are shown in Table 1. Compared with the unscreened group, the proportion of men and participants aged 55 to 70 years was higher in the radiographic screening group and the endoscopic screening groups. The endoscopic screening group had a higher percentage of participants with normal BMI (18.5–25). The participants who underwent radiographic screening or endoscopic screening were less likely to be current smokers and had a higher intake of vegetables and fruits than the unscreened group. The endoscopic screening group also had a greater history of diabetes, gastric ulcers, and gastric polyps and cholesterol medications use. There were no apparent differences in salt intake or physical activity. In addition, we compared *Helicobacter pylori* (*H. pylori*) infection and the severity of atrophic gastritis in 15,414 (19.2%) participants for whom blood samples were available at the baseline survey. *H. pylori* infection and atrophic gastritis were defined using blood anti-*H. pylori* IgG titers or pepsinogen (PG) I and II, respectively. The results showed that the proportion of *H. pylori* seropositivity and severity of atrophic gastritis were not significantly different in each group (Table S2).

The HRs of mortality for gastric cancer according to screening groups are shown in Table 2. In the multivariable model (Model 2), compared with that of the unscreened group, the mortality from gastric cancer was significantly lower, 37% (HR = 0.63 [95% CI: 0.54–0.73]) and 61% (HR = 0.39 [95% CI: 0.30–0.51]) in the radiographic and the endoscopic screening groups, respectively. All-site cancer mortality and all-cause mortality were also 17% (HR = 0.83 [95% CI: 0.78–0.88]) and 21% (HR = 0.79 [95% CI: 0.76–0.82]) lower in the radiographic screening group and 14% (HR = 0.86 [95% CI: 0.79–0.94]) and 18% (HR = 0.82 [95% CI: 0.79–0.86]) lower in the endoscopic screening group. In both screening groups, the reduction in the risk of gastric cancer-specific mortality was sufficiently greater than the reduction in the risk of all-cause mortality or all-cancer mortality. Endoscopic screening was more effective than radiographic screening in reducing death from gastric cancer. In a sensitivity analysis (Table 2), excluding cases who died or were diagnosed with any cancers during the first 3 years of follow-up did not change the results of the multivariable models (Model 2).

To ensure the exposure definition of the endoscopic screening group is plausible, we conducted two sensitivity analysis. First, to exclude participants who may have had some symptoms and underwent endoscopy for diagnostic purpose, the analysis excluded participants with a history of gastric ulcer or gastric polyps, or gastric surgery. The results showed that the mortality from gastric cancer was significantly lower, 64% (HR = 0.36 [95% CI: 0.26–0.49]) in the endoscopic screening groups compared with the unscreened group. This result was unchanged from that of the primary analysis (HR = 0.39 [95% CI: 0.30–0.51]). Second, we divided the endoscopic screening group into two groups: those who had received an endoscopy in both Q05 and Q10, and those who had received an endoscopy group in either Q05 or Q10 only. Compared with the unscreened group, the mortality from gastric cancer was significantly lower, 63% (HR = 0.37 [95% CI: 0.28–0.51]) and 55% (HR = 0.45 [95% CI: 0.28–0.73]) in the endoscopy in either Q05 or Q10 only and the endoscopy in both Q05 and Q10, respectively, with no significant differences between the two groups.

Gastric cancer at diagnosis included 10.6% carcinoma in situ and 54.1% localized cancer. The proportion of carcinoma in situ and localized carcinoma was higher in the radiographic and endoscopic screening groups than was that in the unscreened group (Table S3). The HRs of incidence for gastric cancer according to screening groups are shown in Table 2. In the multivariable model (Model 2), compared with that of the unscreened group, the incidence of gastric cancer was 6% (HR = 0.94 [95% CI: 0.85–1.04]) and 12% (HR = 0.88 [95% CI: 0.77–1.01]) lower, exhibiting a marginal significance, in the radiographic and endoscopic screening groups, respectively.

To examine the impact of screening on cancer incidence in detail, we divided cancers into carcinoma in situ and advanced cancers (Table 3). Compared with that in the unscreened group, the incidence of advanced gastric cancer was significantly reduced by 12% (HR = 0.88 [95% CI: 0.79–0.98]) and 22% (HR = 0.78 [95% CI: 0.67–0.90]) in the radiographic and endoscopic groups in Model 2, respectively. In contrast, there was a significant increase in the incidence of carcinoma in situ of the stomach in the radiological screening group (HR = 2.04 [95% CI: 1.43–2.91]) and in the endoscopic screening group (HR = 2.31 [95% CI: 1.54–3.47]).

To examine the differences in the effect of radiographic and endoscopic screening on reducing the mortality from gastric cancer

TABLE 1 Baseline characteristics of the study population according to the screening groups

	Unscreened (n = 34,316)	Radiography (n = 33,770)	Endoscopy (n = 12,186)	p-value[a]
Sex, %				
Male	43.3	47.2	47.7	<0.001
Female	56.7	52.9	52.3	
Age at follow-up start (year), %				
50–55	24.0	21.4	21.7	<0.001
55–60	20.7	21.0	21.0	
60–65	18.6	19.9	20.4	
65–70	19.4	21.8	22.5	
>70	17.3	16.0	14.5	
Body mass index (kg/m^2), %				
<18.5	3.3	2.8	3.6	<0.001
18.5–25	65.2	66.4	69.5	
25–30	25.4	26.2	23.0	
>30	3.0	2.5	2.0	
Unknown	3.2	2.1	1.9	
Smoking status, %				
Never	62.9	63.6	62.2	<0.001
Former	12.7	15.6	17.3	
Current	22.2	19.0	19.2	
Unknown	2.3	1.8	1.4	
Alcohol drinking status, %				
Never	51.7	47.9	47.7	<0.001
Former	4.1	3.5	3.7	
Current	41.9	46.9	47.1	
Unknown	2.4	1.7	1.4	
Past history (yes), %				
Diabetes	6.2	6.3	7.1	0.001
Gastric ulcer	3.3	6.5	14.1	<0.001
Gastric polyp	1.1	4.3	9.0	<0.001
Dietary intake (g/day)[b], median (IQR)				
Vegetable	187 (117–284)	200 (126–299)	212 (138–314)	<0.001
Fruits	143 (63–257)	152 (76–259)	165 (87–270)	<0.001
Red meet	31 (15–54)	31 (15–52)	29 (15–48)	<0.001
Fish	59 (33–93)	60 (35–91)	63 (38–94)	<0.001
Salt	11 (8–13)	11 (9–13)	11 (9–13)	<0.001
Coffee drinker, %				
0 to <1/week	18.8	18.4	20.8	<0.001
>1/week to <1/day	22.9	25.4	26.5	
>1/day	34.0	35.3	31.2	
Unknown	24.3	20.9	21.5	
Tea drinker, %				
0 to <1/week	19.3	16.6	12.9	<0.001
>1/week to <1/day	13.1	13.6	11.4	
>1/day	54.8	59.2	66.1	
Unknown	12.8	10.6	9.6	
Physical activity (METs/day)[c], median (IQR)	40 (27–43)	40 (29–43)	40 (29–43)	<0.001
Cholesterol medications use (yes), %	7.9	10.2	11.0	<0.001

Note: Continuous data are presented as median (IQR; interquartile range) and categorical variables are presented as percentage (%).

[a]Kruskal–Wallis test for continuous variables and chi-squared test for categorical variables.

[b]Dietary intake adjusted for total energy intake using the residual method.

[c]Physical activity expressed as metabolic equivalent of task (MET) hours per day.

TABLE 2 HRs of mortality and incidence for gastric cancer according to screening groups

	Unscreened (n = 34,316)	Radiography (n = 33,770)	Endoscopy (n = 12,186)
Mortality			
Gastric cancer			
Cases	422	289	72
Rate[a] (95% CI)	99 (90–109)	66 (59–74)	45 (36–57)
Model 1 HR (95% CI)	Ref.	0.60 (0.52–0.69)	0.47 (0.38–0.58)
Model 2 HR (95% CI)	Ref.	0.63 (0.54–0.73)	0.39 (0.30–0.51)
Model 2 HR (95% CI)[b]	Ref.	0.62 (0.53–0.72)	0.39 (0.30–0.51)
All-site cancer[c]			
Cases	2462	2114	796
Rate[a] (95% CI)	577 (555–601)	484 (464–505)	497 (464–533)
Model 1 HR (95% CI)	Ref.	0.79 (0.74–0.83)	0.81 (0.75–0.88)
Model 2 HR (95% CI)	Ref.	0.83 (0.78–0.88)	0.86 (0.79–0.94)
Model 2 HR (95% CI)[b]	Ref.	0.83 (0.78–0.88)	0.86 (0.79–0.94)
All-cause[c]			
Cases	8533	6967	2605
Rate[a] (95% CI)	2001 (1959–2044)	1595 (1558–1633)	1628 (1567–1692)
Model 1 HR (95% CI)	Ref.	0.74 (0.72–0.77)	0.78 (0.74–0.82)
Model 2 HR (95% CI)	Ref.	0.79 (0.76–0.82)	0.82 (0.79–0.86)
Model 2 HR (95% CI)[b]	Ref.	0.79 (0.77–0.82)	0.82 (0.78–0.86)
Incidence			
Gastric cancer			
Cases	812	841	324
Rate[a] (95% CI)	198 (185–212)	202 (189–216)	214 (192–239)
Model 1 HR (95% CI)	Ref.	0.93 (0.85–1.03)	0.89 (0.78–1.01)
Model 2 HR (95% CI)	Ref.	0.94 (0.85–1.04)	0.88 (0.77–1.01)
Model 2 HR (95% CI)[b]	Ref.	0.92 (0.83–1.02)	0.84 (0.73–0.98)
All-site cancer[c]			
Cases	4212	4231	1711
Rate[a] (95% CI)	1027 (997–1059)	1017 (987–1048)	1133 (1080–1188)
Model 1 HR (95% CI)	Ref.	0.95 (0.91–0.99)	1.03 (0.97–1.09)
Model 2 HR (95% CI)	Ref.	0.97 (0.93–1.01)	1.04 (0.98–1.11)
Model 2 HR (95% CI)[b]	Ref.	0.95 (0.91–1.00)	1.04 (0.97–1.11)

Note: Model 1. Cox proportional hazards regression models was adjusted for sex, age (<55, 55–60, 60–65, 65–70, or >70) and study area (10 PHC areas). Model 2 was further adjusted for smoking status (never, former, current, or unknown), alcohol drinking status (never, former, current, or unknown), body mass index (<18.5, 18.5–25, 25–30, or >30 kg/m^2), history of diabetes mellitus, gastric ulcer, and gastric polyp (yes/no), quintiles of metabolic equivalent of task (METs hours/day), intake of vegetables, fruits, red meat, fish and salt (quartile of energy-adjusted intake), and coffee and tea intake (<1 cup/week, >1 cup/week, 1–3 cups/day, >4 cups/day, or unknown).

Abbreviations: CI, confidence interval; HR, hazard ratio; METs, metabolic equivalents; PHC, Public Health Centers; Ref, reference.

[a]Rates are per 100,000 person-years.

[b]Sensitivity analysis excluded participants who died and were diagnosed with any cancers within 3 years after the follow-up start.

[c]Excluding gastric cancer.

between men and women and among age groups, we performed a stratified analysis. The reduction in mortality of gastric cancer was confirmed in both sexes and all age groups, with no significant interactions by sex and age. In the stratified analysis of all-cause mortality by age group, the interaction was significant. The reduction in all-cause mortality was greater in the 60 years or younger group (Table S4).

To evaluate the impact of more recent screening, the radiographic and endoscopic screening groups were divided according to the time of the screening (at [Q10; 2000–2003] or 5 years before [Q05; 1995–1998] the beginning of follow-up) (Table 4). The HRs for gastric cancer mortality in the groups that underwent endoscopic screening at the beginning and 5 years before the beginning of

TABLE 3 HRs for incidence of gastric cancer by stage according to screening groups

	Unscreened (n = 34,316)	Radiography (n = 33,770)	Endoscopy (n = 12,186)
Advanced cancer			
Cases	762	738	258
Rate[a] (95% CI)	186 (173–200)	177 (165–191)	171 (151–193)
Model 1 HR (95% CI)	Ref.	0.87 (0.78–0.96)	0.78 (0.67–0.90)
Model 2 HR (95% CI)	Ref.	0.88 (0.79–0.98)	0.78 (0.67–0.90)
Model 2 HR (95% CI)[b]	Ref.	0.89 (0.79–1.00)	0.79 (0.67–0.92)
Carcinoma in situ			
Cases	45	102	63
Rate[a] (95% CI)	11 (8–15)	25 (20–30)	42 (33–53)
Model 1 HR (95% CI)	Ref.	2.05 (1.44–2.92)	2.43 (1.63–3.61)
Model 2 HR (95% CI)	Ref.	2.04 (1.43–2.91)	2.31 (1.54–3.47)
Model 2 HR (95% CI)[b]	Ref.	1.86 (1.20–2.86)	1.77 (1.06–2.95)

Note: Advanced cancer does not include carcinoma in situ which are high-grade dysplasia or cancer cells only in the top layer of cells of the mucosa. Model 1. Cox proportional hazards regression models was adjusted for sex, age (<55, 55–60, 60–65, 65–70, or >70) and study area (10 PHC areas). Model 2 was further adjusted for smoking status (never, former, current, or unknown), alcohol drinking status (never, former, current, or unknown), body mass index (<18.5, 18.5–25, 25–30, or >30 kg/m^2), history of diabetes mellitus, gastric ulcer, and gastric polyp (yes/no), quintiles of metabolic equivalent of task (METs hours/day), intake of vegetables, fruits, red meat, fish and salt (quartile of energy-adjusted intake), and coffee and tea intake (<1 cup/week, >1 cup/week, 1–3 cups/day, >4 cups/day, or unknown).

Abbreviations: CI, confidence interval; HR, hazard ratio; PHC, public health center; Ref, reference.

[a]Rates are per 100,000 person-years.

[b]Sensitivity analysis excluded participants who died and were diagnosed with any cancers within 3 years after the beginning of follow-up.

follow-up were HR = 0.37 (95% CI: 0.27–0.50) and HR = 0.45 (95% CI: 0.29–0.69) in Model 2, respectively. When the HRs for all-cause and all-cancer mortality were considered, there was a reduction in gastric cancer mortality at both time points, with no difference in the impact of the timing of endoscopy screening. Similarly, in the radiographic screening groups, there was no difference in the effectiveness of the timing of screening on the reduction of mortality from gastric cancer.

4 | DISCUSSION

This population-based prospective cohort study in Japan found that endoscopic screening reduced the incidence of advanced gastric cancer and mortality from gastric cancer in the Japanese population. To our knowledge, this is the first prospective study of a large general Japanese population to evaluate the effectiveness of endoscopic screening on mortality from gastric cancer. The strengths of this study are its prospective design in a large general population with a long follow-up period and high follow-up and response rates. Moreover, the effectiveness of endoscopic screening was compared not only with an unscreened group, but also with that of radiographic screening within the same population.

In this study, at the time of the response to Q05 (1995–1998) and Q10 (2000–2003), 36.9% and 31.1% were in the radiographic screening group, and 7.4% and 10.9% were in the endoscopic screening group (Table S1). In Japan, a national program of radiological screening for gastric cancer was initiated in 1983,[3] and endoscopic screening was introduced as population-based screening for gastric cancer on a trial basis in some regions after the 1990s. Considering that endoscopic screening was introduced later than radiographic screening in Japan, it is reasonable that the endoscopic screening group was less common than the radiographic screening group during the period from Q05 (1995–1998) to Q10 (1995 to 2003) of this study. In another large population-based cohort study of Japanese residents conducted in 1988–1997 in a different region than the JPHC, the proportion of residents who underwent radiographic screening for gastric cancer was 35% (30,771/87,312).[19] The percentage of those who took the radiographic screening was close to the percentage in our study, supporting the validity of the definition of radiographic screening in our study. In addition, the percentage of the endoscopic screening group increased from 7.4% to 10.9% between Q05 and Q10 because endoscopic screening became more widely used. However, according to the Comprehensive Survey of Living Conditions by the Ministry of Health, Labour and Welfare in Japan, the percentage of persons aged 40 years or older who had undergone gastric cancer screening in the past year was 28.7% in 2007, which was lower than that in our study.[20] There are two possible reasons why the percentage of gastric cancer screening was higher in this

TABLE 4 HRs for the mortality and incidence of gastric cancer according to the timing of screening

		Radiography (n = 33,770)		Endoscopy (n = 12,186)	
	Unscreened (n = 34,316)	5 years before FU start (n = 10,166)	FU start (n = 23,604)	5 years before FU start (n = 3430)	FU start (n = 8756)
Mortality					
Gastric cancer					
Cases	422	94	195	23	49
Rate (95% CI)	99 (90–109)	73 (60–89)	63 (55–73)	51 (34–77)	43 (32–56)
Model 1 HR (95% CI)	Ref.	0.63 (0.40–1.00)	0.49 (0.34–0.70)	0.44 (0.29–0.68)	0.36 (0.27–0.49)
Model 2 HR (95% CI)	Ref.	0.70 (0.56–0.88)	0.61 (0.51–0.72)	0.45 (0.29–0.69)	0.37 (0.27–0.50)
All-site cancer[b]					
Cases	2462	701	1413	227	569
Rate[a] (95% CI)	577 (555–601)	544 (505–586)	459 (435–483)	505 (444–575)	494 (455–537)
Model 1 HR (95% CI)	Ref.	0.87 (0.80–0.94)	0.75 (0.70–0.80)	0.84 (0.73–0.96)	0.80 (0.73–0.89)
Model 2 HR (95% CI)	Ref.	0.89 (0.82–0.97)	0.79 (0.74–0.85)	0.89 (0.77–1.03)	0.85 (0.77–0.94)
All-cause[b]					
Cases	8533	2448	4519	754	1851
Rate[a] (95% CI)	2001 (1959–2044)	1900 (1826–1977)	1467 (1425–1510)	1678 (1562–1802)	1608 (1537–1683)
Model 1 HR (95% CI)	Ref.	0.86 (0.82–0.90)	0.69 (0.67–0.72)	0.82 (0.76–0.89)	0.77 (0.73–0.81)
Model 2 HR (95% CI)	Ref.	0.88 (0.84–0.92)	0.74 (0.72–0.77)	0.87 (0.80–0.93)	0.81 (0.77–0.86)
Incidence					
Gastric cancer					
Cases	812	236	605	89	235
Rate[a] (95% CI)	198 (185–212)	192 (169–218)	207 (191–224)	209 (170–257)	217 (191–246)
Model 1 HR (95% CI)	Ref.	0.90 (0.78–1.04)	0.95 (0.85–1.05)	0.89 (0.52–1.54)	1.35 (0.98–1.86)
Model 2 HR (95% CI)	Ref.	0.91 (0.78–1.05)	0.95 (0.85–1.06)	0.92 (0.74–1.16)	0.93 (0.80–1.10)
All-site cancer[b]					
Cases	4212	1266	2965	463	1248
Rate[a] (95% CI)	1027 (997–1059)	1028 (973–1086)	1013 (977–1050)	1086 (992–1190)	1151 (1089–1216)
Model 1 HR (95% CI)	Ref.	0.94 (0.88–1.00)	0.95 (0.91–1.00)	1.01 (0.91–1.11)	1.05 (0.98–1.12)
Model 2 HR (95% CI)	Ref.	0.95 (0.89–1.01)	0.97 (0.93–1.02)	1.02 (0.92–1.13)	1.06 (0.99–1.13)

Note: The radiographic screening and the endoscopic screening groups were divided according to the timing of the screening. Five years before FU start group received a screening at 5 years before the beginning of follow-up (Q05; 1995–1998) and the FU start group received a screening at the beginning of follow-up (Q10; 2000–2003). Model 1; Cox proportional hazards regression models was adjusted for sex, age (<55, 55–60, 60–65, 65–70, or >70) and study area (10 PHC areas). Model 2 was further adjusted for smoking status (never, former, current, or unknown), alcohol drinking status (never, former, current, or unknown), body mass index (<18.5, 18.5–25, 25–30, or >30 kg/m^2), history of diabetes mellitus, gastric ulcer, and gastric polyp (yes/no), quintiles of metabolic equivalent of task (METs hours/day), intake of vegetables, fruits, red meat, fish and salt (quartile of energy-adjusted intake), and coffee and tea intake (<1 cup/week, >1 cup/week, 1–3 cups/day, >4 cups/day, or unknown).

Abbreviations: CI, confidence interval; FU, follow-up; HR, hazard ratio; Ref, reference.

[a]Rates are per 100,000 person-years.

[b]Excluding gastric cancer.

study area. One is that more people in the present study area are health conscious than in other areas of Japan, and the other is that the gastric radiography and gastric endoscopy included tests for diagnostic purposes that were not for gastric cancer screening purposes.

Endoscopic screening reduced the mortality and incidence of gastric cancer by 61% and 12%, respectively. In the most recent meta-analysis and systematic review including six cohort studies and four nested case–control studies comprising 342,013 individuals from Asia,[14] the combined results indicated that endoscopic screening was associated with a 40% relative risk reduction in the gastric cancer mortality, but there was no association between endoscopic screening and incidence of gastric cancer. Although our study found that endoscopic screening reduced mortality from gastric cancer similar to the results of a meta-analysis,[14] the reduction in mortality from gastric cancer in our study was greater than that in the meta-analysis. In the meta-analysis,[14] there was significant heterogeneity because of the differences in

interventions and comparators, which may make the effectiveness of endoscopic screening appear weaker. In our study, the incidence of advanced gastric cancer significantly decreased. This might have been due to the resection of precancerous lesions of gastric cancer at the endoscopic screening. The incidence of carcinoma in situ of the stomach increased in the endoscopic screening group. This result suggests that carcinoma in situ is more likely to be detected in the endoscopic screening group. The participants in the endoscopic screening group might have undergone endoscopic screening prior to the follow-up period or might have undergone frequent endoscopic screening. We can assume that this intervention detected carcinoma in situ of the stomach at an early stage and reduced the incidence of advanced gastric cancer.

To evaluate the impact of more recent screening, we compared the status of endoscopic screening at and 5 years prior to the beginning of follow-up. The results revealed that participants who had undergone endoscopic screening at the beginning of follow-up had a slightly lower mortality rate from gastric cancer than did those who had undergone endoscopic screening 5 years prior to the beginning of follow-up. However, considering the similar trend in the reduction of all-site cancer deaths and all-cause deaths, the difference in the effect of the timing of screening on mortality reduction was not considered significant. In our study, we collected the status of endoscopic screening twice at intervals of 5 years, but the status of endoscopic screening during that period and after the beginning of follow-up was unknown. Moreover, the questionnaire only addressed the status of screening performed within 1 year of the date on which the questionnaire was answered; it did not collect the status of screening performed more than 1 year prior to the questionnaire. In Japan, biennial endoscopic screening for gastric cancer is recommended for people aged 50 years and older.[3] Because of the high frequency of endoscopic screening in Japan, it is possible that the group that received screening 5 years prior to the beginning of follow-up also included participants who underwent frequent screenings. Consequently, exposure (frequency of screening) might have been misclassified, and no difference might have been observed in the effect of more recent screening. In addition, because of the design of this study as described above, it is not possible to conclude whether the frequency of biennial endoscopic gastric cancer screening currently recommended in Japan for persons aged 50 years and older is appropriate or not.

There were several limitations to our study. First, there was a potential selection bias; that is, participants who had undergone radiographic and endoscopic screening were biased to include more health-conscious individuals, and the effect of gastric cancer screening might have been overestimated. In our stratified analysis by age, the effect of radiographic screening and endoscopic screening was significantly greater in the younger age groups. This might have been because health-conscious individuals in the younger age groups were more likely to undergo screening. However, we indirectly accounted for this potential selection bias by calculating the risk reduction for all-cause mortality except gastric cancer. This approach is useful for examining the effects of a bias that cannot be controlled using available information on known confounding factors.[19] Second, because it was a self-administered survey, the exposures and covariates might have been misclassified. Third, unadjusted potential confounders may have been present. Although *H. pylori* infection is associated with the incidence and mortality of gastric cancer,[21,22] it was not adjusted for in the multivariable analysis model. Because endoscopic examination was performed before the eradication of *H. pylori*, the endoscopic screening group might have included many participants who had undergone *H. pylori* eradication.

In conclusion, endoscopic screening reduced the incidence of advanced gastric cancer and the mortality from gastric cancer in a Japanese population. The effectiveness of endoscopic screening on reducing gastric cancer mortality was greater than that of radiographic screening.

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CONFLICT OF INTEREST

T. Sobue, M. Iwasaki, M. Inoue, and N. Sawada is an Editorial Board Member of *Cancer Science* as of 27 May 2022. The remaining authors have no conflict of interest.

DATA AVAILABILITY STATEMENT

For information on how to apply for access to JPHC data and/or biospecimens, please follow the instructions at https://epi.ncc.go.jp/en/jphc/805/8155.html.

ETHICS STATEMENT

Approval of the research protocol by an Institutional Reviewer Board: The study was conducted in compliance with the provisions of the Declaration of Helsinki. The study protocol was approved by the institutional review board of the National Cancer Center, Tokyo, Japan (13-021), and by the ethical review board of Osaka University, Osaka, Japan (14020 and 19354-2).

INFORMED CONSENT

The participants were informed of the study objectives, and those who completed the survey questionnaire were regarded as having consented to participation.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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