Table 1 Odds ratio (OR) and 95 % confidence interval (95 % CI) of gastric cancer risk in all and subgroup subjects according to quartiles of total reactive oxygen species (ROS)

	Q1 (lower)	Q3		Q5		*P* trend
	Ref	HR	95 % CI	HR	95 % CI	
Overall						
ROS, (median, case/control), *U*[a]	90/92	119/119		158/158		
n, (case/control)	101/98	98/98		103/99		
Univariate OR (95 % CI)	1	0.97	(0.65–1.45)	1.01	(0.68–1.51)	0.91
aOR (95 % CI)[b]	1	1.08	(0.69–1.70)	1.17	(0.74–1.86)	0.29
Sex						
Men						
ROS, (median, case/control), *U*[a]	88.5/92.5	119/119		158/160		
n, (case/control)	72/80	63/68		73/51		
Univariate OR (95 % CI)	1	1.03	(0.64–1.64)	1.59	(0.98–2.57)	0.14
aOR (95 % CI)[b]	1	1.10	(0.66–1.82)	1.68	(0.99–2.84)	0.10
Women						
ROS, (median, case/control), *U*[a]	90/89.5	119/120		157/157		
n, (case/control)	29/18	35/30		30/48		
Univariate OR (95 % CI)	1	0.72	(0.34–1.56)	**0.39**	**(0.18–0.82)**	**0.04**
aOR (95 % CI)[b]	1	0.82	(0.36–1.87)	0.47	(0.21–1.05)	0.21
Smoking						
Never						
ROS, (median, case/control), *U*[a]	90/91	119.5/119.5		154.5/156		
n, (case/control)	52/45	46/56		38/52		
aOR (95 % CI)[c]	1	0.64	(0.36–1.14)	**0.50**	**(0.27–0.92)**	0.11
aOR (95 % CI)[d]	1	0.78	(0.42–1.44)	0.63	(0.33–1.23)	0.62
Ever						
ROS, (median, case/control), *U*[a]	88/93	119/119		159/160		
n, (case/control)	49/53	52/42		65/47		
aOR (95 % CI)[c]	1	1.39	(0.78–2.46)	1.66	(0.94–2.92)	0.19
aOR (95 % CI)[d]	1	1.46	(0.78-2.72)	**1.95**	**(1.04–3.64)**	0.08
Alcohol drink						
No						
ROS, (median, case/control), *U*[a]	90/92	119/120		157/156.5		
n, (case/control)	51/45	50/42		43/60		
aOR (95 % CI)[c]	1	0.97	(0.54–1.74)	**0.52**	**(0.29–0.94)**	0.20
aOR (95 % CI)[d]	1	1.13	(0.60–2.13)	0.60	(0.32–1.14)	0.60
Yes						
ROS, (median, case/control), *U*[a]	90/92	120/118		158.5/160		
n, (case/control)	50/53	48/56		60/39		
aOR (95 % CI)[c]	1	0.97	(0.55–1.70)	**2.01**	**(1.11–3.63)**	0.14
aOR (95 % CI)[d]	1	1.05	(0.58–1.93)	**2.29**	**(1.19–4.44)**	0.07
Family history of gastric cancer						
No						
ROS, (median, case/control), *U*[a]	90/91	119/119		158/158.5		
n, (case/control)	89/87	86/89		92/92		
aOR (95 % CI)[c]	1	0.92	(0.60–1.40)	0.96	(0.62–1.47)	0.90
aOR (95 % CI)[d]	1	1.07	(0.68–1.68)	1.09	(0.68–1.74)	0.55
Yes						
ROS, (median, case/control), *U*[a]	87/94	118.5/121		158/149		

Table 1 continued

	Q1 (lower)	Q3		Q5		*P* trend
	Ref	HR	95 % CI	HR	95 % CI	
n, (case/control)	12/11	12/9		11/7		
aOR (95 % CI)[c]	1	2.02	(0.51–8.08)	2.06	(0.49–8.73)	0.54
aOR (95 % CI)[d]	1	1.81	(0.36–9.27)	2.13	(0.39–11.63)	0.48
BMI						
≤25 kg/m^2						
ROS, (median, case/control), *U*[a]	90/91	119/119		157/160		
n, (case/control)	81/80	78/71		87/73		
aOR (95 % CI)[c]	1	1.09	(0.70–1.72)	1.17	(0.74–1.85)	0.35
aOR (95 % CI)[d]	1	1.11	(0.68–1.80)	1.26	(0.77–2.07)	0.14
>25 kg/m^2						
ROS, (median, case/control), *U*[a]	87.5/93.5	119/119		167.5/155		
n, (case/control)	20/18	20/27		16/26		
aOR (95 % CI)[c]	1	0.56	(0.22–1.40)	0.47	(0.18–1.23)	0.11
aOR (95 % CI)[d]	1	0.85	(0.30–2.43)	0.55	(0.18–1.63)	0.22
H. pylori						
Negative						
ROS, (median, case/control), *U*[a]	88.5/86	117/121		151/158		
n, (case/control)	6/19	9/25		7/32		
aOR (95 % CI)[c]	1	1.31	(0.32–5.37)	0.36	(0.08–1.60)	0.18
aOR (95 % CI)[d]	1	1.29	(0.30–5.52)	0.22	(0.04–1.12)	0.10
Positive						
ROS, (median, case/control), *U*[a]	90/93	119/119		159/158		
n, (case/control)	95/79	89/73		96/67		
aOR (95 % CI)[c]	1	1.05	(0.68–1.63)	1.26	(0.80–1.97)	0.25
aOR (95 % CI)[d]	1	1.07	(0.69–1.66)	1.25	(0.80–1.97)	0.24
CagA						
Negative						
ROS, (median, case/control), *U*[a]	89.5/93.5	120/119		154/157		
n, (case/control)	26/24	22/25		29/33		
aOR (95 % CI)[c]	1	0.81	(0.36–1.83)	0.86	(0.39–1.88)	0.69
aOR (95 % CI)[d]	1	1.03	(0.43–2.48)	0.99	(0.44–2.25)	1.00
Positive						
ROS, (median, case/control), *U*[a]	90/91	119/119		158.5/160		
n, (case/control)	75/74	76/73		74/66		
aOR (95 % CI)[c]	1	1.07	(0.67–1.70)	1.12	(0.68–1.82)	0.55
aOR (95 % CI)[d]	1	1.08	(0.67–1.74)	1.21	(0.73–2.02)	0.36
Atrophy						
Negative						
ROS, (median, case/control), *U*[a]	86/91	119/121		151/157		
n, (case/control)	18/35	24/41		15/50		
aOR (95 % CI)[c]	1	1.12	(0.50–2.48)	0.63	(0.26–1.52)	0.29
aOR (95 % CI)[d]	1	1.23	(0.52–2.93)	0.56	(0.22–1.45)	0.21
Positive						
ROS, (median, case/control), *U*[a]	90/93	119/118		159/159		
n, (case/control)	83/63	74/57		88/49		

Table 1 continued

	Q1 (lower)	Q3		Q5		*P* trend
	Ref	HR	95 % CI	HR	95 % CI	
aOR (95 % CI)[c]	1	1.04	(0.64–1.69)	1.45	(0.88–2.38)	0.08
aOR (95 % CI)[d]	1	0.98	(0.60–1.60)	1.41	(0.86–2.32)	0.11

Conditional logistic analysis was used for measuring the associations for overall, male, and female paired subjects, and unconditional logistic analysis was used for a stratified analysis in subgroups by smoking status, alcohol consumption, family history of gastric cancer, BMI status, *H. pylori* infection, CagA seropositivity, or atrophy status

'$P < 0.05$' is the definition for the significance of bold

[a] Total ROS: 1 Unit = 1 mg/L H_2O_2

[b] Adjusted for BMI (continuous), family history of gastric cancer (no/yes), history of diabetes (no/yes), smoke status (no/ever), alcohol drink (<1d/w, ≥1d/w), salt intake (continuous), *H. pylori* (negative/positive), and atrophy (no/yes)

[c] Adjusted for matched variables including age (continuous), sex, study area, blood donation date, and fasting time at donation

[d] Further adjustment including BMI (continuous), family history of gastric cancer (no/yes), history of diabetes (no/yes), smoke status (no/ever), alcohol drink (<1d/w, ≥1d/w), salt intake (continuous), *H. pylori* (negative/positive), or atrophy (no/yes)

activity in this study, the results with inverse associations by BMI status between ROS levels and gastric cancer risk could not be explained as an underlying mechanism of ROS.

Our study has several limitations. First, there were 36,745 (38 %) eligible subjects participating in the survey who provided blood samples. Compared with nonparticipants, participants in the health check-up survey, especially women, had different socio-economic statuses and favorable lifestyle profiles (e.g., less smoking and alcohol consumption). Therefore, we were cautious in generalizing or interpreting the results in this study [8]. Second, the relatively small sample size of this study was not available for conducting further analysis regarding histologic subtype. Third, we only measured the total ROS level; the components of ROS may have different roles or functions in oxidant stress.

In summary, the overall distribution of ROS apparently was not associated with the development of gastric cancer. However, exogenous factors creating extremely high levels of ROS, such as smoking and alcohol consumption, increased the risk of development of gastric cancer.

Acknowledgments This study was supported by the National Cancer Center Research and Development Fund (23-A-31[toku] and 26-A-2; since 2011), a Grant-in-Aid for Cancer Research from the Ministry of Health, Labor, and Welfare of Japan (from 1989 to 2010), and a Grant-in-Aid for the Third-Term Comprehensive Ten-Year Strategy for Cancer Control from the Ministry of Health, Labor, and Welfare of Japan. We are indebted to the Aomori, Iwate, Ibaraki, Niigata, Osaka, Kochi, Nagasaki, and Okinawa Cancer Registries for providing their incidence data. We also appreciate all the members of the JPHC study.

Conflict of interest No potential conflicts of interest were disclosed.

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JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2016, 46(3) 284–286
doi: 10.1093/jjco/hyv191
Advance Access Publication Date: 10 January 2016
Epidemiology Note

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Epidemiology Note

Quantification of the increase in thyroid cancer prevalence in Fukushima after the nuclear disaster in 2011—a potential overdiagnosis?

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Received 15 September 2015; Accepted 20 November 2015

Abstract

A thyroid ultrasound examination programme has been conducted in Fukushima Prefecture, Japan, after the nuclear disaster in 2011. Although remarkably high prevalence of thyroid cancer was observed, no relevant quantitative evaluation was conducted. We calculated the observed/expected (O/E) ratio of thyroid cancer prevalence for the residents aged ≤20 years. Observed prevalence was the number of thyroid cancer cases detected by the programme through the end of April 2015. Expected prevalence was calculated as cumulative incidence by a life-table method using the national estimates of thyroid cancer incidence rate in 2001–10 (prior to the disaster) and the population of Fukushima Prefecture. The underlying assumption was that there was neither nuclear accident nor screening intervention. The observed and estimated prevalence of thyroid cancer among residents aged ≤20 years was 160.1 and 5.2, respectively, giving an O/E ratio of 30.8 [95% confidence interval (CI): 26.2, 35.9]. When the recent increasing trend in thyroid cancer was considered, the overall O/E ratio was 22.2 (95% CI: 18.9, 25.9). The cumulative number of thyroid cancer deaths in Fukushima Prefecture, estimated with the same method (annual average in 2009–13), was 0.6 under age 40. Combined with the existing knowledge about radiation effect on thyroid cancer, our descriptive analysis suggests the possibility of overdiagnosis. Evaluation including individual-level analysis is required to further clarify the contribution of underlying factors.

Key words: early detection of cancer, radioactive hazard release, thyroid neoplasms, ultrasonography

Following the Fukushima Daiichi nuclear disaster on 11 March 2011, a thyroid ultrasound examination programme (Thyroid Screening Program) was established for residents aged ≤18 years of Fukushima Prefecture, Japan (1). The purpose of this programme was to assess the effect of the disaster on the incidence of childhood or adolescent thyroid cancer in the devastated area. The first 3 years were allocated to an 'Initial' phase, which served as a control period for evaluating the following 'Full-scale' phase (2,3). As of 30 April 2015, 300 476 children have been tested in the Initial phase (screening rate, 81.7%) (4). A total of 113 cases were either found to have or were suspected of having thyroid malignancy, of whom 99 underwent surgical treatment. However, no relevant quantitative evaluation was conducted so far. We recently estimated the prevalence of age-specific thyroid cancer in Fukushima Prefecture prior to the disaster (5). Here, we aimed to compare the observed prevalence of thyroid cancer in the Thyroid Screening Program with the estimated historical controls on the assumption that there was neither nuclear accident nor screening intervention.

We calculated the observed/expected (O/E) ratio of thyroid cancer prevalence for residents in Fukushima Prefecture aged ≤20 years.

Observed prevalence was calculated by the number of thyroid cancer cases detected by the Thyroid Screening Program through the end of April 2015. Participants of the programme are residents of Fukushima Prefecture, including those who evacuated outside the prefecture, who were born between 2 April 1992 and 1 April 2011. Age range at the time of the disaster was 0–19 years. The number of detected cases was corrected for screening rate by multiplying the inverse of the age-specific screening rate (4).

Expected prevalence was obtained from our previous report (5,6), calculated by a life-table method using the national estimates of thyroid cancer incidence rate in 2001–10 (prior to the disaster) and the population of Fukushima Prefecture. In brief, using a life-table method, 5-year age-specific cumulative risk of thyroid cancer incidence in 2010 was calculated from thyroid cancer incidence and mortality rates, and all-cause mortality rates (7,8). Then, the calculated 5-year cumulative risk was converted into 1-year cumulative risk using spline smoothing. Finally, age-specific prevalence of thyroid cancer was estimated by multiplying the age-specific cumulative risk in 2010 by the 0-year-old population in the corresponding calendar year.

Because thyroid cancer incidence rate in Japan has recently been increasing (9), expected prevalence in 2014 was also estimated by multiplying the average annual percent change during the 10 years (males 1.2% per year; females 4.5% per year; 0–19 years old). The 95% confidence interval (CI) of O/E ratio was calculated assuming a Poisson distribution. The age-specific cumulative risk of thyroid cancer deaths under age 40 was calculated by applying the same life-table method to the mortality data in the latest 5 years (2009–13).

Figure 1 shows the estimated thyroid cancer prevalence and number of malignant cases (including suspected malignancy) detected by the Thyroid Screening Program. The estimated prevalence of thyroid cancer among residents aged ≤20 years in 2010 in Fukushima Prefecture was 1.2 for males and 4.0 for females. The corresponding observed number of malignant cases was 54.8 for males and 105.3 for females.

Table 1 shows results for the O/E ratio. The observed and estimated prevalence of thyroid cancer among residents in Fukushima Prefecture aged ≤20 years was 160.1 and 5.2, respectively, giving an O/E ratio of 30.8 (95% CI: 26.2, 35.9). The O/E ratio was higher for males than for females: 46.1 (95% CI: 34.5, 59.8) and 26.6 (95% CI: 21.7, 32.0), respectively. When we assume that the recent increasing trend in thyroid cancer continues, the overall O/E ratio was 22.2 (95% CI: 18.9, 25.9).

The estimated cumulative number of thyroid cancer deaths in Fukushima Prefecture (annual average in 2009–13) was 0.10 (0.02 for males and 0.08 for females) by age 29, and 0.60 (0.27 for males and 0.33 for females) by age 39.

Using a modelling approach, Jacob et al. estimated that the screening factor in Fukushima Prefecture was 7.4 (95% CI: 0.96, 17.3) (10). Our estimate of screening impact was three to four times higher than this previous result. In their estimation, the detection rate of the screening programme was assumed to be 2.1 times higher in Fukushima than that in Chernobyl, based on the ratio of the numbers of nodules larger than 10 and 5 mm. However, the actual ratio observed in the Fukushima program was 3.4 (4). Screening in Chernobyl was performed nearly 15 years ago; recent improvements in diagnosis would have further increased the detection rate. The upper limit of 95% CI of their estimate would be 28.0 when applying the ratio observed in the Fukushima program. This value is close to our estimates.

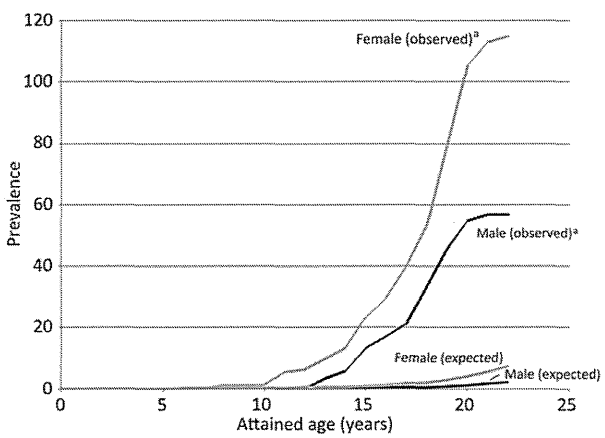

Figure 1. Age-specific prevalence of thyroid cancer in Fukushima Prefecture, expected in 2010 and observed as of the end of April 2015. [a]Confirmed by aspiration biopsy (including suspected malignancy). The detected number was corrected for screening rate.

Table 1. Observed and expected thyroid cancer prevalence in Fukushima Prefecture, as of the end of 2014

	Sex	Number of malignant cases[a]	Percentage among target population	O/E ratio	95% CI
Observed (age at screening ≤20)[b]	Males	54.8	0.032		
	Females	105.3	0.064		
	Total	160.1	0.047		
Expected (attained age ≤20)					
Based on average incidence rate in 2001–10[c]	Males	1.2	0.001	46.1	34.5, 59.8
	Females	4.0	0.002	26.6	21.7, 32.0
	Total	5.2	0.002	30.8	26.2, 35.9
Based on incidence rate in 2014[d]	Males	1.3	0.001	41.4	31.0, 53.7
	Females	5.9	0.004	17.9	14.6, 21.6
	Total	7.2	0.002	22.2	18.9, 25.9

O/E, observed/expected; CI, confidence interval.

[a]Including suspected malignancy.

[b]Corrected for age-specific screening rate.

[c]Calculated using the national incidence rate between 2001 and 2010.

[d]Calculated using the national incidence rate extrapolated to 2014 using the average annual percent change between 2001 and 2010.

Radiation-induced thyroid cancer cases are not expected to be detected before 3 years after the exposure according to the finding in Chernobyl (11). That is why the first 3 years were allocated to the Initial phase of the Thyroid Screening Program (it was actually extended by 1 year). We limited our analysis to those aged 20 years, which corresponds to 3 years at maximum after the potential radiation exposure. Even when we extended the analysis to age 21 years, no increase in O/E ratio was observed [males and females: 23.9 (95% CI: 20.4, 27.8), based on incidence rate in 2001–2010]. An estimated effective radiation exposure dose was available for 65 (57.5%) of the 113 detected cases, and was 2.2 mSv maximum and <1 mSv among 45 cases (71.4%) (4). This is within the annual effective dose from natural sources (2.4 mSv on average, with elevated values up to 10–20 mSv) (12).

The excess relative risk of thyroid cancer among children exposed to radiation from the Chornobyl accident was estimated to be 5.25 per gray (95% CI: 1.70, 27.5) (13). If this dose–response gradient can be applied to the Fukushima case within a short latency period, the observed high prevalence of thyroid cancer is unlikely to be explained by radiation exposure. Additionally, our estimate of cumulative number of thyroid cancer deaths in Fukushima was less than 1 under age 40, suggesting a possibility that detected cases would not become fatal. Taken together, our descriptive analysis suggests the possibility of overdiagnosis, though evaluation including individual-level analysis is required to further clarify the contribution of underlying factors.

Our estimates have several uncertainties. Firstly, although the overall screening rate was high (81.7%), there was variation with age at disaster (0–5 years: 85.7%; 6–10 years: 95.8%; 11–15 years: 83.1%; 16–18 years: 52.7%) (4). Given that the oldest age group had a low participation rate, we conducted a sensitivity analysis excluding the oldest age group (limiting to attained age of 18 years or younger). O/E ratio was 32.1 (95% CI: 25.6, 39.5), almost the same as the overall result (30.8; see Table 1). Secondly, to ensure data stability, we calculated the expected prevalence of thyroid cancer in Fukushima Prefecture using the national estimate of thyroid cancer incidence rate. A population-based cancer registry was started in Fukushima Prefecture in 2010: incidence rates of thyroid cancer among juveniles in 2011 were similar to the national estimates: 0.0 vs. 0.9 for 15–19 years old and 4.6 vs. 4.7 for 20–24 years old (per 100 000 population). Finally, we did not have information to distinguish cancers which could be ascertained even in the absence of screening programme and the cancers which could be detected only when screening programme was conducted.

In summary, during the first 3 years after the nuclear disaster in Fukushima, Japan, the Thyroid Screening Program targeting juveniles has identified 20–30 times more thyroid cancer cases than would be expected if the programme had not been implemented. The estimated cumulative number of thyroid cancer deaths in Fukushima (annual average in 2009–13) was 0.6 under age 40. Combined with the existing knowledge about radiation effect on thyroid cancer, our descriptive analysis suggests the possibility of overdiagnosis. Evaluation including individual-level analysis is required to further clarify the contribution of underlying factors.

Author's contributions

K.K.: Conception and design of the study, analysis, interpretation of data and drafting of the paper. K.-i.K.: analysis and revision of the paper for critical intellectual content. S.T.: conception and design of the study, and revision of the paper.

Acknowledgements

The authors sincerely thank Dr Megumi Hori at the National Cancer Center, Japan, for her technical assistance in this study.

Funding

This work was supported by Grants-in-aid for the Cancer Control Policy from the Ministry of Health, Labour and Welfare, Japan (H26-Ganseisaku-Shitei-002, H26-Ganseisaku-Ippan-013). The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. Funding to pay the Open Access publication charges for this article was provided by the former grant (H26-Ganseisaku-Shitei-002).

Conflict of interest statement

S.T. is a member of the Prefectural Oversight Committee for Fukushima Health Management Survey.

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COMMENTARY

Have we Comprehensively Evaluated the Effectiveness of Endoscopic Screening for Gastric Cancer?

Chisato Hamashima

Abstract

Endoscopy has been increasingly used in clinical practice and as a standardized examination procedure for gastrointestinal diseases. However, only a few studies on endoscopic screening for evaluating mortality reduction from gastric cancer have been carried out. Even if a high detection rate is obtained in clinical practice, such a rate cannot be directly accepted as evidence providing the effectiveness of cancer screening. Endoscopic screening for gastric cancer is not an exception of possibility to detect overdiagnosis. If detection rate is used for the evaluation of the effectiveness of cancer screening, the possibility of overestimating the effectiveness of cancer screening cannot be ruled out. To avoid the effect of overdiagnosis and confirm the effectiveness of endoscopic screening, mortality reduction from gastric cancer must be carefully evaluated by conducting reliable studies. The burden of gastric cancer remains real and this cannot be ignored in Eastern Asian countries. To determine the best available method for gastric cancer screening, evaluation of its effectiveness is a must. Endoscopic screening for gastric cancer has shown promising results, and thus deserves further comprehensive evaluation to reliably confirm its effectiveness and how its optimal use can be strategically promoted.

Keywords: Gastric cancer screening - upper gastrointestinal endoscopy - mortality reduction - overdiagnosis

Asian Pac J Cancer Prev, **16 (8)**, 3591-3592

Endoscopy has been increasingly used in clinical practice and as a standardized examination procedure for gastrointestinal diseases. Notably, the uses of upper gastrointestinal series with barium meal for diagnostic examination have progressively decreased. This situation has ushered the gradual introduction of endoscopic screening in clinical settings. In fact, high detection rates of gastric cancer have been reported with endoscopic screening (Tashiro et al., 2006; Lu et al., 2014). Regarding effectiveness, there is great expectation that endoscopic screening has a high possibility of reducing mortality from gastric cancer. However, only a few studies on endoscopic screening for evaluating mortality reduction from gastric cancer have been carried out. To evaluate the effectiveness of cancer screening, the appropriate target population and study design with final outcomes should be identified. The European guidelines for quality assurance in cervical cancer screening previously defined the ranking of study designs and outcomes for the evaluation of cervical cancer screening (International Agency for Research on Cancer, 2006). The basic concept can be adopted for the assessment of endoscopic screening. To confirm the effectiveness of endoscopic screening, the following basic requirements should be included in the evaluation points: target population, outcome, and study design.

The target of cancer screening is an asymptomatic individual with an average risk, which is different from individuals presenting with symptoms. Even if a high detection rate is obtained in clinical practice, such rate cannot be directly translated as evidence providing the effectiveness of cancer screening. The target subjects are usually different between cancer screening and clinical practice. In a previous Japanese study, although the subjects of endoscopic screening were the selected participants who were examined by multiphasic health check-up, the comparators were selected from patients in the hospital (Hosaokawa et al., 2008). To evaluate the effectiveness of endoscopic screening, comparators should also be chosen from the asymptomatic population. This is because patients might have risks of gastric cancer even if they did not have examination histories of upper gastrointestinal series with barium meal and endoscopy.

The effectiveness of cancer screening should be evaluated based on mortality reduction from cancer. Although the detection rate is often reported as the outcome measure in cancer screening, it is not a preferable indicator for showing evidence regarding the effectiveness of cancer screening. Cancers detected by screening include early stages of gastric cancer which has a possibility to progress to the death of the individual or overdiagnosis cases. Overdiagnosis is defined as the detection of cancers that might never progress to manifest symptoms during a person's life and it could not be the cause of death (International Agency for Research on Cancer, 2002). Since overdiagnosis leads to unnecessary examinations and overtreatment, patients who are diagnosed as having

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indolent cancers do not have any benefit from cancer screening. Endoscopic screening for gastric cancer is not an exception. Endoscopy can detect cases of early stage cancer which is often the target for endoscopic surgical resection. Although there is currently no report of overdiagnosis for gastric cancer screening, the numbers of detected cancer by endoscopic screening were twice the expected numbers (Hamashima et al., 2006). These cases might be included in the overdiagnosis cases. If detection rate is used for the evaluation of the effectiveness of cancer screening, the possibility of overestimating the effectiveness of cancer screening cannot be ruled out. To avoid the effect of overdiagnosis and confirm the effectiveness of endoscopic screening, mortality reduction from gastric cancer must be carefully evaluated by conducting reliable studies.

The most reliable method for evaluating mortality reduction is a randomized controlled trial (RCT) (International Agency for Research on Cancer, 2006). In fact, the efficacies of mammographic screening and colorectal cancer screening using fecal occult blood test have been evaluated by RCTs. However, the previous results related to such effectiveness of gastric cancer screening were solely based on a few observational studies (Hamashima et al., 2008). Recently, our group has published the results of a community-based case-control study to evaluate the effectiveness of endoscopic screening for gastric cancer. The findings of this study suggest a 30% reduction in gastric cancer mortality by endoscopic screening within 36 months before the date of gastric cancer diagnosis (Hamashima et al., 2013). Interestingly, a Korean study also reported a 57% mortality reduction by endoscopic screening of a nested case-control study based on the national database (Cho, 2014). These results suggest a high possibility of achieving mortality reduction from gastric cancer by endoscopic screening. However, the results have been obtained from observational studies only. Realistically, it is difficult to perform RCT for endoscopic screening in Korea and Japan, countries that have already established national programs for gastric cancer screening (Oshima, 1994; Kim et al., 2011). Although case-control and cohort studies are the second best methods, there is a serious need for the accumulation of more valid evidence from Asian countries if the introduction of endoscopic screening to communities is to be realized.

The burden of gastric cancer remains real and this cannot be ignored in Eastern Asian countries. To determine the best available method for gastric cancer screening, evaluation of its effectiveness is a must. Endoscopic screening for gastric cancer has shown promising results, and thus deserves further comprehensive evaluation to reliably confirm its effectiveness and how its optimal use can be strategically promoted.

Acknowledgements

The author thanks Dr. Edward Barroga, Senior Medical Editor of Tokyo Medical University, for editing the manuscript.

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PLOS | ONE

RESEARCH ARTICLE

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

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OPEN ACCESS

Citation: Hamashima C, Shabana M, Okamoto M, Osaki Y, Kishimoto T (2015) Survival Analysis of Patients with Interval Cancer Undergoing Gastric Cancer Screening by Endoscopy. PLoS ONE 10(5): e0126796. doi:10.1371/journal.pone.0126796

Academic Editor: John Green, University Hospital Llandough, UNITED KINGDOM

Received: November 4, 2014

Accepted: April 8, 2015

Published: May 29, 2015

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.

Funding: This study was supported by a Grant-in-Aid for H25-Third Term Comprehensive Control Research for Cancer 022 from the Japanese Ministry of Health, Labour and Welfare.

Competing Interests: The authors have declared that no competing interests exist.

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

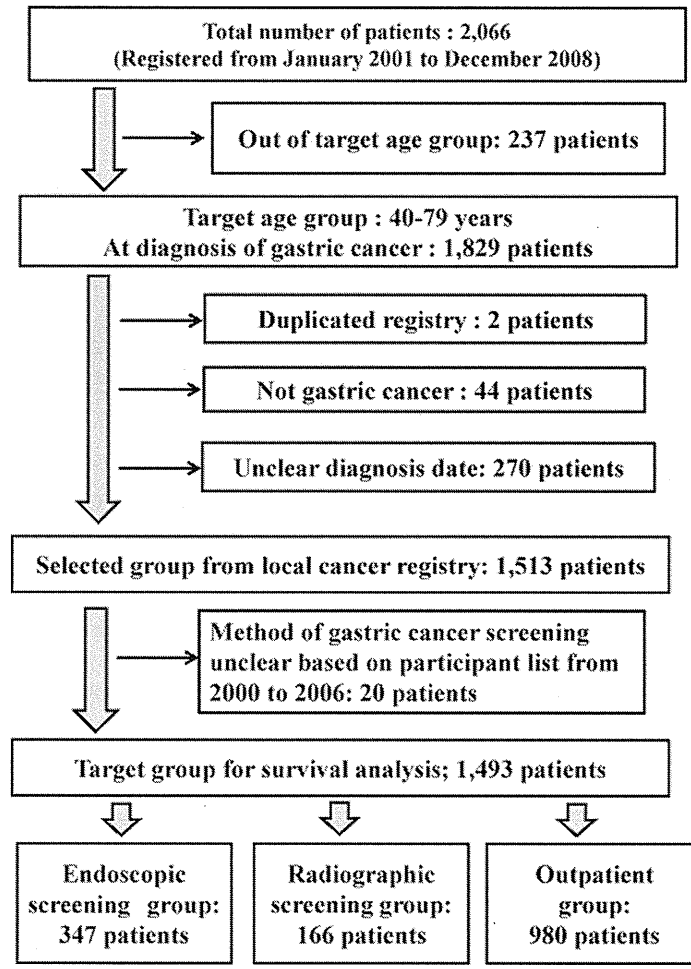


Fig 1. Flow-chart of the selection process for the target group. There were 2,066 potential subjects with gastric cancer in the 4 cities examined in Tottori Prefecture (i.e., Tottori, Yonago, Kurayoshi, and Sakaiminato). The following patients were excluded: those who 1) were over 80 years old and less 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).

doi:10.1371/journal.pone.0126796.g001

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	

doi:10.1371/journal.pone.0126796.t001

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].

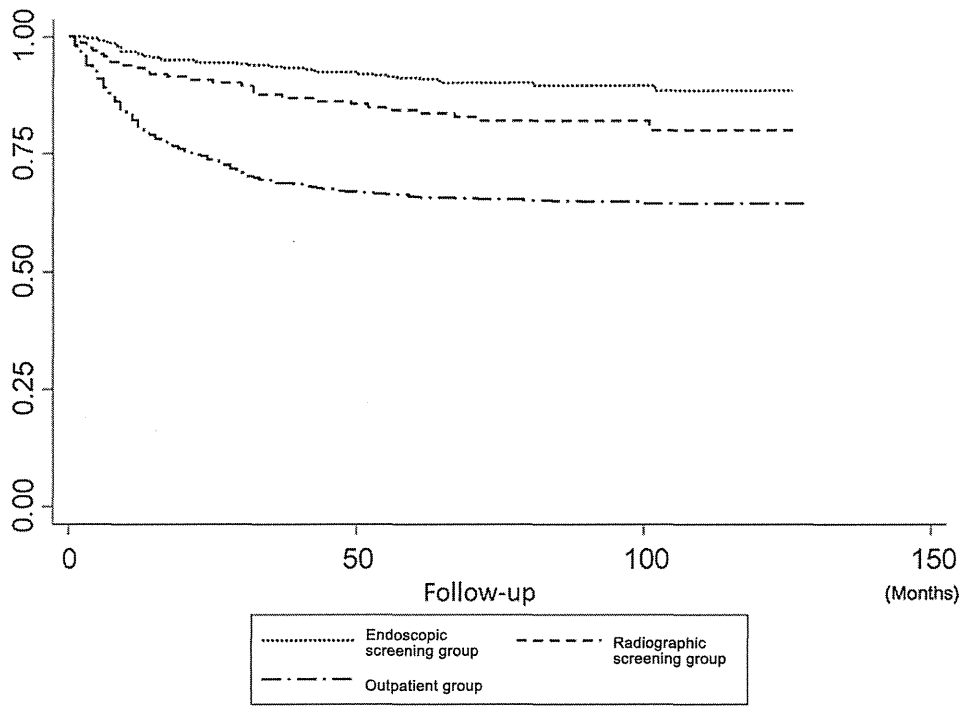
3) Gastric cancers were also classified histologically into intestinal and diffuse types according to Lauren's criteria [13].

doi:10.1371/journal.pone.0126796.t002

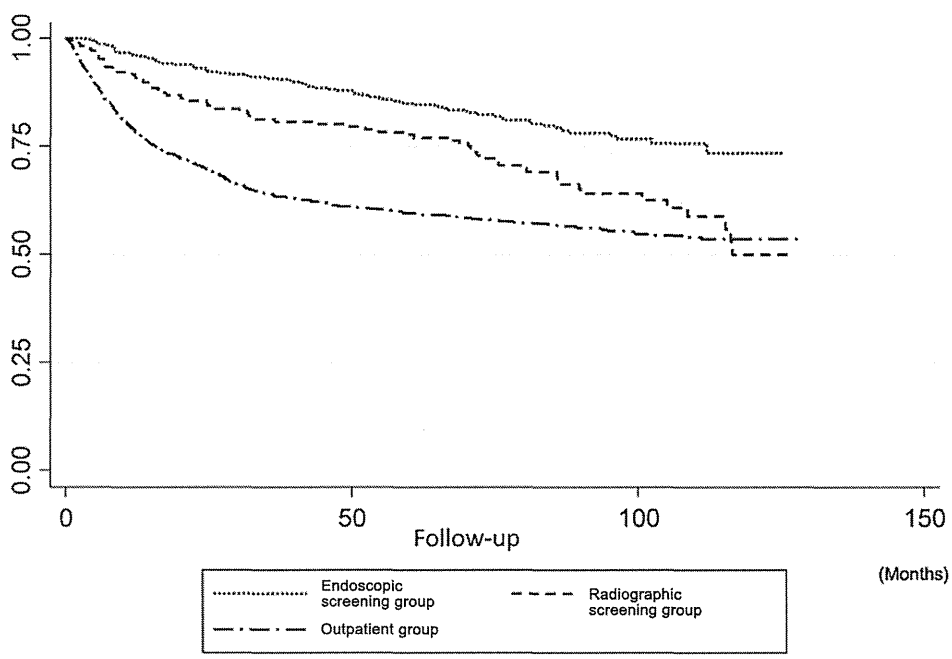
HR, hazard ratio; CI, confidence interval

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%

A


1.00
0.75
0.50
0.25
0.00
0
50
100
150
Follow-up
(Months)
Endoscopic screening group
Radiographic screening group
Outpatient group

B


1.00
0.75
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0.25
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50
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150
Follow-up
(Months)
Endoscopic screening group
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 ($P = 0.001$).

doi:10.1371/journal.pone.0126796.g002

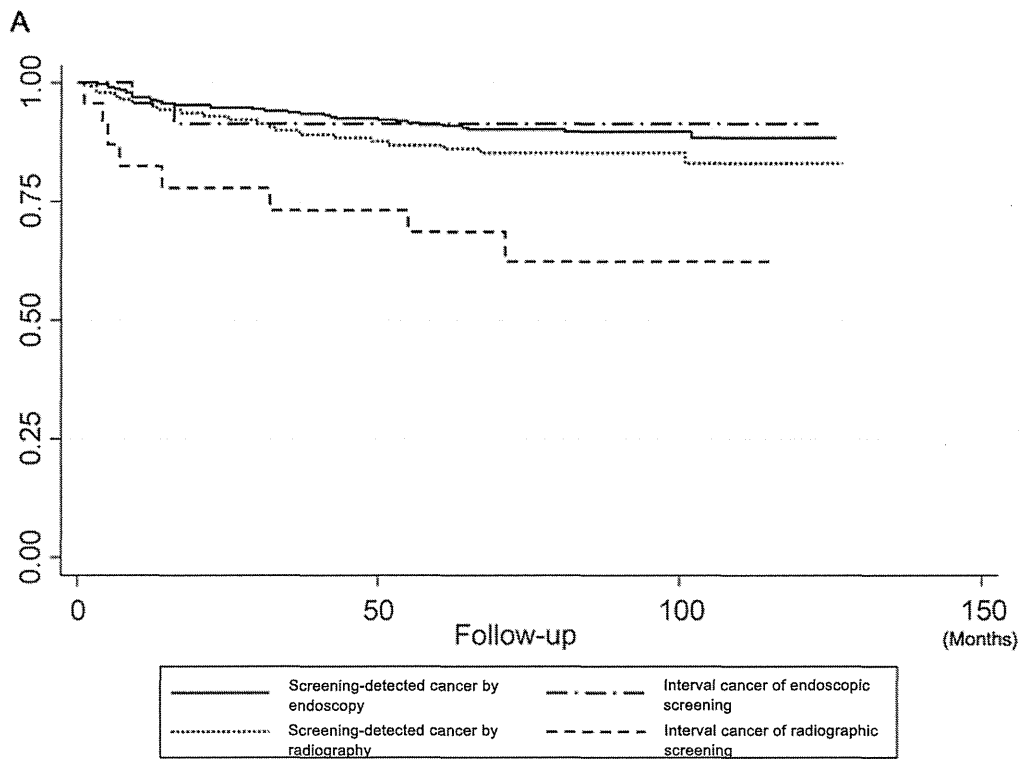
CI: 0.213–3.691). Although the hazard ratio of screen-detected cancer in the radiographic screening group was 1.506, it was not significantly different (95%CI: 0.871–2.603). The hazard ratios of interval cancer in the radiographic screening group were always significantly higher: 4.352 for gastric cancer 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


A
1.00
0.75
0.50
0.25
0.00
0
50
100
150
Follow-up
(Months)
Screening-detected cancer by endoscopy
Interval cancer of endoscopic screening
Screening-detected cancer by radiography
Interval cancer of radiographic screening

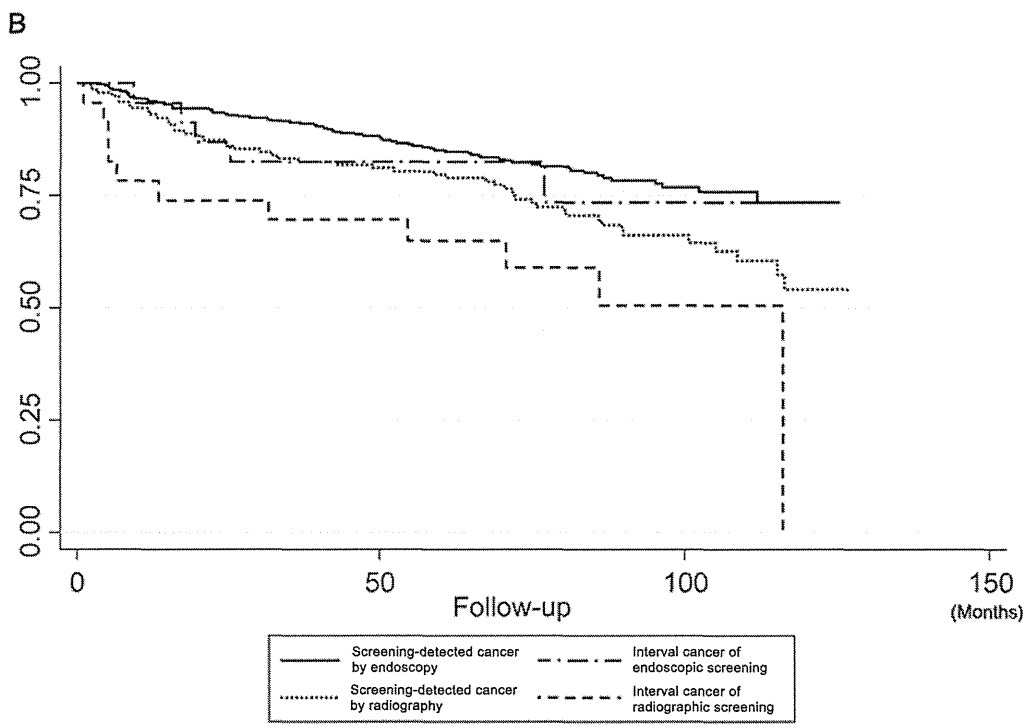

B
1.00
0.75
0.50
0.25
0.00
0
50
100
150
Follow-up
(Months)
Screening-detected cancer by endoscopy
Interval cancer of endoscopic screening
Screening-detected cancer by radiography
Interval cancer of radiographic screening

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).

doi:10.1371/journal.pone.0126796.g003

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

doi:10.1371/journal.pone.0126796.t004