SPECIAL REPORT

Breast-Cancer Screening — Viewpoint of the IARC Working Group

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In November 2014, experts from 16 countries met at the International Agency for Research on Cancer (IARC) to assess the cancer-preventive and adverse effects of different methods of screening for breast cancer. (The members of the working group for volume 15 of the IARC Handbook are listed at the end of the article; affiliations are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.) This update of the 2002 IARC handbook on breast-cancer screening[1] is timely for several reasons. Recent improvements in treatment outcomes for late-stage breast cancer and concerns regarding overdiagnosis call for reconsideration. The definition of what constitutes the best implementation of mammographic screening programs (e.g., which age groups should be screened and with what frequency) needs to be revisited in light of the results of recent studies. New studies on clinical breast examination and self-examination warrant the reevaluation of these screening practices, and imaging techniques other than mammography, which were not evaluated in the 2002 handbook, now warrant rigorous scientific evaluation. Finally, the screening of women at high risk for breast cancer requires a thorough reassessment, particularly in the context of the improved data that are now available on possible alternative screening methods.

In preparation for the meeting, the IARC scientific staff performed searches of the openly available scientific literature according to topics listed in an agreed-upon table of contents; searches were supplemented by members of the working group on the basis of their areas of expertise. Group chairs and subgroup members were selected by the IARC according to field of expertise and the absence of real or apparent conflicts of interest. During the meeting, care was taken to ensure that each study summary was written or reviewed by someone who was not associated with the study being considered. All studies were assessed and fully debated, and a consensus on the preliminary evaluations was achieved in subgroups before the evaluations were reviewed by the entire working group. During the final evaluation process, the working group discussed preliminary evaluations to reach consensus evaluations. (For details on the process used and on the evaluation criteria, see the working procedures on the IARC handbooks website.[2]) This article briefly summarizes the evaluation of the scientific evidence reviewed at the meeting (Table 1). The full report is presented in volume 15 of the IARC Handbooks of Cancer Prevention.[3]

Breast cancer is the most frequently diagnosed cause of death from cancer in women worldwide,[4,5] the second leading cause of death from cancer in women in developed countries,[4,5] and the leading cause of death from cancer in low- and middle-income countries, where a high proportion of women present with advanced disease, which leads to a poor prognosis.[6] Established risk factors for breast cancer include age, family or personal history of breast cancer or of precancerous lesions, reproductive factors, hormonal treatment, alcohol consumption, obesity (for postmenopausal breast cancer only), exposure to ionizing radiation, and genetic predisposition.[7]

Screening for breast cancer aims to reduce mortality from this cancer, as well as the morbidity associated with advanced stages of the disease, through early detection in asymptomatic women. The key to achieving the greatest potential effects from this screening is providing early access to effective diagnostic and treatment services. Comprehensive quality assurance is essential to maintaining an appropriate balance between benefits and harms.[8]

Table 1. Evaluation of Evidence Regarding the Beneficial and Adverse Effects of Different Methods of Screening for Breast Cancer in the General Population and in High-Risk Women.*

Method	Strength of Evidence†
Mammography	
Reduces breast-cancer mortality in women 50–69 yr of age	Sufficient
Reduces breast-cancer mortality in women 70–74 yr of age‡	Sufficient
Reduces breast-cancer mortality in women 40–44 yr of age§	Limited
Reduces breast-cancer mortality in women 45–49 yr of age§	Limited¶
Detects breast cancers that would never have been diagnosed or never have caused harm if women had not been screened (overdiagnosis)	Sufficient
Reduces breast-cancer mortality in women 50–74 yr of age to an extent that its benefits substantially outweigh the risk of radiation-induced cancer from mammography	Sufficient
Produces short-term negative psychological consequences when the result is false positive	Sufficient
Has a net benefit for women 50–69 yr of age who are invited to attend organized mammographic screening programs	Sufficient
Can be cost-effective among women 50–69 yr of age in countries with a high incidence of breast cancer	Sufficient
Can be cost-effective in low- and middle-income countries	Limited
Ultrasonography as an adjunct to mammography in women with dense breasts and negative results on mammography	
Reduces breast-cancer mortality	Inadequate
Increases the breast-cancer detection rate	Limited
Reduces the rate of interval cancer‖	Inadequate
Increases the proportion of false positive screening outcomes	Sufficient
Mammography with tomosynthesis vs. mammography alone	
Reduces breast-cancer mortality	Inadequate
Increases the detection rate of in situ and invasive cancers	Sufficient
Preferentially increases the detection of invasive cancers	Limited
Reduces the rate of interval cancer‖	Inadequate
Reduces the proportion of false positive screening outcomes	Limited
Clinical breast examination	
Reduces breast-cancer mortality	Inadequate
Shifts the stage distribution of tumors detected toward a lower stage	Sufficient
Breast self-examination	
Reduces breast-cancer mortality when taught	Inadequate
Reduces the rate of interval cancer when taught‖	Inadequate
Reduces breast-cancer mortality when practiced competently and regularly	Inadequate
Screening of high-risk women	
MRI as an adjunct to mammography	
Reduces breast-cancer mortality in women with a *BRCA1* or *BRCA2* mutation	Inadequate
Increases the detection rate of breast cancer in women with lobular carcinoma in situ or atypical proliferations	Inadequate
Clinical breast examination as an adjunct to MRI and mammography	
Increases the detection rate of breast cancer in women with a high familial risk	Inadequate
Ultrasonography as an adjunct to mammography	
Increases the detection rate of breast cancer in women with a personal history of breast cancer	Inadequate
Increases the proportion of false positive screening outcomes in women with a personal history of breast cancer as compared with those without such a history	Inadequate
MRI as an adjunct to mammography plus ultrasonography	

Table 1. (Continued.)

Method	Strength of Evidence†
Increases the proportion of false positive screening outcomes in women with a personal history of breast cancer as compared with those without such a history	Inadequate
MRI as an adjunct to mammography vs. mammography alone	
Increases the proportion of false positive screening outcomes in women with lobular carcinoma in situ or atypical proliferations	Limited

* For the complete evaluation statements, see International Agency for Research on Cancer[2] or the IARC Handbooks of Cancer Prevention website (http://handbooks.iarc.fr). MRI denotes magnetic resonance imaging.
† For detailed information on the evaluation criteria, see the working procedures section of the IARC Handbooks of Cancer Prevention website (http://handbooks.iarc.fr/workingprocedures/index.php).
‡ The evidence for a reduction in breast-cancer mortality from mammography screening in women in this age group was considered to be sufficient. However, published data for this age category did not allow for the evaluation of the net benefit.
§ The evidence for a reduction of breast-cancer mortality from mammography screening in women in this age group was considered to be limited. Consequently, the net benefit for women in this age group was not assessed.
¶ The majority of the voting members of the IARC Working Group considered the evidence as limited; however, the vote was almost evenly divided between limited and sufficient evidence.
‖ An interval cancer is a cancer that develops in the interval between routine screenings for that particular cancer.

The most common means of screening women for breast cancer is standard mammography (film or digital), offered either by organized programs or through opportunistic screening. Organized screening programs are characterized by invitations to join a target population at given intervals, systematic recalls for the assessment of detected abnormalities, and delivery of test results, treatment, and follow-up care, with regular monitoring and evaluation of the program and a national or regional team responsible for service delivery and quality. Opportunistic screening typically provides screening to women on request and coincidently with routine health care.

As a consequence of the results of randomized, controlled trials that showed a reduction in breast-cancer mortality several decades ago,[1] mammographic screening has been implemented to a great extent in high-income countries and regions and less so in countries in Central and Eastern Europe, through either opportunistic or organized screening. Most countries in Latin America have national recommendations or guidelines, including those calling for mammographic screening combined with clinical breast examination and breast self-examination. In other low- and middle-income countries, breast-cancer screening is promoted primarily by advocacy groups and periodic campaigns to promote breast-cancer awareness.

In 2002, on the basis of findings from randomized, controlled trials, the previous IARC Handbook Working Group concluded that the evidence for the "efficacy of screening by mammography as the sole means of screening in reducing mortality from breast cancer" was sufficient for women 50 to 69 years of age, limited for women 40 to 49 years of age, and inadequate for women younger than 40 or older than 69 years of age.[1] We carefully reviewed the results of all available randomized, controlled trials and reaffirmed the findings from the previous evaluation of the efficacy of mammographic screening in women 50 to 69 years of age; the evidence of efficacy for women in other age groups was considered inadequate.

The working group recognized that the relevance of randomized, controlled trials conducted more than 20 years ago should be questioned, given the large-scale improvements since then in both mammographic equipment and treatments for breast cancer. More recent, high-quality observational studies were considered to provide the most robust data with which to evaluate the effectiveness of mammographic screening. The working group gave the greatest weight to cohort studies with long follow-up periods and the most robust designs, which included those that accounted for lead time, minimized temporal and geographic differences between screened and unscreened participants, and controlled for individual differences that may have been related to the primary outcome. Analyses of invitations to screenings (rather than actual attendance) were

considered to provide the strongest evidence of screening effectiveness, since they approximate the circumstances of an intention-to-treat analysis in a trial. After careful consideration of the limitations of case–control studies in the evaluation of effectiveness, these studies were also considered to provide information that was relevant to organized screening programs and to other venues, such as opportunistic screening, for which cohort data were not available. Among ecologic studies, only those that controlled for time- and treatment-related factors in design or analysis were considered to be informative.

Some 20 cohort and 20 case–control studies, all conducted in the developed world (Australia, Canada, Europe, or the United States) were considered to be informative for evaluating the effectiveness of mammographic screening programs, according to invitation or actual attendance, mostly at 2-year intervals. Most incidence-based cohort mortality studies, whether involving women invited to attend screening[9-13] or women who attended screening,[14-17] reported a clear reduction in breast-cancer mortality, although some estimates pertaining to women invited to attend were not statistically significant.[12,13] Women 50 to 69 years of age who were invited to attend mammographic screening had, on average, a 23% reduction in the risk of death from breast cancer; women who attended mammographic screening had a higher reduction in risk, estimated at about 40%. Case–control studies that provided analyses according to invitation to screening were largely in agreement with these results. Evidence from the small number of informative ecologic studies was largely consistent with that from cohort and case–control studies. A substantial reduction in the risk of death from breast cancer was also consistently observed in women 70 to 74 years of age who were invited to or who attended mammographic screening in several incidence-based cohort mortality studies.[17-19] Fewer studies assessed the effectiveness of screening in women 40 to 44 or 45 to 49 years of age who were invited to attend or who attended mammographic screening, and the reduction in risk in these studies was generally less pronounced.[20-23] Overall, the available data did not allow for establishment of the most appropriate screening interval.

The most important harms associated with early detection of breast cancer through mammographic screening are false positive results, overdiagnosis, and possibly radiation-induced cancer. Estimates of the cumulative risk of false positive results differ between organized programs and opportunistic screening. The estimate of the cumulative risk for organized programs is about 20% for a woman who had 10 screens between the ages of 50 and 70 years.[24] Less than 5% of all false positive screens resulted in an invasive procedure. Owing to differences in health systems and quality control for screening performance, recall rates for additional investigation tend to be higher in opportunistic screening (e.g., in the United States)[25] than in organized screening programs. Overall, studies show that having a false positive mammogram has short-term negative psychological consequences for some women.[26]

Overdiagnosis can be estimated on the basis of data from observational studies conducted in organized programs or through statistical modeling. There is an ongoing debate about the preferred method for estimating overdiagnosis. After a thorough review of the available literature, the working group concluded that the most appropriate estimation of overdiagnosis is represented by the difference in the cumulative probabilities of breast-cancer detection in screened and unscreened women, after allowing for sufficient lead time. The Euroscreen Working Group calculated a summary estimate of overdiagnosis of 6.5% (range, 1 to 10%) on the basis of data from studies in Europe that adjusted for both lead time and contemporaneous trends in incidence.[27,28] When the same comparators were used, corresponding estimates of overdiagnosis in randomized, controlled trials after a long follow-up period from the end of screening were similar (4 to 11%).[29,30] Similar non-European and more recent European observational studies have led to higher estimates of overdiagnosis.

Radiation-induced breast cancer is a concern in women who are offered screening. The estimated cumulative risk of death from breast cancer due to radiation from mammographic screening is 1 to 10 per 100,000 women, depending on age and the frequency and duration of screening. It is smaller by a factor of at least 100 than the estimates of death from breast cancer that are prevented by mammographic screening for a wide range of ages.[31]

After a careful evaluation of the balance be-

tween the benefits and adverse effects of mammographic screening, the working group concluded that there is a net benefit from inviting women 50 to 69 years of age to receive screening. A number of other imaging techniques have been developed for diagnosis, some of which are under investigation for screening. Tomosynthesis, magnetic resonance imaging (MRI) (with or without the administration of contrast material), ultrasonography (handheld or automated), positron-emission tomography, and positron-emission mammography have been or are being investigated for their value as supplementary methods for screening the general population or high-risk women in particular.

Evidence for population screening with other imaging techniques is based solely on data from observational studies. The use of adjunct ultrasonography in women with dense breasts and negative results on mammography may increase the detection rate of cancers, but it also increases false positive screening outcomes.[32] As compared with mammography alone, mammography with tomosynthesis increases rates of detection of both in situ and invasive cancers and may reduce false positive screening outcomes[33]; however, evidence for a reduction in breast-cancer mortality was inadequate (Table 1) and the radiation dose received with dual acquisition is increased.

Clinical breast examination is a simple, inexpensive technique. In three trials in which women were randomly assigned to receive either clinical breast examination or no screening, breast cancers detected at baseline and in the early years of the trials tended to be of a smaller size and less advanced stage in the former group of women than in the latter.[34-36] Results on breast-cancer mortality have not yet been reported. In addition, five observational studies, conducted mostly in the 1970s, reported that clinical breast examination combined with mammographic screening increased the breast-cancer detection rate by 5 to 10 percentage points as compared with mammography alone.[1]

As has been previously reported,[1] the available data from randomized, controlled trials and observational studies generally did not show a reduction in breast-cancer mortality when breast self-examination was either taught or practiced competently and regularly (Table 1). Overall, surveys in general populations have shown that the numbers of women who report practicing breast self-examination are probably too few to have had an effect on mortality from breast cancer.

Women with a family history of breast cancer, with or without a known genetic predisposition, are at increased risk for breast cancer and therefore may benefit from intensified monitoring, with a combination of methods, from an earlier age and possibly at shorter intervals than women at average risk. However, high-risk women may be more sensitive to ionizing radiation,[37] and screening from an earlier age increases the risk of radiation-induced cancer. A number of observational studies have evaluated the sensitivity, specificity, incremental rate of breast-cancer detection, and false positive outcomes associated with various imaging techniques in high-risk women (Table 1). There is abundant literature showing that the use of MRI as an adjunct to mammography significantly increases the sensitivity of screening in women with a high familial risk and a *BRCA1* or *BCRA2* mutation as compared with mammography alone, but the addition of MRI also decreases the specificity[38]; data for other high-risk groups were fewer and provided weaker evidence.[39] The sensitivity of ultrasonography was found to be similar to or lower than that of mammography and was consistently lower than that of MRI.[40] The evidence regarding other screening techniques was too sparse to allow any conclusions.

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RESEARCH ARTICLE

Survival Analysis of Patients with Interval Cancer Undergoing Gastric Cancer Screening by Endoscopy

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Data Availability Statement: These data are from the Tottori Cancer Registry and the patients listed as participant of gastric cancer screening from 4 city governments, namely Tottori, Yonago, Sakaiminato, and Kurayoshi based on their local rules. Since these data included personal information, the Tottori Cancer Registry and 4 city governments only allowed their limited use specifically for evaluation studies on gastric cancer screening. The authors are unable to make the dataset available in public. The data analyzed for this study are housed at 4 city governments (Tottori, Yonago, Sakaiminato, and Kurayoshi) and the Tottori Prefecture Cancer

Abstract

Aims

Interval cancer is a key factor that influences the effectiveness of a cancer screening program. To evaluate the impact of interval cancer on the effectiveness of endoscopic screening, the survival rates of patients with interval cancer were analyzed.

Methods

We performed gastric cancer-specific and all-causes survival analyses of patients with screen-detected cancer and patients with interval cancer in the endoscopic screening group and radiographic screening group using the Kaplan-Meier method. Since the screening interval was 1 year, interval cancer was defined as gastric cancer detected within 1 year after a negative result. A Cox proportional hazards model was used to investigate the risk factors associated with gastric cancer-specific and all-causes death.

Results

A total of 1,493 gastric cancer patients (endoscopic screening group: n = 347; radiographic screening group: n = 166; outpatient group: n = 980) were identified from the Tottori Cancer Registry from 2001 to 2008. The gastric cancer-specific survival rates were higher in the endoscopic screening group than in the radiographic screening group and the outpatients group. In the endoscopic screening group, the gastric cancer-specific survival rate of the patients with screen-detected cancer and the patients with interval cancer were nearly equal (P = 0.869). In the radiographic screening group, the gastric cancer-specific survival rate of the patients with screen-detected cancer was higher than that of the patients with interval cancer (P = 0.009). For gastric cancer-specific death, the hazard ratio of interval cancer in the endoscopic screening group was 0.216 for gastric cancer death (95%CI: 0.054-0.868) compared with the outpatient group.

Registry. Tottori Prefecture government manages the Tottori Prefecture Cancer Registry. Procedures for applying for access to those data are available on the following web-site: Tottori city government http://www.city.tottori.lg.jp/: Yonago city government http://www.city.yonago.lg.jp/: Kurayoshi city government http://www.city.kurayoshi.lg.jp/: Sakaiminato city government https://www.city.sakaiminato.lg.jp/: Tottori Prefecture government http://www.pref.tottori.lg.jp/). Please contact C. Hamashima (chamashi@ncc.go.jp) for specifics regarding the data used for this study.

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Conclusion

The survival rate and the risk of gastric cancer death among the patients with screen-detected cancer and patients with interval cancer were not significantly different in the annual endoscopic screening. These results suggest the potential of endoscopic screening in reducing mortality from gastric cancer.

Introduction

Gastric cancer is the third leading cause of cancer death in both sexes worldwide, with its number reaching about 723,000 in 2012 [1]. Although half of the total number of gastric cancer has been reported in Eastern Asia, the burden of gastric cancer has also remained in Eastern and South Europe. In most countries, gastric cancer screening has not been commonly carried out, except in Korea and Japan which have performed gastric cancer screening as a national program [2, 3]. The Japanese screening program for gastric cancer is limited to upper gastrointestinal series using barium meal (i.e., radiographic screening), whereas the Korean screening program consists of both radiographic and endoscopic screenings. However, studies evaluating mortality reduction from gastric cancer by endoscopic screening remain limited [4, 5].

Mortality reduction from gastric cancer is a long-term effect of gastric cancer screening. On the other hand, evaluation of interval cancer can provide an early estimate of the impact of screening programs [6]. Interval cancer is defined as cases that are diagnosed after negative results of screening in the periods between routine and scheduled screenings [6]. The rate of interval cancer and the survival rate are directly affected the effectiveness of the cancer screening program. The sensitivity of endoscopic screening was previously calculated based on the rate of interval cancer using cancer registry data [7, 8]. On the other hand, there are only a few studies related to survival analysis of patients with gastric cancer detected by endoscopic screening [9, 10]. The survival of patients with interval cancer in endoscopic screening also remains unclear. To evaluate the impact of interval cancer on the effectiveness of endoscopic screening, the survival rates of patients with interval cancer were analyzed and compared with those of patients with screen-detected cancers between endoscopic and radiographic screenings based on the Tottori Cancer Registry in Japan.

Methods

Screening programs

The subjects of our study were selected from gastric cancer cases registered in 4 cities (i.e., Tottori, Yonago, Kurayoshi, and Sakaiminato) in Tottori Prefecture, Japan. Endoscopic screening has been conducted in Tottori, Yonago, and Sakaiminato since 2000 and in Kurayoshi since 2001. Gastric cancer screening is offered annually by local governments, and both radiography and endoscopy are used in these cities. All individuals aged 40 years and over can participate in the gastric cancer screening programs. There is no upper age limit for the target population for gastric cancer screening. Individuals can choose either endoscopy or radiography for gastric cancer screening based on their preference. Since the introduction of endoscopic screening, the participation rate in gastric cancer screening has increased, although the participation rate in gastric cancer screening involving both methods has remained at about 25% [11].

Physicians who can perform endoscopic screening were approved by the local committee for gastric cancer screening based on certain requirements [11]. Although endoscopic

screening has been performed in clinical settings, the results have been evaluated based on monitor screen review by the local committee, including experienced endoscopists in each city.

Target group

The subjects of our study were selected from gastric cancer cases registered in 4 cities (Tottori, Yonago, Kurayoshi, and Sakaiminato) in the Tottori Cancer Registry from 2001 to 2008. There were 2,066 potential subjects with gastric cancer in the 4 cities in Tottori Prefecture. Detailed information of all the potential cases was obtained from the local cancer registries, and the following cases were excluded: patients who 1) were more than 80 years old and less than 39 years old at the time of gastric cancer diagnosis, 2) had registry duplication, 3) lacked the diagnosis date for gastric cancer, or 4) had a diagnosis other than gastric cancer. The selected patients with gastric cancers were divided into 3 groups according to the detection process used in the participant list of gastric cancer screening from 2000 to 2006 in the 4 cities. Screening histories were investigated from the participant lists and matching was based on name, sex, and birthday. When there was no screening history, the patients were defined as belonging to the outpatient group.

The screening group was divided into patients with screen-detected cancer and patients with interval cancer based on the screening results. Patients with screen-detected cancer patients were identified after a positive result of gastric cancer screening. Since the screening interval of both endoscopic screening and radiographic screening was 1 year, interval cancer was defined as cancer detected within 1 year after a negative result on cancer screening.

Follow-up

Follow-up was continued from the date of diagnosis to the date of death or up to December 31, 2011 based on the Tottori Cancer Registry. The mean follow-up period was 66.4 ± 38.6 months. Since the local cancer registry system did not collect the stages of all gastric cancers, we obtained detailed information from the database for gastric cancer screening of the Tottori Medical Association. However, information on gastric cancer patients who had never been screened was not available. Tumor location was recorded using the Japanese Classification of Gastric Carcinoma [12], in which the stomach is anatomically divided into 3 portions: upper, middle, and lower. Clinical stage was determined based on the Japanese Classification of Gastric Carcinoma [12]. Gastric cancers were also classified histologically into intestinal and diffuse types according to Lauren's criteria [13].

Statistical analysis

The characteristics of the target groups were compared using the chi-square test. Survival analysis was performed using the Kaplan-Meier method with the log-rank test. The obtained curves show the proportion of individuals alive over time starting at the time of cancer diagnosis. Gastric cancer-specific survival and all-causes survival rates were calculated. A Cox proportional hazards model was used to investigate the risk factors associated with gastric cancer death and all-causes death for the endoscopic and radiographic screening group. Analyses were carried out using STATA 13.0 (STATA, College Station, TX, USA). All test statistics were two tailed, and P values of < 0.05 were considered to indicate a statically significant difference.

Ethics statement

This study used the data of the local cancer registry and the population lists of gastric cancer screening. These were not included in the informed consents for the collection of the screening

results and health data. Based on the Japanese guideline for epidemiological studies developed by the national government, informed consent is not required for an observational study using secondary data without human materials [14]. Our study was survival analysis using the secondary data from the local cancer registry and the population lists of gastric cancer screening. Therefore, obtaining informed consent was waived in this study based on the Japanese guideline for epidemiological studies. This was confirmed by the Institutional Review Board of the National Cancer Center of Japan. Finally, this study was approved by the Institutional Review Board of the National Cancer Center of Japan on October 22, 2007.

Results

The procedure used for the selection of the target population is shown in **Fig 1**. A total of 2,066 subjects were selected from the Tottori Cancer Registry, of which 237 patients were not within the target age for the analysis. Most subjects who were excluded from the target group were more than 80 years old at the time of diagnosis, which was not the actual target for cancer screening. Two patients who had registry duplication, 44 patients who were not cases of gastric cancers, and 270 patients in whom the date of diagnosis was unclear were also excluded. From the list of participants with gastric cancer screening from 2000 to 2006, 20 patients whose screening methods were unclear were excluded. The remaining 1,493 patients were finally divided into 3 groups according to the cancer detection procedure as follows: endoscopic screening group (n = 347), radiographic screening group (n = 166), and outpatient group (n = 980; symptoms detected in outpatients). In the endoscopic screening group, the number of patients with screen-detected cancer was 324 and that of patients with interval cancer was 23. In the radiographic screening group, the number of patients with screen-detected cancer was 143 and that of patients with interval cancer was 23.

The results of the comparison of the basic characteristics of the endoscopic screening group, radiographic screening group, and outpatient group are shown in **Table 1**. The proportion of male patients was significantly higher than that of female patients in all groups. The age distribution was different between the 3 groups. Although more than 50% of the patients in the endoscopic and radiographic screening groups were 70 years and over, the proportion of the 70 years and over age group was lower in the outpatient group than in both the endoscopic and radiographic screening groups.

In the outpatient group, detailed information could not be obtained from the Tottori Cancer Registry, and the clinical stage and location were unknown in more than 70% of the patients in the outpatient group. The characteristics of the patients with screen-detected cancer and patients with interval cancer were compared between the endoscopic and radiographic screening groups (**Table 2**). The proportion of stage I was approximately 50% among the screen-detected cancer in the endoscopic screening and radiographic screening groups. The clinical stage was unknown in most of the patients with interval cancer. The clinical stage distribution was not significantly different between the endoscopic screening group and the radiographic screening group ($P = 0.415$). The numbers of screen-detected cancer according to histological types using both screening methods were also not significantly different ($P = 0.581$).

The results of the Kaplan-Meier analysis of survival in patients with gastric cancer detected by screening and outpatients are shown in **Fig 2A**. The 5-year survival rates were 91.2 ± 1.5% (95%CI: 87.5–93.8) for the endoscopic screening group, 84.3 ± 2.9% (95%CI: 87.5–93.8) for the radiographic screening group, and 66.0 ± 1.6% (95%CI: 62.8–68.9) for the outpatient group. There were significant differences in the gastric cancer-specific survival rate between the endoscopic screening group and the outpatient group ($P < 0.001$), as well as between the radiographic screening group and the outpatient group ($P < 0.001$). The gastric cancer-specific rate

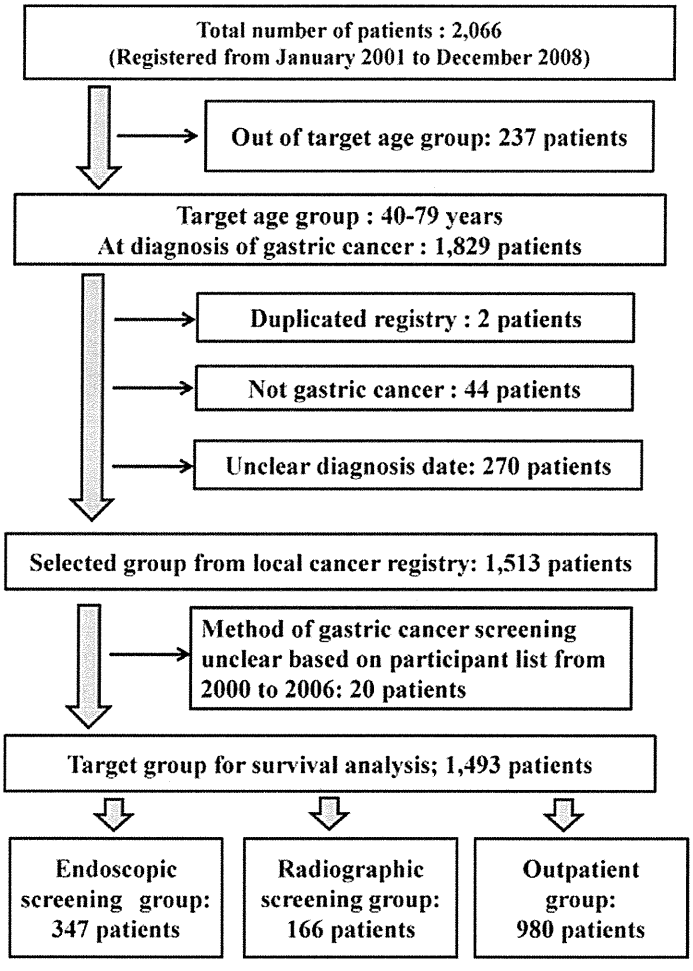

Fig 1. Flow-chart of the selection process for the target group. There were 2,066 potential subjects with gastric cancer in the 4 cities examined in Tottori Prefecture (i.e., Tottori, Yonago, Kurayoshi, and Sakaiminato). The following patients were excluded: those who 1) were over 80 years old and less than 39 years old at the time of gastric cancer diagnosis, 2) had registry duplication, 3) lacked the date for gastric cancer diagnosis, or 4) had a diagnosis other than gastric cancer. Two patients who had registry duplication, 44 patients who were not cases of gastric cancers, and 270 patients in whom the date of diagnosis was unclear were also excluded. From the local registry, 1,513 subjects were selected. Based on the participants list for gastric cancer from 2000 to 2006, 20 subjects whose screening methods were unclear were excluded. The remaining 1,493 subjects were divided into 3 groups according to the method of cancer detection: endoscopic screening group (n = 347), radiographic screening group (n = 166), and outpatient group (n = 980).

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was significantly higher in the patients in the endoscopic screening group than in the patients in the radiographic screening group (P = 0.013). There were significant differences in the all-causes survival rates between the endoscopic screening group and the outpatient group (P < 0.001) (Fig 2B). The all-causes survival rates of the radiographic screening group were also significantly higher than those of the outpatient group (P = 0.011). There were significant differences in the all-causes survival rates between the endoscopic screening group and the radiographic group (P = 0.001).

Table 1. Basic characteristics of the endoscopic screening group, radiographic screening group, and outpatient group.

	Endoscopic screening group		Radiographic screening group		Outpatient group		P-value
	Number of patients	(%)	Number of patients	(%)	Number of patients	(%)	
Total number	347		166		980		
Age group							
40–49 years	9	2.6	1	0.6	94	9.6	< 0.001
50–59 years	25	7.2	15	9.0	254	25.9	
60–69 years	122	35.2	46	27.7	273	27.9	
70–79 years	191	55.0	104	62.7	359	36.6	
Sex							
Male	226	65.1	98	59.0	710	72.4	< 0.001
Female	121	34.9	68	41.0	270	27.6	

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The gastric cancer-specific survival rates of the patients with screen-detected cancer and patients with interval cancer in the screening groups are shown in **Fig 3A.** In the endoscopic screening group, the 5-year survival rate of the patients with screen-detected cancer was 91.9 ± 1.6% (95%CI: 87.5–93.8) and that of the patients with interval cancer was 91.3 ± 5.9% (95%CI: 69.5–97.8). In the radiographic screening group, the 5-year survival rate of the patients with screen-detected cancer was 86.8 ± 2.9% (95%CI: 79.9–91.5) and that of the patients with interval cancer was 68.7 ± 2.9% (95%CI: 45.2–83.7). In the endoscopic screening group, there were no significant differences in the gastric cancer-specific survival rates between the patients with screen-detected cancer and the patients with interval cancer (P = 0.869). The gastric cancer-specific survival rate was significantly higher in the patients with interval cancer in the endoscopic screening group than in the outpatient group (P = 0.018). In the radiographic screening group, there was a significant difference in the gastric cancer-specific survival rates between the patients with screen-detected cancer and the patients with interval cancer (P = 0.009). The gastric cancer-specific survival rate of the patients with interval cancer in the radiographic screening was not significantly different from that of the patients in the outpatient group (P = 0.961).

The all-causes survival rates of the patients with screen-detected cancer and patients with interval cancer patients in the screening groups are shown in **Fig 3B**. In the endoscopic screening group, there were no significant differences in the all-causes cancer survival rates between the patients with screen-detected cancer and the patients with interval cancer (P = 0.786). The all-causes survival rate of the patients with interval cancer in the endoscopic screening group was significantly higher than that of the patients in the outpatient group (P = 0.047). In the radiographic screening group, the all-causes survival rates of the patients with screen-detected cancer were significantly higher than those of the patients with interval cancer (P = 0.045). The all-causes survival rate of the patients with interval cancer in the radiographic screening group was not significantly different from that of the patients in the outpatient group (P = 0.771).

The results of the Cox proportional hazards analysis of gastric cancer death and all-causes death in the endoscopic screening group, radiographic screening group, and outpatient group are shown in **Table 3**. Compared with the risk of the outpatient group for gastric cancer death, the hazard ratio of interval cancer in the endoscopic screening group was lower (0.216, 95%CI: 0.054–0.868), but that of interval cancer in the radiographic screening group was equal (1.020, 95%CI: 0.506–2.055). There were no differences among sex, age group, and city in which the patients lived. For all-causes death, although the hazard ratio of the interval cancer in the endoscopic screening group was lower, it was not significantly different (0.420, 95%CI: 0.174–1.014).

Table 2. Comparison of the number of screen-detcted cancer and interval cancer in the endoscopic screening group and the radiographic screening group.

	Endoscopic screening group				Radiographic screening group			
	Screen-detected cancer		Interval cancer		Screen-detected cancer		Interval cancer	
	Number	(%)	Number	(%)	Number	(%)	Number	(%)
Total number	324		23		143		23	
Sex								
Male	214	66.0	12	52.2	84	58.7	14	60.9
Female	110	34.0	11	47.8	59	41.3	9	39.1
Age group								
40–49 years	9	2.8	0	0.0	1	0.7	0	0.0
50–59 years	22	6.8	3	13.0	14	9.8	1	4.3
60–69 years	116	35.8	6	26.1	36	25.2	10	43.5
70–79 years	177	54.6	14	60.9	92	64.3	12	52.2
City								
Tottori	144	44.4	13	56.5	76	53.1	9	39.1
Yonago	137	42.3	5	21.7	46	32.2	8	34.8
Kurayoshi	9	2.8	0	0.0	9	6.3	4	17.4
Sakaiminato	34	10.5	5	21.7	12	8.4	2	8.7
Location								
U	68	21.0	0	0.0	27	18.9	6	26.1
M	148	45.7	11	47.8	74	51.7	8	34.8
L	103	31.8	11	47.8	37	25.9	7	30.4
Unknown	5	1.5	1	4.3	5	3.5	2	8.7
Stage								
I	181	55.9	2	8.7	77	53.8	1	4.3
II	22	6.8	0	0.0	12	8.4	0	0.0
III	24	7.4	0	0.0	8	5.6	0	0.0
IV	9	2.8	0	0.0	2	1.4	1	4.3
Unknown	88	27.2	21	91.3	44	30.8	21	91.3
Histology								
Intestinal type	226	69.8	18	78.3	94	65.7	13	56.5
Diffuse type	87	26.9	1	4.3	42	29.4	7	30.4
Others	2	0.6	1	4.3	2	1.4	0	0.0
Unknown	9	2.8	3	13.0	5	3.5	3	13.0

U, Upper body; M, Middle body; L, Lower body

1) The location, histological type, and stage of all gastric cancers were studied. Tumor location was recorded using the Japanese Classification of Gastric Carcinoma, in which the stomach is anatomically divided into 3 portions, namely, upper, middle, and lower. [12]

2) Clinical stage was also used for determination of the clinical stage based on the Japanese Classification of Gastric Carcinoma [12].

3) Gastric cancers were also classified histologically into intestinal and diffuse types according to Lauren's criteria [13].

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HR, hazard ratio; CI, confidence interval

The risk factors associated with gastric cancer-specific death and all-causes death in the endoscopic screening group and radiographic screening group were also analyzed (Table 4). For gastric cancer death, the hazard ratio of interval cancer in the endoscopic screening group was nearly equal to that of screen-detected cancer in the endoscopic screening group (0.886, 95%

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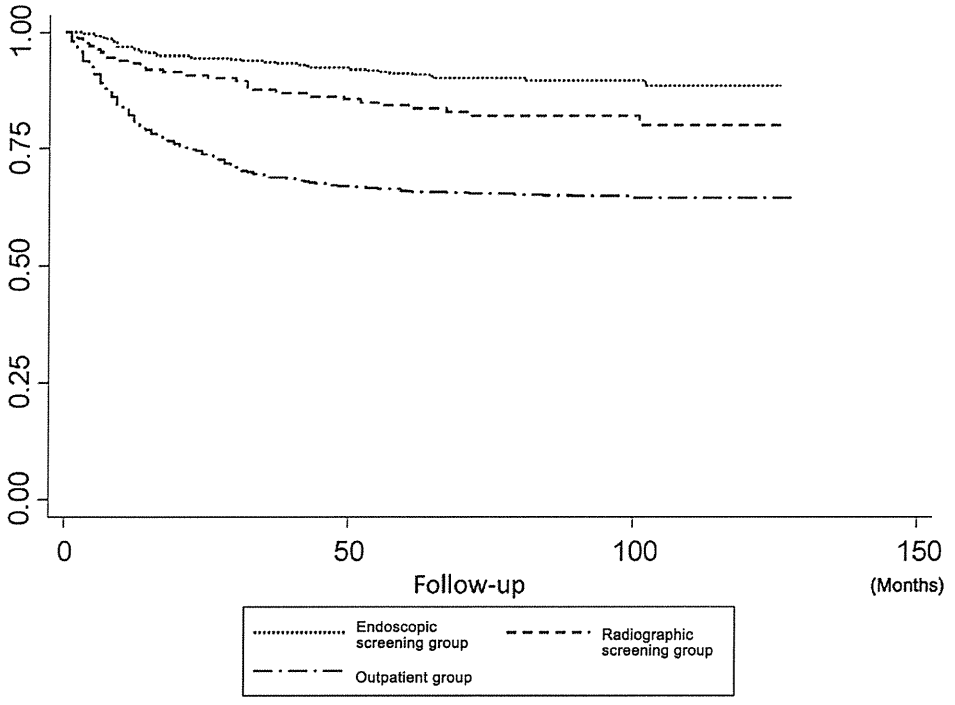
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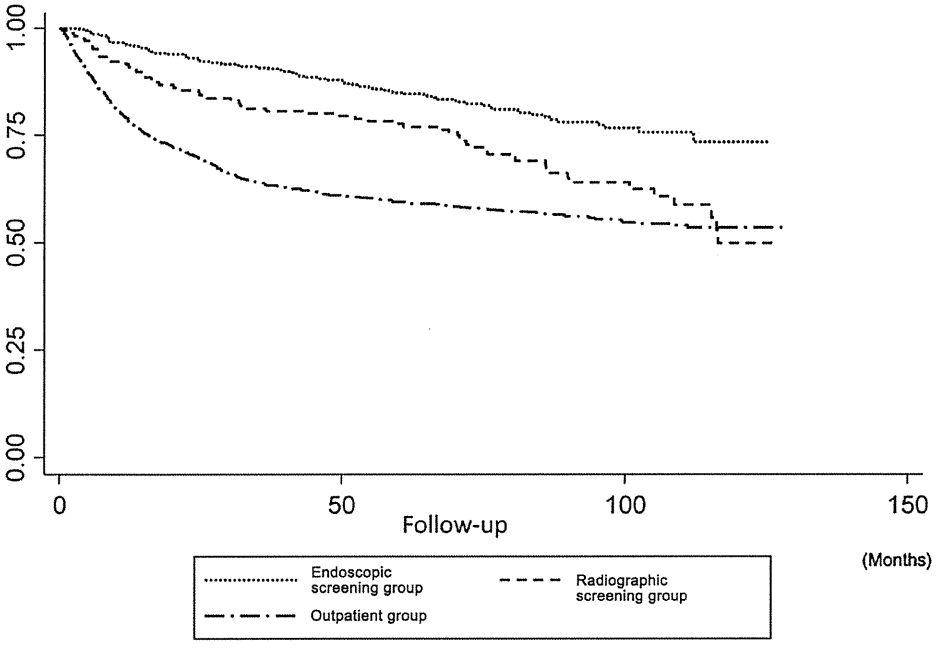
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Radiographic screening group
Outpatient group

Fig 2. Survival analyses of gastric cancer patients classified under the endoscopic screening, radiographic screening, and outpatient groups. Of the 1,493 gastric cancer patients, 347 patients were classified under the endoscopic screening group, 166 patients under the radiographic screening group, and 980 patients under the outpatient group. **A.** Gastric cancer-specific survival rates of the 3 different groups. There were significant differences in the gastric cancer-specific survival rate between the endoscopic screening group and the outpatient group ($P < 0.001$), as well as between the radiographic screening group and the outpatient group ($P < 0.001$). The gastric cancer-specific survival rates of the patients in the endoscopic screening group was significantly higher than those of the patients in the radiographic group ($P = 0.013$). **B.** All-causes survival rates of the 3 different groups. There was a significant difference in the all-causes survival rate between the endoscopic screening group and the outpatient group ($P < 0.001$). The all-causes survival rate of the patients in the radiographic screening group was significantly higher than that of the patients in the outpatient group ($P = 0.011$). There was a significant difference in the all-causes survival rate between the endoscopic screening group and the radiographic group ($P = 0.001$).

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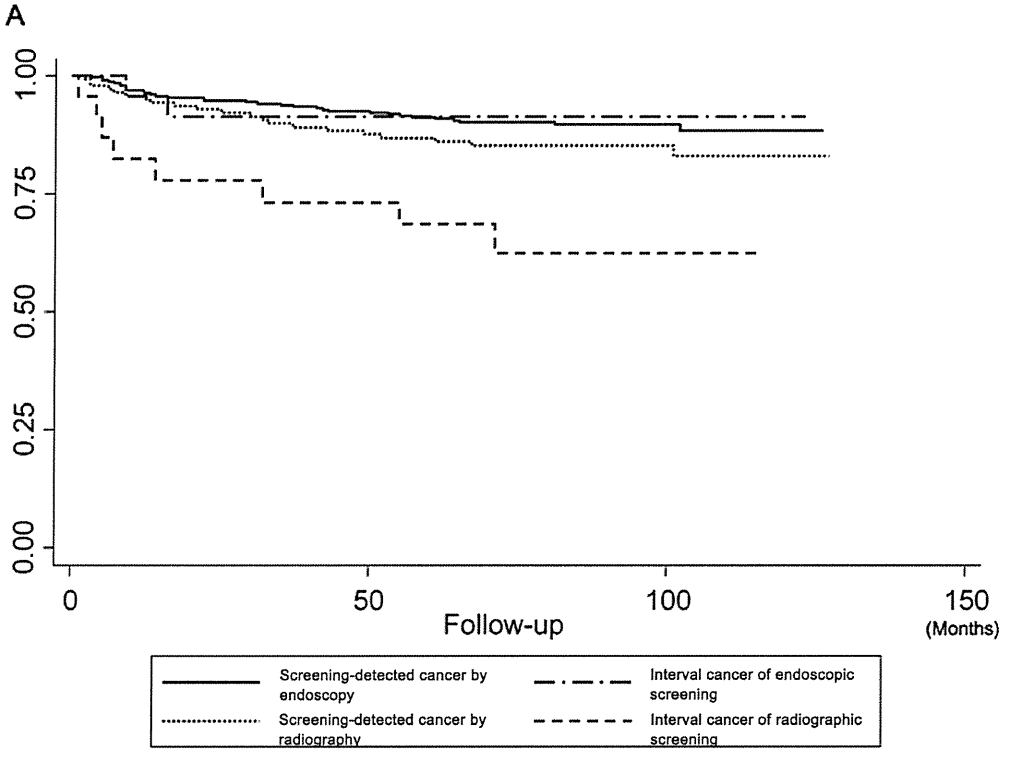
CI: 0.213–3.691). Although the hazard ratio of screen-detected cancer in the radiographic screening group was 1.506, it was not significantly different (95%CI: 0.871–2.603). The hazard ratios of interval cancer in the radiographic screening group were always significantly higher: 4.352 for gastric cancer death (95%CI; 2.009–9.427) and 3.091 for all-causes death (95%CI: 1.634–5.849). In the endoscopic screening group, since the hazard ratio of interval cancer was 0.886 for gastric cancer death (95%CI: 0.213–3.691) and 1.117 for all-causes death (95%CI: 0.450–2.771), the risk of interval cancer was nearly equal to that of screen-detected cancer.

Discussion

The present study showing the survival rate of patients with interval cancer indicated that the endoscopic screening group had a better prognosis than the radiographic screening group and outpatient group, as demonstrated by the results of gastric cancer-specific survival and all-causes survival analyses. The survival rate and the risk of gastric cancer death for patients with interval cancer were similar to those of patients with screen-detected cancer in the endoscopic screening group. Thus, interval cancer can potentially be used as an indicator for predicting the early effects of cancer screening. Interval cancer includes cases missed at the previous screening and cases which appeared because they grew rapidly as the preclinical phase (sojourn time) was shorter than the screening interval [15, 16]. Because of the good prognosis of interval cancer in endoscopic screening, the results suggest a possibility of reducing mortality from gastric cancer by endoscopic screening. However, this can be misleading because the survival rate of patients with screen-detected cancers is overestimated by length bias, lead time bias and over-diagnosis. Since we used the survival rate of patients with screen-detected cancers for comparison, there is a need for prudent interpretation of the survival rate of patients with interval cancer in the present study.

On the other hand, sensitivity can also be a factor for predicting the effectiveness of cancer screening. Greater sensitivity leads to high cancer detection rates during screening and lower interval cancer rates. Several studies have reported that the sensitivity of endoscopic screening is usually higher than that of radiographic screening [7, 8]. This implies that the rate of interval cancer is lower in endoscopic screening than in radiographic screening. Since endoscopic screening has a potential to detect early-stage cancer, localized cancer was reportedly more frequent in patients who had undergone endoscopic screening than in those who had undergone radiographic screening [8, 17, 18]. In mammographic screening, several studies have shown that interval cancers and screen-detected cancers have different clinicpathologic characteristics [15, 16, 19–21]. Although we could not obtain detailed information regarding the specific clinical stage of the interval cancers, the interval cancers on endoscopic screening for gastric cancer in a previous study were early-stage cancers only, whereas those on radiographic screening included late-stage cancers [7].

The survival rates of patients with interval cancer have been reported to be lower than those of patients with screen–detected cancer in mammographic screening [19, 20]. In the present study involving endoscopic screening for gastric cancer, the survival rates of the patients with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Follow-up
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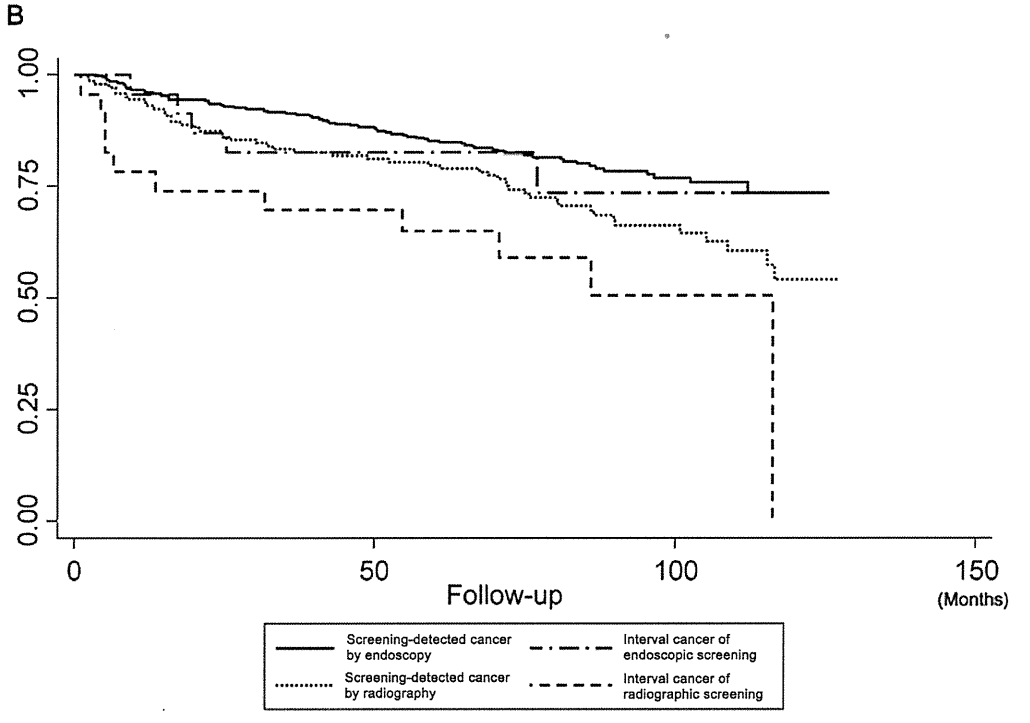
Screening-detected cancer by endoscopy
Interval cancer of endoscopic screening
Screening-detected cancer by radiography
Interval cancer of radiographic screening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Screening-detected cancer by endoscopy
Interval cancer of endoscopic screening
Screening-detected cancer by radiography
Interval cancer of radiographic screening

Fig 3. Survival analyses of patients with screen-detected cancer and patients with interval cancer in the endoscopic and radiographic screening groups. In the endoscopic screening group, there were 324 patients with screen-detected cancer and 23 patients with interval cancer. In the radiographic screening group, there were 143 patients with screen-detected cancer and 23 patients with interval cancer. **A.** Gastric cancer-specific survival rates of patients in the 4 different groups. In the endoscopic screening group, there was no significant difference in the gastric cancer-specific survival rates between the patients with screen-detected cancer and the patients with interval cancer (P = 0.869). The gastric cancer-specific survival rate was significantly higher in the patients with interval cancer in the endoscopic screening group than in the outpatient group (P = 0.018). In the radiographic screening group, there was a significant difference in the gastric cancer-specific survival rates between the patients with screen-detected cancer and the patients with interval cancer patients (P = 0.009). The gastric cancer-specific survival rate of the patients with interval cancer in the radiographic screening was not significantly different from that of the patients in the outpatient group (P = 0.961). **B.** All-causes cancer survival rates of patients with the 4 different groups. In the endoscopic screening group, there was no significant difference in the all-causes cancer survival rates between the patients with screen-detected cancer and the patients with interval cancer (P = 0.786). The all-causes survival rate of the patients with interval cancer in the endoscopic screening group was significantly higher than that of the patients in the outpatient group (P = 0.047). In the radiographic screening group, the all-causes cancer survival rate of the patients with screen-detected cancer was significantly higher than that of the patients with interval cancer (P = 0.045). The all-causes survival rate of the patients with interval cancer in the radiographic screening group was not significantly different from that of the patients in the outpatient group (P = 0.771).

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screen-detected cancer and the patients with interval cancers were not significantly different and higher than that of patients in the outpatient group. The risk of gastric cancer death from interval cancer in the endoscopic screening group was similar to that of gastric cancer death from screen-detected cancer in the endoscopic screening group. Although the screening interval was 1 year for endoscopic screening and radiographic screening in the study areas, a better prognosis might be expected for endoscopic screening. These results suggest that it may be possible to extend the endoscopic screening interval to more than 1 year. In fact, mortally reduction was shown in the screening programs in Korea with a screening interval of 2 years [8]. Although the number of endoscopic examinations has rapidly increased in Japan [22], insufficient capacity may be more of a barrier for endoscopic screening not to be introduced in local

Table 3. Cox proportional hazard analysis of gastric cancer death and all-causes death in the endoscopic screening group, radiographic screening group, and outpatient group.

	Gastric cancer death			All-causes death		
Characteristics	HR	(95%CI)	P-value	HR	(95%CI)	P-value
Group						
Outpatient group	1	-	-	1	-	-
Screen-detected cancer by endoscopic screening	0.245	(0.171–0.350)	< 0.001	0.385	(0.297–0.497)	< 0.001
Interval cancer in endoscopic screening	0.216	(0.054–0.868)	0.031	0.420	(0.174–1.014)	0.054
Screen-detected cancer by radiographic screening	0.368	(0.236–0.571)	< 0.001	0.647	(0.481–0.870)	0.004
Interval cancer in radiographic screening	1.020	(0.506–2.055)	0.957	1.104	(0.607–2.008)	0.746
Sex						
Male	1	-	-	1	-	-
Female	0.961	(0.776–1.191)	0.718	0.772	(0.640–0.932)	0.007
Age						
40–49 years	1	-	-	1	-	-
50–59 years	1.109	(0.699–1.759)	0.660	1.121	(0.732–1.717)	0.600
60–69 years	1.230	(0.793–1.907)	0.355	1.385	(0.926–2.070)	0.113
70–79 years	1.346	(0.879–2.060)	0.172	1.902	(1.291–2.804)	0.001
City						
Tottori	1	-	-	1	-	-
Yonago	0.881	(0.702–1.105)	0.273	0.975	(0.810–1.175)	0.794
Kurayoshi	1.154	(0.841–1.585)	0.374	1.133	(0.856–1.501)	0.383
Sakaiminato	0.732	(0.484–1.110)	0.142	0.743	(0.523–1.056)	0.098

doi:10.1371/journal.pone.0126796.t003

Table 4. Cox proportional hazard analysis of gastric cancer death and all-causes death for the endoscopic screening group and radiographic screening group.

	Gastric cancer death			All-causes death		
Characteristics	HR	(95%CI)	P-value	HR	(95%CI)	P-value
Group						
Screen-detected cancerby endoscopic screening	1	-	-	1	-	-
Interval cancerin endoscopic screening	0.886	(0.213–3.691)	0.868	1.117	(0.450–2.771)	0.811
Screen-detected cancer by radiographic screening	1.506	(0.871–2.603)	0.143	1.642	(1.136–2.373)	0.008
Interval cancer in radiographic screening	4.352	(2.009–9.427)	< 0.001	3.091	(1.634–5.849)	0.001
Sex						
Male	1	-	-	1	-	-
Female	0.786	(0.467–1.325)	0.367	0.465	(0.311–0.695)	<0.001
Age						
40–49 years	1	-	-	1	-	-
50–59 years	1.718	(0.211–13.969)	0.613	2.001	(0.250–16.014)	0.513
60–69 years	0.964	(0.128–7.247)	0.972	1.771	(0.242–12.979)	0.574
70–79 years	1.333	(0.183–9.707)	0.776	3.249	(0.453–23.321)	0.241
City						
Tottori	1	-	-	1	-	-
Yonago	1.208	(0.722–2.022)	0.472	1.188	(0.832–1.695)	0.343
Kurayoshi	0.423	(0.058–3.105)	0.397	0.512	(0.125–2.098)	0.352
Sakaiminato	0.757	(0.294–1.951)	0.564	0.663	(0.330–1.333)	0.249
Location						
U	1	-	-	1	-	-
M	0.237	(0.130–0.430)	< 0.001	0.390	(0.259–0.588)	<0.001
L	0.338	(0.184–0.620)	< 0.001	0.413	(0.264–0.656)	<0.001
Unknown	0.532	(0.127–2.238)	0.389	0.944	(0.402–2.219)	0.895
Stage						
I	1	-	-	1	-	-
II	7.343	(2.831–19.045)	< 0.001	2.458	(1.330–4.543)	0.004
III	13.154	(5.539–31.237)	< 0.001	3.197	(1.789–5.712)	< 0.001
IV	52.876	(20.820–134.284)	< 0.001	12.244	(5.967–25.124)	< 0.001
Unknown	4.881	(2.287–10.418)	< 0.001	1.760	(1.179–2.626)	0.006
Histology						
Intestinal type	1	-	-	1	-	-
Diffuse type	3.403	(2.028–5.711)	< 0.001	1.639	(1.134–2.367)	0.009
Others	2.663	(0.361–19.639)	0.337	2.964	(0.934–9.404)	0.065
Unknown	3.956	(1.518–10.310)	0.005	2.179	(1.051–4.515)	0.036

Group

HR, hazard ratio; CI, confidence interval

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communities. If the screening interval can be extended, endoscopic screening may be used efficiently even with limited resources.

A notable constraint of the present study is the lack of data regarding the clinical stage of the interval cancer. To evaluate the effects of interval cancer, follow-up of the participants of a population-based screening based on the cancer registry is needed. In Japan, cancer registries have not yet been prepared at the national level, and the registry method has not yet been standardized as of 2014 [23, 24]. The Tottori Cancer Registry is one of the most reliable systems with a long history in Japan. Although information about disease extension has been obtained as an alternative item for the clinical stage, this information is often lacking [25]. The quality of the Tottori Cancer Registry was, however, not optimal since the percentage of death-certification-only cases was 15.1% in 2007 which was lower than the national average [26]. Even if there was a notification of new cases in the cancer registration system, detailed information was often lacking because the clinical stage was not a necessary item. Fortunately, additional information could be obtained for the screening group from the Tottori Medical Association database because the association has the responsibility of implementing gastric cancer screening programs and collecting detailed information for quality assurance. However, we could not obtain additional detailed information regarding the numbers of medical institutions in Tottori Prefecture for the outpatient group and the interval cancer cases in both screening groups. These limitations prevented us from obtaining stage information sufficiently, thus careful interpretation of the results in reference to these contains is required.

This study has other limitations. First, the background difference should be considered between the endoscopic screening group and the radiographic screening group. Endoscopic screening has been performed in clinical practice in Tottori Prefecture. The age of the participants in endoscopic screening was more advanced than that of the participants in radiographic screening [7]. Individuals aged more than 70 years could be screened by physicians using endoscopy in their own private practice. Since younger people who have family physicians were fewer than older people who have family physicians, there was little opportunity for the younger people to be tested in clinical practice. Second, since there was no information as to whether or not the patients participated in opportunistic screenings, the outpatient group might include cancer patients which were detected by these screenings. Selection bias may also be considered in the selection of the screening method at the individual level. Third, the survival rate was different among hospitals in Japan [27]. Moreover, the present results are limited to local areas in Japan. Finally, subgroup analysis could not be adequately performed because of the small sample size.

In conclusion, the gastric cancer-specific and all-causes survival rates of patients with screen-detected cancers and patients with interval cancers were nearly equal in the annual endoscopic screening. The risk of gastric cancer death was lower in the patients with screen-detected and interval cancers in the endoscopic screening group than in the outpatient group. These results suggest the potential of endoscopic screening in reducing mortality from gastric cancer. However, additional studies must be performed to more extensively evaluate mortality reduction from gastric cancer by endoscopic screening as well as to investigate the impact of interval cancer on the effectiveness of endoscopic screening for gastric cancer.

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Author Contributions

Conceived and designed the experiments: CH TK. Performed the experiments: MS MO YO. Analyzed the data: CH TK. Contributed reagents/materials/analysis tools: CH MS. Wrote the paper: CH TK.

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