

# Potential capacity of endoscopic screening for gastric cancer in Japan

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## Key words

Cancer screening, capacity, gastric cancer, medical resource, upper gastrointestinal endoscopy

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In 2016, the Japanese government decided to introduce endoscopic screening for gastric cancer as a national program. To provide endoscopic screening nationwide, we estimated the proportion of increase in the number of endoscopic examinations with the introduction of endoscopic screening, based on a national survey. The total number of endoscopic examinations has increased, particularly in clinics. Based on the national survey, the total number of participants in gastric cancer screening was 3 784 967. If 30% of the participants are switched from radiographic screening to endoscopic screening, approximately 1 million additional endoscopic examinations are needed. In Japan, the participation rates in gastric cancer screening and the number of hospitals and clinics offering upper gastrointestinal endoscopy vary among the 47 prefectures. If the participation rates are high and the numbers of hospitals and clinics are small, the proportion of increase becomes larger. Based on the same assumption, 50% of big cities can provide endoscopic screening with a 5% increase in the total number of endoscopic examinations. However, 16.7% of the medical districts are available for endoscopic screening within a 5% increase in the total number of endoscopic examinations. Despite the Japanese government's decision to introduce endoscopic screening for gastric cancer nationwide, its immediate introduction remains difficult because of insufficient medical resources in rural areas. This implies that endoscopic screening will be initially introduced to big cities. To promote endoscopic screening for gastric cancer nationwide, the disparity of medical resources must first be resolved.

Gastric cancer has continued to create a serious burden worldwide, particularly in East Asian countries. Although the incidence of gastric cancer has decreased, the highest mortality rates have been reported in East Asian countries at 24 per 100 000 men and 9.8 per 100,000 women in 2012.<sup>(1)</sup> However, prevention and screening programs for gastric cancer in these countries remain lacking, except in Korea and Japan.<sup>(2)</sup>

In Korea, gastric cancer screening by upper gastrointestinal endoscopy (i.e., endoscopic screening) and upper gastrointestinal series using barium meal (i.e., radiographic screening) has been provided for the population aged 40 years and over since 2002.<sup>(3)</sup> In fact, endoscopic screening has already become the mainstream of gastric cancer screening in Korea.<sup>(4)</sup> In contrast, radiographic screening has been used as the sole national gastric cancer screening program in Japan.<sup>(5)</sup>

In 2016, the Japanese government decided to introduce endoscopic screening for gastric cancer as a national program in reference to the guidelines published by the National Cancer Center (Tokyo, Japan). In these guidelines, endoscopic screening is recommended for population-based screening based on the results of case-control studies carried out in Korea and Japan.<sup>(6)</sup> The endoscopic examinations have been provided mainly in private clinics that play a central role for upper gastrointestinal examinations in primary care. Endoscopic

examination has been carried out in clinical practice. The ideal target in the clinical setting has been limited to symptomatic patients because health insurance does not cover cancer screening for asymptomatic people. However, endoscopic examination has been used for opportunistic screening.

If endoscopic screening is to be adopted as a national program in Japan, additional endoscopic examinations are required. To our knowledge, there is still no study estimating the necessary numbers of endoscopic examinations for gastric cancer screening as a national program. In Japan, disparities of access to clinical practice have been serious issues in rural areas because of insufficient hospitals or clinics and primary care physicians. Thus, to be able to provide endoscopic screening nationwide, the estimated number of endoscopic examinations that can be used for endoscopic screening needs to be determined.

## Materials and Methods

**Data sources.** In Japan, the national government undertakes the “Survey of Medical Institutions” in September every 3 years and reports the total numbers of examinations per month.<sup>(7)</sup> From the data obtained, the total numbers of specific equipment and examinations are calculated among hospitals and clinics in the whole nation, prefectures, secondary medical

districts, and municipalities. There are three types of medical districts in Japan responsible for health care plans in regional areas. The first type is responsible for providing the usual care at the municipal level, and the third type is responsible for providing specific health care services at the prefecture levels. The second type is the actual unit that provides health care services and includes several neighborhood municipalities. In

2014, there were 341 secondary medical districts in Japan. The total number of endoscopic examinations was calculated 12 times the actual data in the Survey of Medical Institutions. The total number of endoscopic examinations and participants in gastric cancer screening among 47 prefectures are shown in Table 1.<sup>(7-9)</sup> The national average of the total number of endoscopic examinations was 260 296 per prefecture, but a huge

**Table 1. Total number of endoscopic examinations and participants in gastric cancer screening among 47 Japanese prefectures**

	Total population aged $\geq 40$ years (2014) <sup>†</sup>	Total number of endoscopic examinations (2014) <sup>‡</sup>	Number of examinations per person aged $\geq 40$ years	Total number of participants in gastric cancer screening (2012) <sup>§</sup>	Participation rate in gastric cancer screening, % (2012) <sup>§</sup>
Japan	75 168 865	12 233 892	0.16	3 784 967	5.0
Hokkaido	3 375 031	581 532	0.17	172 984	5.1
Aomori	861 206	117 648	0.14	94 730	11.0
Iwate	820 436	111 804	0.14	90 129	11.0
Miyagi	1 346 547	245 496	0.18	154 373	11.5
Akita	704 451	147 204	0.21	56 053	8.0
Yamagata	717 137	142 908	0.20	98 465	13.7
Fukushima	1 199 945	302 652	0.25	103 793	8.6
Ibaragi	1 756 734	227 028	0.13	93 547	5.3
Tochigi	1 176 388	171 696	0.15	90 028	7.7
Gunma	1 195 185	234 192	0.20	55 199	4.6
Saitama	4 185 480	472 980	0.11	142 664	3.4
Chiba	3 624 497	503 844	0.14	235 921	6.5
Tokyo	7 365 271	1 242 516	0.17	254 882	3.5
Kanagawa	5 199 367	728 136	0.14	148 274	2.9
Niigata	1 446 562	240 768	0.17	115 005	8.0
Toyama	670 203	136 824	0.20	54 288	8.1
Ishikawa	684 992	173 424	0.25	37 185	5.4
Fukui	478 355	104 652	0.22	25 759	5.4
Yamanashi	520 046	74 052	0.14	40 189	7.7
Nagano	1 313 004	283 320	0.22	53 737	4.1
Gifu	1 239 917	147 456	0.12	64 919	5.2
Shizuoka	2 258 051	424 548	0.19	138 121	6.1
Aichi	4 143 364	479 424	0.12	271 398	6.6
Mie	1 105 081	184 152	0.17	39 995	3.6
Shiga	786 663	116 220	0.15	21 588	2.7
Kyoto	1 518 836	235 608	0.16	41 269	2.7
Osaka	5 131 625	756 108	0.15	151 513	3.0
Hyogo	3 310 832	493 536	0.15	117 726	3.6
Nara	843 979	105 660	0.13	29 047	3.4
Wakayama	627 916	125 844	0.20	26 222	4.2
Tottori	355 043	74 424	0.21	16 604	4.7
Shimane	444 342	98 172	0.22	13 813	3.1
Okayama	1 142 743	196 512	0.17	86 962	7.6
Hiroshima	1 683 544	315 996	0.19	73 819	4.4
Yamaguchi	902 174	145 656	0.16	26 483	2.9
Tokushima	485 314	74 004	0.15	19 440	4.0
Kagawa	606 333	109 128	0.18	32 214	5.3
Ehime	884 244	140 040	0.16	46 922	5.3
Kochi	479 164	65 604	0.14	30 144	6.3
Fukuoka	2 912 339	565 848	0.19	103 758	3.6
Saga	499 195	97 344	0.20	31 519	6.3
Nagasaki	875 505	173 940	0.20	41 343	4.7
Kumamoto	1 091 603	244 788	0.22	63 662	5.8
Oita	729 635	166 104	0.23	38 672	5.3
Miyazaki	690 481	127 560	0.18	30 434	4.4
Kagoshima	1 035 904	219 528	0.21	71 594	6.9
Okinawa	744 201	108 012	0.15	38 581	5.2

<sup>†</sup>Data from Report on Basic Resident Register (2014).<sup>(9)</sup> <sup>‡</sup>Data from Survey of Medical Institutions (2014).<sup>(7)</sup> <sup>§</sup>Data from Report on Regional Public Health Services and Health Promotion Services (2012).<sup>(8)</sup> Participation rates in gastric cancer screening were calculated using the target population based on the Basic Resident Register as a denominator.

disparity among the 47 prefectures examined could be observed.

Since 1983, radiographic screening programs for gastric cancer have been carried out nationwide with the results reported annually. The target population of gastric cancer screening is individuals aged 40 years and above. Participation rates in gastric cancer screening were calculated using the target population based on the Basic Resident Register as a denominator. When further examination is needed on the basis of the results of the radiographic screening, endoscopic examination is carried out. In 2012, the total number of participants in radiographic screening for gastric cancer was 3 784 967 and this only covered 5% of the target population (Table 1).<sup>(8)</sup> The recall rate of radiographic screening was 8.8% as the national average, and 271 810 individuals underwent endoscopic examinations for diagnosis.<sup>(8)</sup>

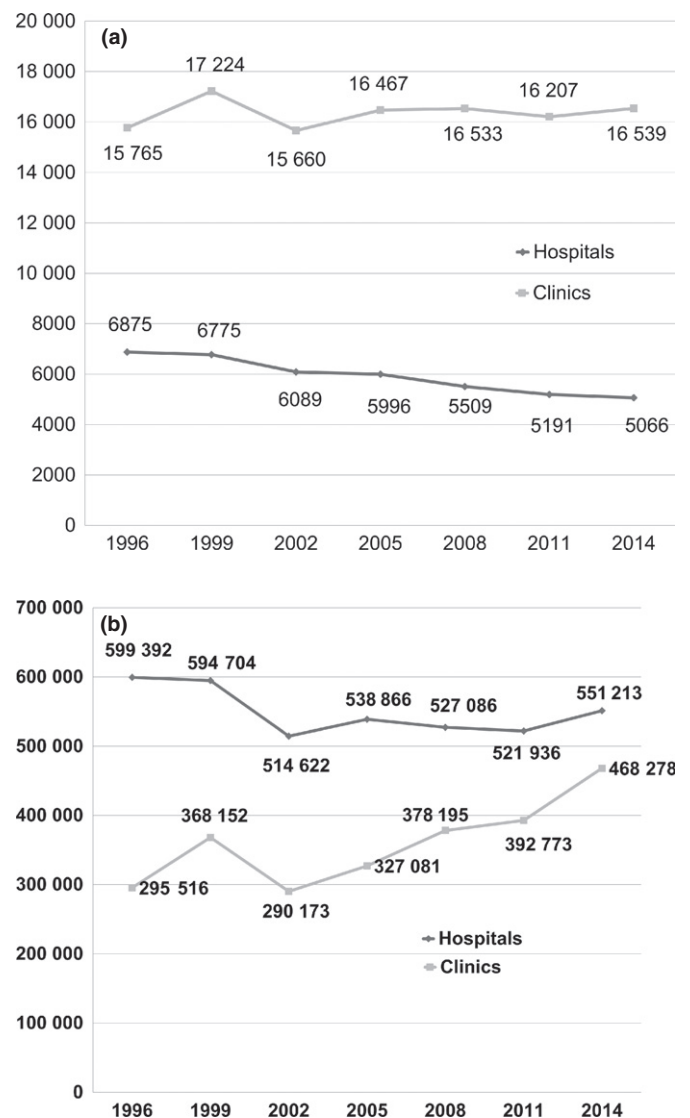
**Estimation of potential capacity.** Based on the abovementioned national survey, we estimated the proportion of increase in the number of endoscopic examinations with the introduction of endoscopic screening. In radiographic screening, the mass survey has been mainly carried out in rural areas. Radiographic screening has also been undertaken through the system within clinical practice, particularly in urban areas. When a number of participants in radiographic screening switch to endoscopic screening, the number of endoscopic screenings is increased and that of diagnostic endoscopy carried out after obtaining positive results in radiographic screening is decreased. After the introduction of endoscopic screening in several areas, the total participation rates of gastric cancer screening with the combined endoscopic screening and radiographic screening have increased, although the proportion of increase was limited. However, replacement from radiographic screening to endoscopic screening has rapidly changed and has had a bigger impact. In Yonago, which introduced endoscopic screening in 2000, the proportion of endoscopic screening within gastric cancer screening has increased from 27.7% to 77.0% between 2000 and 2007.<sup>(10)</sup> At the national level, the percentage increase in endoscopic screening was estimated accordingly from the 0% to 100% replacement rate of gastric cancer screenings by endoscopic screening according to the different participation rates in the radiographic screening. As 318 municipalities within 1722 municipalities have already introduced endoscopic screening in 2013, the maximum replacement rate was assumed as 81.7%.<sup>(11)</sup> After the introduction of endoscopic screening, the participation rate of gastric cancer screening increased from 20.7% to 26.7%, and the proportion of increase was limited to 6 points.<sup>(10)</sup> As the participation rates of gastric cancer screening were markedly different among the municipalities,<sup>(8)</sup> an increase in the participation rate cannot be easily predicted. Therefore, we calculated the replacement rate on the basis of a 15-point increase (20.0%) from the current participation rate, which is an optimistic assumption to be achieved in 10 years at the latest after the introduction of endoscopic screening.

The participation rates of gastric cancer screening differed among the 47 prefectures.<sup>(8)</sup> Increased proportions of endoscopic examinations were estimated at the prefectural levels, as well as in big cities and secondary medical districts on the basis of the same scenario with the current participation rates at each secondary medical district. In this study, big cities were defined as cities with a total population of more than 300 000 that have secondary medical districts.

## Results

**Trends in total numbers of endoscopic examinations.** Based on the Survey of Medical Institutions, the total number of hospitals and clinics offering endoscopic examinations slightly decreased from 1996 to 2014 (Fig. 1a).<sup>(7)</sup> Although the number of these hospitals has decreased every year, the number of these clinics increased to 16 539 in 2014. The total monthly number of endoscopic examinations has gradually increased in the same period (Fig. 1b). Moreover, the number of endoscopic examinations per month has decreased in hospitals. Conversely, the number of endoscopic examinations per month has increased in clinics and its proportion occupied 45.9% of the total number of endoscopic examinations. The average number of examinations per month was 108.8 per hospital and 28.3 per clinic. The increase in the number of endoscopic examinations per year was more than 2 000 000 from 1996 to 2014.

**Estimation of necessary number of endoscopic examinations.** At present, the total number of radiographic screenings



**Fig. 1.** Trends in the total number of hospitals and clinics in Japan offering endoscopic examinations (a) and trends in the total number of endoscopic examinations in Japan per month (b) from 1996 to 2014, based on the Survey of Medical Institutions.<sup>(7)</sup>

carried out each year is approximately 4 million, whereas the total number of endoscopic examinations carried out each year in clinical practice is approximately 12 million.<sup>(7,8)</sup> If 30% of gastric cancer screenings are replaced by endoscopic screening, the total number of endoscopic examinations will increase by 8.6%, that is, 1 053 947 (Fig. 2). If the participation rate increases to 20%, the proportion of increase in endoscopic examinations needed will be 34.3%.

The proportion of increase in endoscopic examinations per year if 30% of gastric cancer screening is replaced by endoscopic screening was compared among 47 prefectures in Japan (Table 2). The proportion of increase was defined on the basis of the current participation rate in gastric cancer screening and the total number of endoscopic examinations in each prefecture. In area where the participation rate was not particularly high and sufficient medical institutions were available, the total increase in the number of endoscopic examinations was limited, as shown in Shimane Prefecture. Conversely, a substantial increase in the number of endoscopic examinations is needed in prefectures that have retained high participation rates for gastric cancer screening. An increase of more than 20% is required in Aomori and Iwate Prefectures; however, these prefectures cannot introduce endoscopic screening very easily.

Based on the same condition of switching 30% from radiographic screening to endoscopic screening on a 5% participation rate, the proportions of increase in endoscopic examinations per year were compared among big cities and secondary medical districts (Table 3). In 50% of the big cities, endoscopic screening can be introduced with a proportion of increase of <5%. In 16.7% of the secondary medical districts, endoscopic screening can be introduced with a proportion of increase of <5%. The actual introduction of endoscopic screening might therefore be limited to big cities initially.

## Discussion

Although gastric cancer has decreased worldwide,<sup>(1)</sup> gastric cancer screening has continued to play a central role in cancer prevention programs, particularly in Korea and Japan, two countries whose incidence and mortality rates from gastric cancer have remained high. In Japan, endoscopic examinations

have been commonly carried out in clinical practice, the total number of which has increased over the years. These examinations were particularly limited to clinical practice and not for cancer screening. Thus, an additional increase in the number of endoscopic examinations is required when endoscopic screening is actually introduced. In 2013, more than 300 municipalities introduced endoscopic screening in Japan. However, the number of municipalities that conducted more than 100 endoscopic screenings was limited to 200.<sup>(11)</sup> Currently, the participation rate in gastric cancer screening in Japan is not high. However, if 30% of the participants in the mass survey for the radiographic screening of gastric cancer switched to endoscopic screening, 1 053 947 additional endoscopic examinations will be needed. This number is comparable to an 8.6% increase in the total number of endoscopic examinations. Radiographic screenings have been provided as a mass survey, mainly using mobile buses. However, such a system cannot be adopted for endoscopic screening because the endoscope used must be thoroughly cleaned and disinfected by an automatic processor.<sup>(12)</sup> When endoscopic screening is introduced, endoscopic examination is needed after the endoscopic resection of early stage cancer. Thus, follow-up examination for benign lesions including peptic ulcer and gastroesophageal reflux disease will increase, and diagnostic examination after radiographic screening will also remain. Therefore, an increase in the total number of endoscopic examinations in both clinical practice and cancer screening is a must.

Insufficient medical resources can be a barrier to participating in cancer screenings, and this can lead to geographic disparity in terms of access to cancer screening.<sup>(13-15)</sup> In the present study, the proportion of increase in endoscopic examinations was different among the 47 prefectures evaluated when using the same scenario (Table 2). As the incidence of gastric cancer is higher in the northern area (Tohoku) than in the other areas, the participation rates in gastric cancer screening there have been continuously higher. However, the number of medical institutions that provide endoscopic examination remains insufficient. These issues can become a barrier to the introduction of endoscopic screening, particularly in Tohoku. If 30% of gastric cancer screenings are replaced by endoscopic screening in half of the big cities, the proportion of increase was limited to 5%,

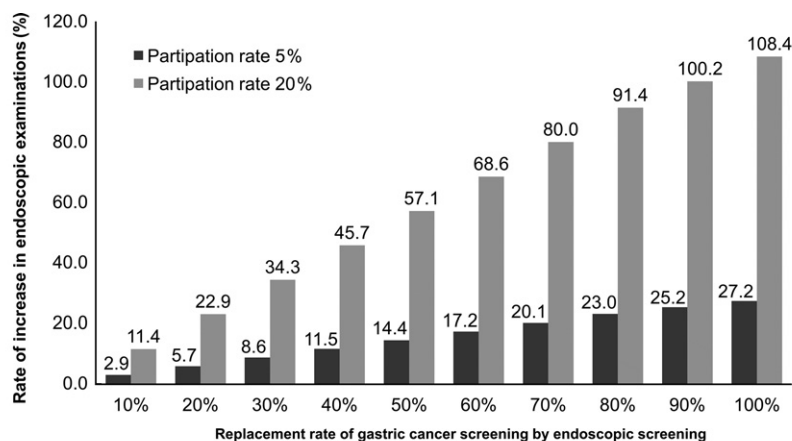


Fig. 2. Proportions of increase in endoscopic examinations in Japan after switching from radiographic screening to endoscopic screening for gastric cancer. All participants have been screened by radiographic screening. If 30% of the mass survey in radiographic screening is replaced by endoscopic screening, the total number of endoscopic examinations will increase by 8.6%. If the participation rate increased from 5% to 20%, the proportion of increase in endoscopic examinations needed is 34.3%.

Participation rate	Replacement rate of gastric cancer screening by endoscopic screening										
	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%	
5% (2012)	Increase number	351 316	702 631	1 053 947	1 405 263	1 756 579	2 107 894	2 459 210	2 810 526	3 079 879	3 332 445
	% increase	2.9	5.7	8.6	11.5	14.4	17.2	20.1	23.0	25.2	27.2
20%	Increase number	1 397 877	2 795 754	4 193 631	5 591 508	6 989 386	8 387 263	9 785 140	11 183 017	12 254 767	13 259 721
	% increase	11.4	22.9	34.3	45.7	57.1	68.6	80.0	91.4	100.2	108.4

**Table 2. Comparison of proportions of increase in endoscopic examinations among 47 Japanese prefectures if 30% of gastric cancer screenings are replaced by endoscopic screening**

Prefecture	Current number of endoscopic examinations	Increase in number of endoscopic examinations	Proportion of increase in endoscopic examinations, %
Japan	12 233 892	1 053 947	8.6
Hokkaido	581 532	48 989	8.4
Aomori	117 648	26 063	22.2
Iwate	111 804	25 453	22.8
Miyagi	245 496	43 279	17.6
Akita	147 204	15 393	10.5
Yamagata	142 908	27 060	18.9
Fukushima	302 652	28 929	9.6
Ibaragi	227 028	25 531	11.2
Tochigi	171 696	25 343	14.8
Gunma	234 192	15 016	6.4
Saitama	472 980	40 297	8.5
Chiba	503 844	65 464	13.0
Tokyo	1 242 516	70 823	5.7
Kanagawa	728 136	40 946	5.6
Niigata	240 768	32 292	13.4
Toyama	136 824	14 984	11.0
Ishikawa	173 424	9944	5.7
Fukui	104 652	7143	6.8
Yamanashi	74 052	11 307	15.3
Nagano	283 320	14 431	5.1
Gifu	147 456	17 991	12.2
Shizuoka	424 548	38 790	9.1
Aichi	479 424	74 810	15.6
Mie	184 152	11 399	6.2
Shiga	116 220	5938	5.1
Kyoto	235 608	11 006	4.7
Osaka	756 108	42 060	5.6
Hyogo	493 536	33 122	6.7
Nara	105 660	8283	7.8
Wakayama	125 844	7353	5.8
Tottori	74 424	4597	6.2
Shimane	98 172	3875	3.9
Okayama	196 512	24 593	12.5
Hiroshima	315 996	20 903	6.6
Yamaguchi	145 656	7421	5.1
Tokushima	74 004	5402	7.3
Kagawa	109 128	9071	8.3
Ehime	140 040	13 147	9.4
Kochi	65 604	8519	13.0
Fukuoka	565 848	28 977	5.1
Saga	97 344	8438	8.7
Nagasaki	173 940	11 496	6.6
Kumamoto	244 788	18 209	7.4
Oita	166 104	10 796	6.5
Miyazaki	127 560	8522	6.7
Kagoshima	219 528	19 402	8.8
Okinawa	108 012	11 141	10.3

Proportions of increase in endoscopic examinations per year were compared among 47 prefectures if 30% of gastric cancer screenings were replaced by endoscopic screening. The proportion of increase was defined based on the current participation rate in gastric cancer screening and the total number of endoscopic examinations in each prefecture.

but in secondary medical districts, the proportion of increase was limited to 17%. Even if the participation rate has not been very high, switching from radiographic screening to endoscopic screening is not easy in rural areas because of the insufficient numbers of medical institutions capable of performing endoscopy. Similar situations have been reported in cancer screenings for colorectal and breast cancers in the USA. In particular, the capacity for colonoscopy and mammograms was limited in rural areas, and it was difficult to increase the capability for additional volumes in rural as well as urban areas.<sup>(16,17)</sup> Even if a greater impact on mortality reduction from gastric cancer can be achieved, the benefits in rural areas are unfortunately limited, and the disparity between rural and urban areas has become larger.

Although medical resources are limited for endoscopic screening of gastric cancer, urgent solutions should be considered for improving the availability of endoscopic examination. In consideration of the current situation, we suggest several solutions that can be instituted immediately. First, the role of radiographic screening should be continued until sufficient resources for endoscopic screening have been prepared because an immediate increase in the number of endoscopic examinations cannot be anticipated. Second, a primary care physician should be encouraged to participate in endoscopic screening because of the limited number of endoscopists who are approved by academic societies. Upper gastrointestinal endoscopy has become indispensable in primary care, and the number of examinations has increased, mainly in private clinics. In the USA, primary physicians and surgeons carry out colonoscopies for colorectal cancer screening.<sup>(18,19)</sup> In some areas, physicians who participate in endoscopic screening have not been limited to approved endoscopists, and primary care physicians could participate in the program if they have met certain requirements.<sup>(12)</sup> Except for the clinical training period after graduation from university, there are few opportunities for primary care physicians to be trained in endoscopy. However, a training system for the endoscopic technique and establishing a diagnosis is needed. As an additional merit, the increasing availability of primary care physicians is advantageous in increasing the participation rate in endoscopic screening.<sup>(19)</sup> Third, the aim of endoscopic examination should be clarified. At present, we are not able to obtain the specific number of endoscopic examinations classified into clinical practice and cancer screening. In clinical practice, endoscopic examination has been carried out for asymptomatic individuals and has been covered by health insurance.<sup>(20)</sup> This is, however, considered inappropriate according to the basic rule of health insurance in Japan. To secure a certain capacity of endoscopic screening for gastric cancer, endoscopic examinations should be divided according to their actual aim, particularly in clinical practice. Finally, we also considered the burden to the co-medical staff who have important roles to play in endoscopic screening. In actuality, the labor time for endoscopic examination covers the time before and after the procedure, including the time for cleaning and disinfection of the endoscope used.<sup>(21)</sup> These works have been mainly undertaken by nurses. To increase the total number of endoscopic examinations, labor sharing in endoscopic screening should be considered.

To the best of our knowledge, this is the first study to investigate the potential capacity of endoscopic screening for gastric cancer in Japan. Although the Japanese government has already approved endoscopic screening in communities, most

**Table 3. Proportions of increase in the total endoscopic examinations if 30% of gastric cancer screenings were replaced by endoscopic screening**

Proportion of increase		0–4.9%	5.0–9.9%	10.0–14.9%	15.0–19.9%	20.0–24.9%	25.0–29.9%	30.0–39.9%	40.0–49.9%	≥50%
Big cities ( <i>n</i> = 64)	Number	32	22	7	2	0	1	0	0	0
	%	50.0	34.4	10.9	3.1	0.0	1.6	0.0	0.0	0.0
Secondary medical districts ( <i>n</i> = 340)	Number	57	102	89	32	26	20	9	4	2
	%	16.7	29.9	26.1	9.4	7.6	5.9	2.6	1.2	0.6

municipalities in Japan are unsure of how to introduce endoscopic screening because of the difficulty in securing sufficient resources for the screenings and in adopting the basic requirements of quality assurance. In the USA, during the early period of introducing colonoscopy screening, national and regional resources were estimated by a questionnaire survey and modeling studies.<sup>(17,18,22–24)</sup> To predict the demand and supply of endoscopic screening, the use of a simulation model with detailed information is an ideal method. However, the available data for these calculations are currently limited because endoscopic screening has been carried out in limited municipalities and the quality of data is not appropriate for use in a prediction model. Although the results can be obtained from several areas that have already introduced endoscopic screening, the actual supply of endoscopic examinations has been unclear in these areas. In addition, the government changed the starting age and screening interval for gastric cancer screening. Basic data collection for a prediction model for medical resources is required to accurately predict the demand and supply of endoscopic screening. Then, further study is needed using simulation model based on the detailed information.

To promote endoscopic screening for gastric cancer, the demand and supply should be estimated both at the national and regional levels based on detailed information and consideration of the local context. In addition, resource allocation and a balance of clinical practice and cancer screening in local areas are also required. Municipal collaboration within the

secondary medical district could also be one of the solutions for securing medical resources for endoscopic screening in rural areas. Additionally, the appropriate target age and screening interval must be identified for the efficient use of limited resources. Further study is warranted on how to provide equal access to endoscopic screening for gastric cancer for the target population.

In conclusion, although the Japanese government has decided to introduce endoscopic screening for gastric cancer nationwide, its rapid introduction remains hindered by insufficient medical resources in rural areas. Thus, endoscopic screening will likely and initially be introduced to big cities. This implies a disparity of medical resources that must be initially resolved to realize a smooth, nationwide implementation of endoscopic screening for gastric cancer.

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#### Disclosure Statement

The authors declare have no conflict of interest.

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