

Ⅱ. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
濱島ちさと、 祖父江友孝 (分担)	スクリーニングと その適用	田中平三、徳 留信寛、辻一 郎、吉池信 男	健康・栄養科学 シリーズ 社 会・環境と健康 改訂第3版	南江堂	東京	2010	101-104
Hamashima C	Recommendations for prostate cancer prevention in the Asia-pacific region.	Asian Pacific Organization for Cancer Prevention	Cancer Report 2010	New Hope in Health Foundation	Turkey	2010	134-137
祖父江友孝、 津金昌一郎、 濱島ちさと (分担)	がんの統計・発生 要因と予防・がん 検診	日本がん治療 認定医機構教 育委員会	がん治療認定 医教育セミナ ーテキスト 第4版	日本がん 治療認定 医機構教 育委員会	東京	2010	13-18
濱島ちさと (分担)	第II章 Principles of Oncology, 4. がんの予防、検診、 2. 「がんの検診」	日本臨床腫瘍 学会編集	新臨床腫瘍学 —がん薬物療 法専門医のため に一改訂第 3版	南江堂	東京	2012	108-111

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
濱島ちさと	がん検診、日常診療に使える ガイドライン特集・より 良い診療を目指して	総合臨床 (増刊号)	59	1131-1134	2010
Hamashima C, Aoki D, Miyagi E, Saito E, Nakayama T, Sagawa M, Saito H, Sobue T	The Japanese research group for development of cervical cancer screening guidelines. : The Japanese guideline for cervical cancer screening.	Jpn J Clin Oncol	40(6)	485-502	2010
濱島ちさと	「有効性評価に基づく子宮 頸がん検診ガイドライン」 におけるHPV検査の位 置づけ	婦人科悪性腫瘍化 学療法研究機構 「化療ニュース」	19(1)	3-5	2010
東尚弘、町井涼 子、青木綾子、濱 島ちさと、中山富 雄、佐川元保、齋 藤博	コンセンサスパネルを用 いた肺がん検診チェッ クリストの適切検討と改定 案作成	CT検診	17(2)	106-114	2010

Higashi T, Machii R, Aoki A, <u>Hamashima C</u> , Saito H	Evaluation and revision of checklists for screening facilities and municipal governmental programs for gastric cancer and colorectal cancer screening in Japan.	Jpn J Clin Oncol	40(11)	1021-1030	2010
関愛子、平井啓、長塚美和、原田和弘、新井弘和、挟間礼子、石川善樹、 <u>濱島ちさと</u> 、齋藤博、渋谷大助	乳がん検診に対する態度の測定	厚生の指標	58(2)	14-20	2011
岡本幹三、尾崎米厚、 <u>岸本拓治</u> 、田原文	鳥取県における75歳未満の高がん死亡率に関する記述疫学的研究	JACR Monograph	15	47-49	2010
<u>岸本拓治</u> 、尾崎米厚、西田道弘、岡本幹三、 <u>濱島ちさと</u>	地域がん登録データを活用した胃内視鏡検診の生存率に関する検討	JACR Monograph	16	80	2010
岡本幹三、黒沢洋一、尾崎米厚、 <u>岸本拓治</u>	超高齢化の進行する地域におけるがんの発生と家族性因子およびライフスタイルに関する前向きコホート研究	JACR Monograph	16	90-92	2010
Masashi K, Shu A keisuke O, Shiho T, Masahiro S, <u>Daisuke S</u> , Katsuaki K, Yoshifumi I, Shuichi O, Toru S	Magnifying endoscopic findings of the surface structure of non-cancerous mucosa surrounding differentiated and undifferentiated gastric carcinoma.	Digestive Endoscopy	23	37-42	2011
加藤勝章、猪股芳文、菊地亮介、島田剛延、 <u>渋谷大助</u>	Helicobacter pylori感染検査によるペプシノゲン法陰性胃がん拾い上げの問題点	日本消化器がん検診学会誌	49(1)	12-19	2011
小越和栄、成澤林太郎、加藤俊幸他	新潟市住民に対する胃がん内視鏡検診	ENDOSCOPIC FORUM for digestive endoscopy	26	5-16	2010
小越和栄	内視鏡による新潟市胃がん住民検診の結果集計について	新潟市医師会報	47	38-45	2011
<u>濱島ちさと</u>	がん検診にかかわるかかりつけ医が知っておくべき事柄	治療（4月増刊号）患者・家族の相談に答えるがん診療サポートガイド	93	755-759	2011
<u>濱島ちさと</u>	がん検診における腫瘍マーカーの応用と可能性	成人病と生活習慣病	41(6)	738-740	2011

<u>濱島ちさと</u>	特集：がん予防のための健 診と生活習慣②、第41回健 康フォーラムin 新橋・講 演4 がん検診の有効性につい て	健康管理	58(11)	2-15	2011
佐川元保、斎藤博、町井涼子、中山富雄、祖父江友孝、 <u>濱島ちさと</u> 、垣添忠生、薄田勝男、相川広一、上野正克、町田雄一郎、田中良、佐久間勉	「がん検診のためのチェックリスト」を用いた精度管理の方法－検診の精度管理を行う側への精度管理の一手法の提示の試み－	日本がん検診・診断学会誌	19(2)	145-155	2011
岡本幹三、黒沢洋一、尾崎米厚、 <u>岸本拓治</u>	鳥取県における多重がん増加に関する疫学的研究－登録方法と進展度から－	JACR Monograph	17	55-57	2011
<u>岸本拓治</u> 、尾崎米厚、岡本幹三、謝花典子、 <u>濱島ちさと</u>	地域がん登録データによる胃内視鏡検診と胃X線検診の生存率比較	日本がん検診・診断学会誌	19(1)	92	2011
岡本幹三、黒沢洋一、尾崎米厚、 <u>岸本拓治</u>	鳥取県における多重がん増加に関する疫学的研究－登録方法と進展度から－	JACR Monograph	17	55-57	2011
安藤圭、 <u>岸本拓治</u> 、尾崎米厚、田原文	動脈硬化症予防プログラムにおける環境・遺伝要因の介入効果およびリバウンドへの影響に関する研究	米子医学雑誌	62(3・4)	128-137	2011
岡本幹三、黒沢洋一、尾崎米厚、 <u>岸本拓治</u>	鳥取県における多重がん増加に関する疫学的研究－登録方法と進展度から－	JACR Monograph	17	55-57	2011
Ohkura T, Taniguchi S, Osaki Y, Yamamoto N, Sumi K, Fujioka Y, Matsuzawa K, Izawa S, Shiochi H, Kinoshita H, Inoue K, Takechi M, <u>Kishimoto T</u> , Shigemasa C	Lower fasting plasma glucose criteria and high triglycerides are effective for screening diabetes mellitus in the rural Japanese population: the Tottori-Kofu Study.	Rural Remote Health	11(3)	1697	2011

Tahara A, Osaki Y, <u>Kishimoto T</u>	Influenc of beta 3-adrenergic receptor Trp64Argpolymorphism on the improvement of metabolic syndrome by exercise-based intervention in Japanese middle-aged males.	Obesity Research & Clinical Practice	5	e109-e117	2011
Osaki Y, Taniguchi S, Tahara A, Okamoto M, <u>Kishimoto T</u>	Metabolic syndrome and incidence of liver and breast cancers in Japan.	Cancer Epidemiology	36	141-147	2012
<u>小越和栄</u>	安全で苦痛のない内視鏡胃がん検診を目指して No 1.	新潟市医師会報	483	35-36	2011
<u>小越和栄</u>	安全で苦痛のない内視鏡胃がん検診を目指して No 2.	新潟市医師会報	484	27-28	2011
<u>小越和栄</u>	安全で苦痛のない内視鏡胃がん検診を目指して No 3.	新潟市医師会報	485	30-31	2011
<u>小越和栄</u>	安全で苦痛のない内視鏡胃がん検診を目指して No 4.	新潟市医師会報	486	27-28	2011
<u>小越和栄</u>	安全で苦痛のない内視鏡胃がん検診を目指して No 5.	新潟市医師会報	487	34-37	2011
<u>小越和栄</u>	安全で苦痛のない内視鏡胃がん検診を目指して No 6.	新潟市医師会報	488	26-28	2011
Sagawa M, Nakayama T, Tanaka M, Sakuma T, Sobue T ; JECS Study Group (Sagawa M, Sobue T, Nishii K, Eguchi K, Nakayama T, Hayashi T, Kobayashi T, Sato T, Tanaka H, Sato M, Ichikawa K, Takahashi S, <u>Hamashima C</u> , et al.)	Sensitivity of endoscopic screening for gastric cancer by the incidence method	Jpn J Clin Oncol	42(12)	1219-1221	2012
<u>濱島ちさと</u>	対策型胃癌検診の現状と胃癌リスク検診の評価	消化器内視鏡	24(10)	1609-1613	2012

<u>濱島ちさと</u>	新しい胃がん検診方式の導入に向けた課題と展望	公衆衛生	76(11)	862-865	2012
<u>濱島ちさと</u>	胃がん検診トピックス	Minds医療情報サービス	19(2)	http://minds.jcqh.or.jp/n/med/8/med0030/T0010112	2012.12.11
<u>濱島ちさと</u>	がん検診の利益と不利益	第32回医療情報学連合大会 32ndJCMI		34-37	2012
佐川元保、西井研治、祖父江友孝、江口研二、中山富雄、佐藤雅美、小林健、田中洋史、高橋里美、林朝茂、鈴木隆一郎、佐藤俊哉、 <u>濱島ちさと</u> 他	CTを用いた肺がん検診の有効性評価のための日本における無作為化比較試験の現況と課題	CT検診	19(3)	196-203	2013
European Colorectal Cancer Screening Guidelines Working Group: [von Karsa L, Patnick J, Segnan N, Atkin W, Halloran S, Lansdorp-Vogelaar I, <u>Hamashima C</u> , et al.]	European guidelines for quality assurance in colorectal cancer screening and diagnosis: overview and introduction to the full supplement publication.	Endoscopy	45(1)	51-59	2013
<u>濱島ちさと</u>	シンポジウム講演録 (医療技術評価 (HTA) の政策利用—諸外国の状況とわが国における課題—): 「HTAの基本概念と政策への応用」	医療と社会	22(3)	226-231	2013
<u>Osaki Y</u> , Ohida T, Kanda H, Kaneita Y, Kishimoto T	Mobile phone use does not discourage adolescent smoking in Japan.	Asian Pac J Cancer Prev	13(3)	1011-1014	2012
<u>Osaki Y</u> , Taniguchi S, Tahara A, Okamoto M, Kishimoto T	Metabolic syndrome and incidence of liver and breast cancers in Japan.	Cancer Epidemiology	36	141-147	2012
小越和榮、成澤林太郎、加藤俊幸、佐野正俊、藤田一隆、月岡恵	胃がん内視鏡検診の有効性—費用対効果も含め—	新潟市医師会報	755	1-5	2013

小林正明、成澤林太郎、佐藤祐一、竹内学、青柳豊	内視鏡治療後における異時性多発胃癌の発生リスクは永続しない	Gastroenterol Endosc	54 (4)	1498-1505	2012
小林正明、水野研一、橋本哲、竹内学、成澤林太郎、青柳豊	早期胃癌に対する画像強調・拡大内視鏡観察の進歩	新潟県医師会報	752	2-7	2012
<u>Hamashima C</u> , Okamoto M, Shabana M, Osaki Y, Kishimoto T	Sensitivity of endoscopic screening for gastric cancer by the incidence method.	Int J Cancer	133(3)	653-659	2013
<u>Hamashima C</u> , Ogoishi K, Okamoto M, Shabana M, Kishimoto T, Fukao A	A Community-based, case-control study evaluating mortality reduction from gastric cancer by endoscopic screening in Japan.	PLoS ONE	8(11)	doi:10.1371/journal.pone.0079088.	2013
Hirai K, Harada K, Seki A, Nagatsuka M, Arai H, Hazama A, Ishikawa Y, <u>Hamashima C</u> , Saito H, Shibuya D	Structural equation modeling for implementation intentions, cancer worry, and stages of mammography adoption.	Psycho-Oncology	22(10)	2339-2346	2013
岸知輝、 <u>濱島ちさと</u>	がん検診受診率算定対象変更に伴うがん検診精度に関する検討	厚生指標	60(12)	13-19	2013
<u>濱島ちさと</u>	[特集：消化管がん診療の新しいエビデンス] がん検診は有効か？	臨床と研究	91(2)	87-92	2014
加藤元嗣、加藤勝章、 <u>濱島ちさと</u> 、天和田進、井上和彦	これからの胃がんの検診はどうあるべきか	THE GI FOREFRONT	9(2)	41-54	2014
Sano H, Goto R, <u>Hamashima C</u>	What is the most effective strategy for improving the cancer screening rate in Japan?	Asian Pac J Cancer Prev	15(6)	2607-2612	2014
<u>尾崎米厚</u>	たばこ対策最前線 未成年への対応 未成年者の喫煙対策	公衆衛生情報	42(11)	27-32	2013
<u>尾崎米厚</u>	物質使用障害の疫学	精神科治療学	28 (増刊号)	10-15	2013

尾崎米厚	鳥取県の高校生の喫煙・飲酒行動および生活習慣～実態調査より～	鳥取県高P連会報	76	1-2	2013
後藤 励、 新井康平、 謝花典子、 濱島ちさと	診療所における内視鏡胃癌検診数の決定要因	日本医療・病院管理学会誌	50(3)	25-34	2013
Goto R, Arai K, Kitada H, Ogoshi K, Hamashima C	Labor resource use for endoscopic gastric cancer screening in Japanese primary care settings: a work sampling study.	PLoS ONE	9(2)	doi:10.1371/journal.pone.0088113.	2014
新井康平、 後藤 励、 謝花典子、 濱島ちさと	内視鏡胃癌検診プログラムへの参加要因	厚生 の 指標		近刊	2014
加藤 俊幸、 佐々木俊哉、 本山展隆、 船越和博、 栗田 聡、 青柳智也、 成澤林太郎	胃癌切除後残胃癌—その特徴と対策	消化器の臨床	16(4)	406-412	2013
加藤 俊幸、 佐々木俊哉、 成澤林太郎、 梨本 篤	X スキルス胃癌 疫学	日本臨牀	72 (増刊号1)	608-614	2014

Ⅲ. 研究成果刊行物・別刷

A Community-Based, Case-Control Study Evaluating Mortality Reduction from Gastric Cancer by Endoscopic Screening in Japan

Chisato Hamashima^{1*}, Kazuei Ogoshi², Mikizo Okamoto³, Michiko Shabana⁴, Takuji Kishimoto⁵, Akira Fukao⁶

1 Cancer Screening Assessment and Management Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan, **2** Niigata Cancer Center Hospital, Niigata, Japan, **3** Division of Health Administration and Promotion, Department of Social Medicine, Faculty of Medicine, Tottori University, Yonago, Tottori, Japan, **4** Department of Internal Medicine, San-in Rosai Hospital, Yonago, Tottori, Japan, **5** Division of Environmental and Preventive Medicine, Department of Social Medicine, Faculty of Medicine, Tottori University, Yonago, Tottori, Japan, **6** Departments of Public Health, School of Medicine, Yamagata University, Yamagata, Yamagata, Japan

Abstract

Aims: Although the incidence of gastric cancer has decreased in the last 3 decades, it remains the second leading cause of cancer death worldwide. In Asian countries, the burden of gastric cancer has remained, and cancer screening is normally expected to reduce gastric cancer death. We conducted a community-based, case-control study to evaluate the reduction of mortality from gastric cancer by endoscopic screening.

Methods: Case subjects were defined as individuals who had died of gastric cancer between 2003 and 2006 in 4 cities in Tottori Prefecture, and between 2006 and 2010 in Niigata City, Japan. Up to 6 control subjects were matched by sex, birth year (± 3 years), and the residence of each corresponding case subject from the population lists in the study areas. Control subjects were required to be disease-free at the time when the corresponding case subjects were diagnosed as having gastric cancer. The odds ratios (ORs) were calculated for those who had participated in endoscopic or radiographic screening before the reference date when the case subjects were diagnosed as having gastric cancer, compared with subjects who had never participated in any screening. Conditional logistic-regression models for matched sets were used to estimate the ORs and 95% confidence intervals (CIs).

Results: The case subjects consisted of 288 men and 122 women for case subjects, with 2,292 matched control subjects. Compared with those who had never been screened before the date of diagnosis of gastric cancer in the case subjects, the ORs within 36 months from the date of diagnosis were 0.695 (95% CI: 0.489–0.986) for endoscopic screening and 0.865 (95% CI : 0.631–1.185) for radiographic screening.

Conclusions: The results suggest a 30% reduction in gastric cancer mortality by endoscopic screening compared with no screening within 36 months before the date of diagnosis of gastric cancer.

Citation: Hamashima C, Ogoshi K, Okamoto M, Shabana M, Kishimoto T, et al. (2013) A Community-Based, Case-Control Study Evaluating Mortality Reduction from Gastric Cancer by Endoscopic Screening in Japan. PLoS ONE 8(11): e79088. doi:10.1371/journal.pone.0079088

Editor: Ju-Seog Lee, University of Texas MD Anderson Cancer Center, United States of America

Received: April 22, 2013; **Accepted:** September 26, 2013; **Published:** November 13, 2013

Copyright: © 2013 Hamashima et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: This study was supported by Grant-in-Aid for Cancer Control from Ministry of Health, Labor and Welfare of Japan (Grant number 15-3 and 20-9). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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

* E-mail: chamashi@ncc.go.jp

Introduction

Although the incidence of gastric cancer has decreased in the last 3 decades, it remains the second leading cause of cancer death worldwide [1]. The highest mortality rates are estimated in Eastern Asia, including Japan. The incidence of gastric cancer in the world was estimated to be about 1 million in 2008, half of which occurred in Eastern Asia.

In Asian countries, the burden of gastric cancer has persisted; however, there is as yet no nationwide population-based screening for gastric cancer except in Korea and Japan [2]. In Japan, there were 49,830 recorded deaths from gastric cancer in 2011, accounting for 13.9% of all cancer deaths [3]. Gastric cancer

screening using upper gastrointestinal series (i.e., radiographic screening), which was developed in Japan, has been conducted for the last 3 decades as a public policy and its inclusion was recommended in the Japanese guidelines for gastric cancer screening [4]. It is expected that cancer screening will continue to prevent gastric cancer deaths in Japan, wherein 3.7 million Japanese participated in gastric cancer screening in 2010 [5].

Endoscopy has been commonly used in clinical practice and is anticipated to be an alternative strategy to radiography for gastric cancer screening. In Korea, endoscopic screening as a national program has been conducted since 2000 [6]. This has been partly adopted in population-based screening in Japan [7–9]. Although

positive results of endoscopic screening have been reported recently, the effectiveness of endoscopic screening remains unclear [7–8,10–12]. To effectively introduce endoscopy as a new method for gastric cancer screening in a community, mortality reduction from gastric cancer must be evaluated by conducting reliable studies. Although a randomized controlled trial is ideal for clarifying such reduction, case-control studies are useful for evaluating the effectiveness of cancer screening on a widespread scale [13]. To evaluate reduction of mortality from gastric cancer by endoscopic screening, we conducted a community-based, case-control study in Tottori and Niigata Prefectures, Japan, where endoscopic screening for gastric cancer has been conducted.

Methods

Study Population

Five cities (i.e., Tottori, Yonago, Kurayoshi and Sakaiminato in Tottori Prefecture and Niigata in Niigata Prefecture) that conducted endoscopic screening for at least 5 years and have local cancer registries were selected [7,9]. These cities had higher mortality rates for gastric cancer than the other cities in Japan (16.2 per 100,000 individuals for men; 6.1 per 100,000 individuals for women) [3]. The age-adjusted mortality rates per 100,000 individuals up to 75 years of age were 20.3 for men and 6.9 for women in Tottori Prefecture and 20.3 for men and 6.0 for women in Niigata Prefecture.

Screening Programs

Similar systems for gastric cancer screening are offered in these 5 cities [7,9]. 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 screening programs for gastric cancer. Endoscopic screening has been conducted since 2000 in Tottori, Yonago, and Sakaiminato, since 2001 in Kurayoshi, and since 2003 in Niigata. Individuals can choose either endoscopy or radiography for gastric cancer screening based on their preference. Participation in gastric cancer screening has increased since the introduction of endoscopic screening, but the participation in gastric cancer screening involving both methods has remained at about 25% [7,9].

Physicians who can perform endoscopic screening were approved by the local committee for gastric cancer screening based on certain requirements [7,9]. 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.

Selection of Case Subjects

The flowchart for the selection of case subjects is shown in **Figure 1**. Case subjects were defined as individuals who had died of gastric cancer from January 2003 to December 2006 in the 4 cities in Tottori Prefecture, and from April 2006 to October 2010 in Niigata City. Those who died of gastric cancer were identified by death certificates, with permission from the Japanese government. Case subjects were also diagnosed as having gastric cancer between January 2003 and December 2006 based on the Tottori Prefecture Cancer Registry and between April 2006 and October 2010 based on the Niigata Prefecture Cancer Registry. The age at diagnosis was limited between the ages of 40 years and 79 years. Individuals who died of malignant lymphoma and other gastric diseases were excluded. The case subjects had lived in the 5 cities from the date of the introduction of endoscopic screening up to the date of diagnosis of gastric cancer.

There were 748 potential subjects with gastric cancer in the 4 cities in Tottori Prefecture (326 in Tottori, 255 in Yonago, 112 in Kurayoshi, and 55 in Sakaiminato) and 1,431 potential subjects in Niigata City based on the death certificates. Detail information of all potential cases were obtained from the local cancer registries, and the following cases were excluded: patients who 1) were over 80 years old and less than 39 years old at the time of diagnosis, 2) lacked the date for gastric cancer diagnosis, or 3) had a diagnosis other than cancer. Most subjects who were excluded from the target group were over 80 years old at the time of diagnosis, which was not the actual target for cancer screening. In the population list of each city, the remaining patients were identified based on documentation of residence from the time of the introduction of endoscopic screening up to the date of gastric cancer diagnosis. There were 1,769 subjects who were excluded because they did not fulfill the basic requirements for case subjects, and the remaining 410 subjects (146 in Tottori Prefecture and 264 in Niigata City) were evaluated in this study.

Selection of Control Subjects

Six control subjects were selected from the list of residents in each city for each matched case. The control subjects were required to be disease-free at the time when the case subjects were diagnosed as having gastric cancer. The control subjects were matched by sex, birth year (± 3 years), and residence of the matched case subjects from the population lists. The population lists at the time of the introduction of endoscopic screening were reconstructed using the population lists at the time of investigation and files of death certificates before the list was made in the study areas. Residence was limited to the same area in each city, because access to screening differed even for subjects who lived in the same city. Even if the subjects were matched, individuals under 40 years of age were excluded because they had no opportunity to be screened. Subjects who had gastric cancer when endoscopic screening was introduced were excluded and other control subjects were selected again based on the basic requirements. Finally, 146 case subjects and 794 matched control subjects in Tottori Prefecture and 264 case subjects and 1,498 matched control subjects in Niigata City were selected. Of the 410 case subjects, 343 had 6 control subjects, 22 had 5, 16 had 4, 12 had 3, 7 had 2, and 10 had 1.

Screening History

The screening histories of the case and control subjects were obtained from the participant lists for both endoscopic and radiographic screenings for gastric cancer from April 2000 to March 2006 in Tottori Prefecture and from April 2003 to March 2010 in Niigata City. For some of the participants from Tottori and Kurayoshi, the method used for gastric cancer screening was unknown as some detailed information was lost. When the screening method was unclear, we assumed that there was no screening history. The end of the exposure period for screening was defined as the time when the case subjects were diagnosed as having gastric cancer.

Statistical Analysis

Conditional logistic-regression models for matched sets were used to estimate the odds ratios (ORs) and 95% confidence intervals (95% CIs). The ORs were calculated for those who had participated in endoscopic or radiographic screening within 12, 24, 36, and 48 months before the reference date when the case subjects were diagnosed as having gastric cancer, compared with individuals who had never participated in any screening. The ORs were also calculated for those who had participated in each

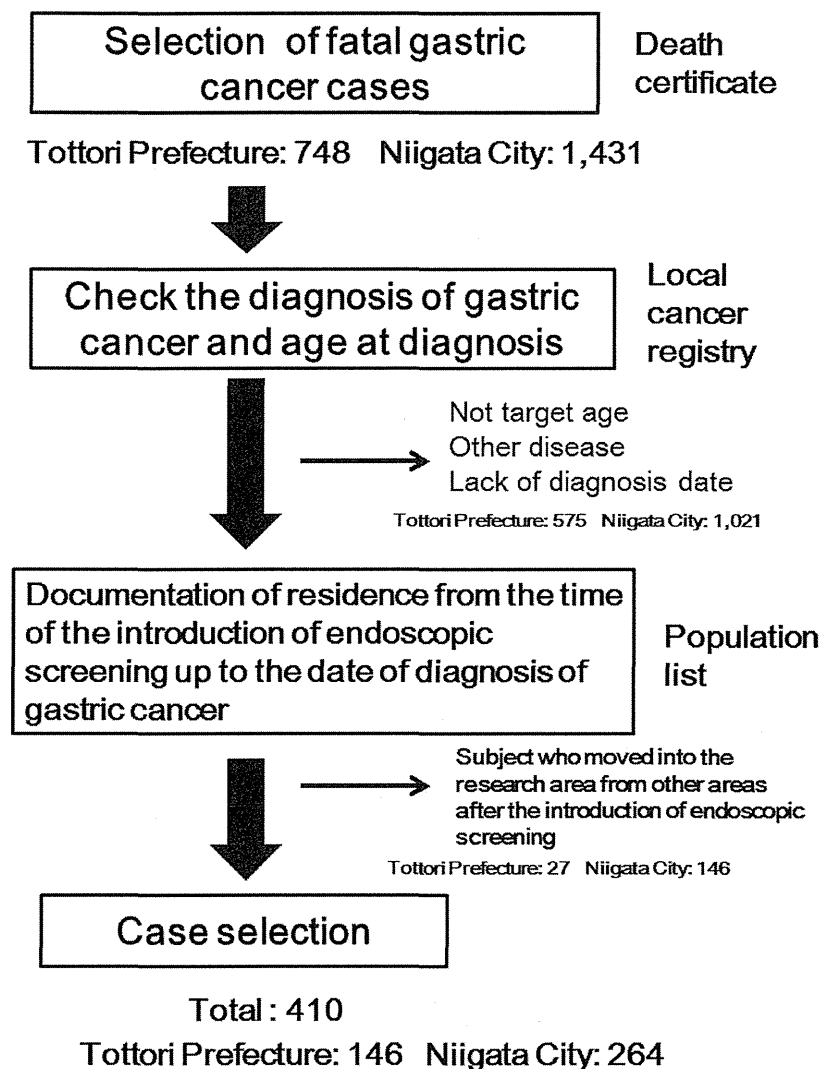


Figure 1. Flowchart for the selection of case subjects. Case subjects were defined as individuals who had died of gastric cancer from January 2003 to December 2006 in the 4 cities of Tottori Prefecture, and from April 2006 to October 2010 in Niigata City. All potential case subjects were referred from the local cancer registries, and excluded subjects included individuals who 1) were over 80 years old and less than 39 years old at the time of diagnosis, 2) lacked the date of gastric cancer diagnosis, or 3) had a diagnosis other than cancer. In the population list of each city, the remaining subjects were identified based on documentation of residence from the time of the introduction of endoscopic screening up to the date of diagnosis. There were 1,769 subjects who were excluded because they did not fulfill the basic requirements for case subjects. The remaining 410 subjects (146 from Tottori Prefecture and 264 from Niigata City) were evaluated in the study. doi:10.1371/journal.pone.0079088.g001

screening category within 36 months before the date of diagnosis, compared with individuals who had never participated in any screening by sex, 2 age groups of the case subjects (40–69 and 70–79 years), and 2 prefectures (Tottori and Niigata). Statistical analyses were carried out using STATA 11.0 (STATA, College Station, TX, USA).

This study used the data of local cancer screening programs and the population lists which 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 no human materials [14]. Since the design of our study was a case-control study,

obtaining informed consent was waived. This study was approved by the Institutional Review Board of the National Cancer Center of Japan.

Results

The total number of case subjects was 410, with 2,292 matched control subjects. The sex and age distributions of the case and control subjects are shown in **Table 1**. There were more men than women as case subjects (288 men, 122 women); 44% of the case subjects for both men and women were over 70 years of age.

The ORs were calculated for those who had participated in endoscopic or radiographic screening within 12, 24, 36, and 48 months before the reference date when the case subjects were

Table 1. Distribution of case and control subjects by sex and age.

Age	Men				Women				Total			
	Cases	(%)	Control	(%)	Cases	(%)	Control	(%)	Cases	(%)	Control	(%)
40–49 years	11	3.8	57	3.6	12	9.8	63	9.2	23	5.6	120	5.2
50–59 years	39	13.5	242	15.1	23	18.9	125	18.2	62	15.1	367	16.0
60–69 years	111	38.5	597	37.2	35	28.7	198	28.8	146	35.6	795	34.7
70 years and over	127	44.1	708	44.1	52	42.6	302	43.9	179	43.7	1010	44.1
Total	288	100.0	1604	100.0	122	100.0	688	100.0	410	100.0	2292	100.0

doi:10.1371/journal.pone.0079088.t001

diagnosed as having gastric cancer, compared with individuals who had never participated in any screening (**Table 2**). Compared with those who had never been screened before the date of diagnosis of gastric cancer in the case subjects, the ORs within 36 months from diagnosis were 0.695 (95% CI: 0.489–0.986) for endoscopic screening and 0.865 (95% CI: 0.631–1.185) for radiographic screening. The ORs of radiographic screening were not changed when the exposure window was changed from 12 months to 48 months. Although the results of radiographic screening suggested a reduction in mortality from gastric cancer, these were not significant. The OR within 12 months from diagnosis was 0.964 (95% CI: 0.660–1.407) for endoscopic screening. The ORs within 12 months were higher in endoscopic screenings than the ORs within 24, 36, and 48 months.

The ORs within 36 months by subgroups including sex, age group of the case subjects and prefecture are shown in **Table 3**. For men, the ORs were 0.560 (95% CI: 0.359–0.873) for endoscopic screening and 0.891 (95% CI: 0.611–1.229) for radiographic screening. The ORs for women were reversed between endoscopic screening and radiographic screening, but they were not significant. The ORs of endoscopic screening were 0.852 (95% CI: 0.504–1.440) in the 40–69 years age group and 0.593 (95% CI: 0.371–0.948) in the 70 years age group. The ORs of radiographic screening in both age groups were 1.015 (95% CI: 0.648–1.591) and 0.748 (95% CI: 0.483–1.161), but these were not significant. Although endoscopic screening was conducted in both prefectures, the ORs of both screening methods did not coincide. The ORs of both screenings were lower in Tottori Prefecture than

in Niigata City. In 4 cities in Tottori Prefecture, the ORs were 0.451 (95% CI: 0.228–0.895) for endoscopic screening, and 0.498 (95% CI: 0.255–0.976) for radiographic screening.

Discussion

To the best of our knowledge, this is first case-control study of endoscopic screening for gastric cancer in communities in Japan. The results suggest a 30% reduction in gastric cancer mortality by endoscopic screening compared with no screening within 36 months before the date of diagnosis of gastric cancer. However, a case-control study may have potential bias, and care is needed when interpreting the results, because some serious biases may lead to a positive effect being found [13,15]. Self-selection bias could not be controlled, and it may have also affected the results. Since the control subjects were screened more often than the case subjects, this will bias the results in favor of screening. To avoid this problem, a randomized controlled study to evaluate efficacy is required before introducing endoscopic screening in communities.

The ORs were higher in radiographic screening than in endoscopic screening even when the screening window was changed from 24 months to 48 months. Most of the case-control studies of radiographic screening suggested a significant decrease by 40–60% in gastric cancer mortality, and the results of previous studies were consistent [4,16–20]. The effectiveness of radiographic screening was lower in the present study than in previous studies. The screening rate for gastric cancer using radiography has gradually decreased in the last decade and has remained at

Table 2. Odds ratios of death from gastric cancer for screened subjects compared with never-screened subjects.

Months before reference date	Number of subjects		Number of subjects screened by endoscopy				Odds ratio (95% CI)	Number of subjects screened by radiography			Odds ratio (95% CI)	
	Cases	Controls	Cases	(%)	Controls (%)	Cases		(%)	Controls (%)			
Within 12 months	410	2292	38	9.3	207	9.0	0.964 (0.660–1.407)	35	8.5	219	9.6	0.837 (0.565–1.240)
24 months	410	2292	41	10.0	301	13.1	0.702 (0.490–1.006)	50	12.2	312	13.6	0.843 (0.601–1.182)
36 months	407	2275	44	10.8	326	14.3	0.695 (0.489–0.986)	60	14.7	363	16.0	0.865 (0.631–1.185)
48 months	387	2167	46	11.9	332	15.3	0.714 (0.507–1.007)	64	16.5	398	18.4	0.843 (0.621–1.146)

The odds ratios were calculated for those who had participated in endoscopic or radiographic screening within 12, 24, 36, and 48 months before the reference date when the case subjects were diagnosed as having gastric cancer, compared with individuals who had never participated in any screening.

doi:10.1371/journal.pone.0079088.t002

Table 3. Odds ratios of death from gastric cancer for subjects screened compared with never-screened subjects within 36 months by sex, age group, and local area.

Subgroup	Months before diagnosis	Number of subjects		Number of subjects screened by endoscopy			Number of subjects screened by radiography			Odds ratio		
		Cases	Controls	Cases (%)	Controls (%)	(%)	Cases (%)	Controls (%)	(%)	(95% CI)	(95% CI)	
Sex	Men	286	1593	26	9.1	236	14.8	42	14.7	241	15.1	0.891 (0.611–1.299)
	Women	121	682	18	14.9	90	13.2	18	14.9	122	17.9	0.801 (0.450–1.425)
Age group of case subjects	40–69 years old	229	1291	20	8.7	128	9.9	29	12.7	160	12.4	1.015 (0.648–1.591)
	70 years old and over	178	984	24	13.5	198	20.1	31	17.4	203	20.6	0.748 (0.483–1.161)
Prefecture	Niigata	264	1498	33	12.5	218	14.6	48	18.2	257	17.2	1.044 (0.728–1.498)
	Tottori	143	777	11	7.7	108	13.9	12	8.4	106	13.6	0.498 (0.255–0.976)

doi:10.1371/journal.pone.0079088.t003

about 12% [5]. When the methods of gastric cancer screening were divided into endoscopy and radiography in study areas, the participation rate for each method was about 10% [7,9]. Radiographic screening needs appropriate quality assurance for the radiographic technology and interpretation of the radiogram. Since most specialists who are in charge of this screening have become older, the quality assurance has become outdated. Because of our small sample size, the low screening rate, and insufficient quality assurance, significant results were difficult to obtain.

Sub-analysis was performed by dividing the subjects into 2 groups of age, sex and prefectures. Although significant results could not be obtained in the sub-analysis, different beneficial effects were found in these groups. Endoscopic screening has been mainly performed in clinical settings, and radiographic screening in mass screening programs in the study areas. Since over 70% of older people have their own family physician [21], they have more chance to be screened by endoscopy based on their physician's recommendation. Therefore, the ORs of the subjects aged 70 years and over are lower than the ORs of the subjects aged 40 to 69 years. Although the basic screening programs were similar in Niigata and Tottori Prefectures, the quality assurance system is different [7,9]. This has resulted in different beneficial effects. In the sub-analysis of sex, the ORs of radiographic screening are similar, but different beneficial effects were found in endoscopic screening. In the study areas, the screening method could be chosen based on individual preference. Preference of the screening method might be different between men and women.

This study had several limitations. Firstly, symptomatic individuals could not be excluded. The subjects of a case-control study to evaluate the effects of cancer screening should be asymptomatic [13,22]. The ORs within 12 months were higher in endoscopic screenings than the ORs within 24, 36, and 48 months. The results suggest that symptomatic individuals might be screened more often within 12 months before diagnosis because of their symptoms. Symptomatic individuals have often participated in cancer screening instead of diagnostic tests, and free-of-charge programs for the elderly people in these cities have promoted examinations of symptomatic individuals.

Secondly, since the background information, including smoking and family history, was not obtained, no adjustments could be made for the differences. Fukao et al. reported differences in family history and smoking between participants and non-participants in gastric cancer screening [23]. Lifestyle might differ between the subjects who participate or not in screening. Since half of the case and control subjects was 70 years old and over, they had a high potential to have co-morbidity. The different results for endoscopic screening among the older and younger age groups might be affected by screening history and co-morbidities.

Thirdly, the screening history outside of community-based screening was unclear. Screening history was identified based on the participant lists for gastric cancer screening from 2000 to 2006. Opportunistic screening was popular in clinical settings, mainly using endoscopy. In addition, in the 40–59 years age group, gastric cancer screening was often performed with regular health check-ups in the workplace [24].

Lastly, since the new screening method had not been well known in the community at the time when endoscopic screening was first introduced, the chance to be screened might have been missed. Since there is no existing system for inviting the target population to participate in cancer screening in most municipalities in Japan, with gastric cancer screening offered annually, most subjects themselves elected to participate irregularly. The minimum period for selection was 3 years after the introduction of

endoscopic screening. There is an argument that one should define the available time for the determination of case subjects to assess the effectiveness of screening accurately [13]. A screening effect is not expected within a short time after introduction; it needs several years [25]. Wahrendorf et al. defined the cases as deaths from colorectal cancer occurring more than 6 years after the introduction of screening that was fully implemented [26]. Although there was an equal chance to participate in both screening modalities, individuals who continued to be screened tended to change to endoscopy. If the long-term effect of radiographic screening continued, the effectiveness of endoscopic screening might be overestimated.

In conclusion, our results suggest a 30% reduction in mortality from gastric cancer by endoscopic screening within 36 months from the diagnosis of gastric cancer in case subjects compared with never-screened subjects. Although this suggests the effectiveness of endoscopic screening for gastric cancer, several limitations, including self-selection bias, remain, and prudent interpretation

is needed. A randomized controlled study to evaluate efficacy is required before introducing endoscopic screening in communities.

Acknowledgments

We thank the Tottori Prefecture Cancer Registry, the Niigata Prefecture Cancer Registry, the local governments (Tottori, Yonago, Kurayoshi, Sakaiminato, and Niigata), and the 4 community health centers (Tottori, Yonago, Kurayoshi, and Niigata).

We appreciate the helpful comments of Professor Tomotaka Sobue and Dr. Hiroshi Saito. We thank Ms. Kanoko Matsushima, Ms. Junko Asai, and Ms. Mayumi Kobayashi for the secretarial assistance.

We are indebted to Associate Professor Edward Barroga (DVM, PhD) of the Department of International Medical Communications of Tokyo Medical University for the editing and reviewing the English manuscript.

Author Contributions

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

References

- International Agency for Research on Cancer. (2008) GLOBOCAN 2008. Available: <http://globocan.iarc.fr/>. Accessed 2013 Apr 12.
- Leung WK, Wu MS, Kakugawa Y, Kim JJ, Yeoh KG, et al. (2008) Asia Pacific Working Group on Gastric Cancer. Screening for gastric cancer in Asia: current evidence and practice. *Lancet Oncol* 9: 279–287.
- National Cancer Center. Center for Cancer Control and Information Services. Available: <http://ganjoho.ncc.go.jp/professional/statistics/index.html>. Accessed 2013 April 12.
- Hamashima C, Shibuya D, Yamazaki H, Inoue K, Fukao A, et al. (2008) The Japanese guidelines for gastric cancer screening. *Jpn J Clin Oncol* 38: 259–267.
- Ministry of Health, Labour and Welfare of Japan (2010) Department of Health Statistics and Information; National survey on cancer screening. Tokyo.
- Kim Y, Jun JK, Choi KS, Lee HY, Park EC (2011) Overview of the National Cancer screening programme and the cancer screening status in Korea. *Asian Pac J Cancer Prev* 12: 725–730.
- Ogoshi K, Narisawa R, Kato T, Fujita K, Sano M (2010) Endoscopic screening for gastric cancer in Niigata City. *Jpn J Endoscopic Forum Digestive Disease* 26: 5–16. (in Japanese)
- Matsumoto S, Yamasaki K, Tsuji K, Shirahama S (2007) Results of mass endoscopic examination for gastric cancer in Kamigoto Hospital, Nagasaki Prefecture. *World J Gastroenterol* 13: 4316–4320.
- Shabana M, Hamashima C, Nishida M, Miura K, Kishimoto T (2010) Current status and evaluation of endoscopic screening for gastric cancer. *Jpn J Cancer Detection & Diagnosis* 17: 229–235 (in Japanese).
- Riecken B, Pfeiffer R, Ma JL, Jin ML, Li JY, et al. (2002) No impact of repeated endoscopic screens on gastric cancer mortality in a prospectively followed Chinese population at high risk. *Prev Med* 34: 22–28.
- Hosokawa O, Miyana T, Katzaki Y, Hattori M, Dohden K, et al. (2008) Decreased death from gastric cancer by endoscopic screening: association with a population-based cancer registry. *Scand J Gastroenterol* 43: 1112–1115.
- Nam JH, Choi IJ, Cho SJ, Kim CG, Jun JK, et al. (2012) Association of the interval between endoscopies with gastric cancer stage at diagnosis in a region of high prevalence. *Cancer* 118: 4953–4960.
- Cronin KA, Weed DL, Connor RJ, Prorok PC (1998) Case-control studies of cancer screening: theory and practice. *J Natl Cancer Inst* 90: 498–504.
- Ministry of Health, Welfare and Labour (2007) Japanese ethical guidelines for epidemiological studies.
- Moss SM (1991) Case-control studies of screening. *Int J Epidemiol* 20: 1–6.
- Oshima A, Hirata N, Ubukata T, Umeda K, Fujimoto I (1986) Evaluation of a mass screening program for stomach cancer with a case-control study design. *Int J Cancer* 38: 829–833.
- Fukao A, Tsubono Y, Tsuji I, Hisamichi S, Sugahara N, et al. (1995) The evaluation of screening for gastric cancer in Miyagi Prefecture, Japan: a population-based case-control study. *Int J Cancer* 60: 45–48.
- Abe Y, Mitsushima T, Nagatani K, Ikuma H, Minamihara Y (1995) Epidemiological evaluation of the protective effect for dying of stomach cancer by screening programme for stomach cancer with applying a method of case-control study: A study of an efficient screening programme for stomach cancer. *Jpn J Gastroenterol* 92: 836–845 (in Japanese).
- Pisani P, Oliver WE, Parkin DM, Alvarez N, Vivas J (1994) Case-control study of gastric cancer screening in Venezuela. *Br J Cancer* 69: 1102–1105.
- Tsubono Y, Hisamichi S (1999) Case-control studies of screening for gastric cancer in Japan. *Jpn J Gastroenterol Mass Survey* 37: 182–185. (in Japanese)
- Ministry of Health, Welfare and Labour (2006) Patient's Behavior Survey 2005. Tokyo.
- Morrison AS (1982) Case definition in case-control studies for the efficacy of screening. *Am J Epidemiol* 115: 6–8.
- Fukao A, Hisamichi S, Komatsu S, Shimizu H, Satoh H, et al. (1992) Comparison of characteristics between frequent participants and non-participants in screening programs for stomach cancer. *Tohoku J Exp Med* 166: 459–469.
- Hamashima C, Yoshida K (2003) What is important for the introduction of cancer screening in the workplace? *Asian Pac J Cancer Prev* 4: 39–43.
- Lee SJ, Boscardin WJ, Stijacic-Cenzer I, Conell-Price J, O'Brien S, et al. (2012) Time lag to benefit after screening for breast and colorectal cancer: meta-analysis of survival data from the United States, Sweden, United Kingdom, and Denmark. *BMJ* 346: e8441.
- Wahrendorf J, Robra BP, Wiebelt H, Oberhausen R, Weiland M, et al. (1993) Effectiveness of colorectal cancer screening: results from a population-based case-control evaluation in Saarland, Germany. *Eur J Cancer Prev* 2: 221–227.

Sensitivity of endoscopic screening for gastric cancer by the incidence method

Chisato Hamashima¹, Mikizo Okamoto², Michiko Shabana³, Yoneatsu Osaki⁴ and Takuji Kishimoto⁴

¹Cancer Screening Assessment and Management Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan

²Division of Health Administration and Promotion, Department of Social Medicine, Faculty of Medicine, Tottori University, Tottori, Japan

³Department of Internal Medicine, San-In Rosai Hospital, Tottori, Japan

⁴Division of Environmental and Preventive Medicine, Department of Social Medicine, Faculty of Medicine, Tottori University, Tottori, Japan

Although radiographic screening for gastric cancer has been conducted in Japan, it is anticipated that endoscopy will become a new screening method because of its high detection rate. The sensitivities of endoscopic and radiographic screening were calculated by the detection method and the incidence method based on the results of community-based screening in Japan. There were 56,676 screenings for gastric cancer using endoscopy and radiography from April 2002 to March 2007 in Yonago, Japan. The target age group was from 40 to 79 years. Screen-detected and interval cancers were investigated based on a screening database linked to the Tottori Cancer Registry. All gastric cancers diagnosed within 1 year after a negative screen were considered interval cancers. Based on the screening history, these were divided into prevalence screening and incidence screening. Prevalence screenings included 7,388 for endoscopic screening and 5,410 for radiographic screening, whereas incidence screenings included 18,021 for endoscopic screening and 11,417 for radiographic screening. The sensitivity of prevalence screening calculated by the incidence method was 0.886 (95% confidence interval [CI] = 0.698–0.976) for endoscopic screening and 0.831 (95% CI = 0.586–0.964) for radiographic screening; however, the difference was not significant ($p = 0.626$). The sensitivity of incidence screening calculated by the incidence method was 0.954 (95% CI = 0.842–0.994) for endoscopic screening and 0.855 (95% CI = 0.637–0.970) for radiographic screening ($p = 0.177$). Endoscopic screening for gastric cancer had a higher sensitivity than radiographic screening by the incidence method in both screening rounds. However, further study is needed to evaluate mortality reduction and to estimate overdiagnosis with endoscopic screening for gastric cancer.

Although the incidence of gastric cancer has declined worldwide, in Eastern Asia, a high incidence of gastric cancer is observed and remains a serious burden.¹ In Japan, there were 50,136 deaths from gastric cancer in 2010, accounting for 14.2% of all cancer deaths.² Gastric cancer screening has been conducted as a national program in Korea and Japan.

Key words: gastric cancer screening, upper gastrointestinal X-ray, upper gastrointestinal endoscopy, interval cancer, incidence method, detection method

This article was published online on 4 March 2013. An error was subsequently identified. This notice is included in the online and print versions to indicate that both have been corrected 28 May 2013.

Grant sponsor: Ministry of Health, Labor and Welfare of Japan;

Grant number: H22-Third Term Comprehensive Control Research for Cancer 022

DOI: 10.1002/ijc.28065

History: Received 20 June 2012; Revised 26 Dec 2012; Accepted 8 Jan 2013; Online 30 Jan 2013

Correspondence to: Chisato Hamashima, Cancer Screening Assessment and Management Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1 Tsukiji Chuo-Ku, Tokyo 104-0045, Japan, Tel.: 81-3-3547-5305, Fax: 81-3-3547-8587, E-mail: chamashi@ncc.go.jp

In Korea, endoscopic screening has been conducted with upper gastrointestinal series (radiographic screening) in the National Cancer Screening Programs since 2000.³ On the other hand, in Japan, radiographic screening is the main method in communities, and endoscopic screening has mainly been performed in clinical settings as opportunistic screening. Opportunistic screening using endoscopy has been performed in several other Asian countries.⁴

It is anticipated that endoscopic screening will become a new technology for gastric cancer screening. To find early cancer, endoscopic screening has been performed in clinical practice and has become disseminated due to the belief that it improves patients' quality of life. Several studies have reported high detection rates and the potential to detect earlier cancer with endoscopic screening than with radiographic screening.^{5,6} In these community-based screening programs, the detection rate of endoscopic screening was reported to be more than twice that of radiographic screening. Although the excess incidence with endoscopic screening at a certain point included both the lead time effect and overdiagnosis, they are difficult to separate. Observational studies have been used to estimate overdiagnosis in breast cancer screening.⁷ To appropriately estimate the proportion of overdiagnosis based on observational studies, long follow-up is required after screening is stopped at upper age limit.⁸ However, as in Japan, there are no upper age limit to the target population

What's new?

Radiographic screening is currently the main method for gastric cancer screening in Japan, but endoscopy is expected to become widely adopted due to its high detection rate. This study compares the sensitivity of radiographic and endoscopic screening using the incidence method based on the results of community-based screenings in Japan. The findings suggest that endoscopic screening for gastric cancer had a higher sensitivity than radiographic screening in both the screenings. However, further study is needed to evaluate mortality reduction and investigate the magnitude of overdiagnosis in endoscopic screening for gastric cancer.

for cancer screening, it is impossible to estimate the proportion of overdiagnosis using the cumulative incidence method.

The incidence method was developed to evaluate the sensitivity of a screening method that avoids overdiagnosis and length bias. The sensitivities and specificities of endoscopic and radiographic screenings have been reported by the detection method based on the Korean National Cancer Screening Program and were also reported from several communities and hospitals in Japan.^{9–12} Although high sensitivity was reported in these studies, it is possible to overestimate the sensitivity of endoscopic screening. Screening for breast, lung and colorectal cancers has already been evaluated using the incidence method.^{13–15} To date, no study has calculated the sensitivities of endoscopic screening and radiographic screening for gastric cancer by the incidence method. Therefore, a comparison of the sensitivity of both screening methods was conducted by the detection and incidence methods based on the results of community-based screening in Japan.

Material and Methods**Study population**

Tottori Prefecture, which is located northwest of Osaka, has the smallest population of all prefectures in Japan. It includes four cities, and Yonago is the second biggest city in Tottori Prefecture. In Tottori Prefecture, gastric cancer was the second leading cause of cancer death in males and the fourth in females in 2010.² The age-adjusted mortality rate per 100,000 for persons aged up to 75 years was 24.4 for males, higher than for the whole country, and 6.2 for females, similar to that for the whole country.²

In Yonago, gastric cancer screening using radiography has been offered annually by local governments since 1983, and endoscopic screening has been added since 2000.⁶ All inhabitants aged 40 years and older could participate in the screening programs for gastric cancer and choose either endoscopy or radiography at the individual level based on their own preference. In 2008, 9,409 individuals were screened by endoscopy, and 2,805 were screened by radiography.⁶ Participation in gastric cancer screening has increased since the introduction of endoscopic screening; however, gastric cancer screening uptake including both methods has remained at around 27%.

Physicians who could perform endoscopic screening were approved by the committee for gastric cancer screening at

the prefectural level based on certain requirements in Tottori prefecture.⁶ In the screening program, endoscopy has been performed essentially without biopsy. If an abnormal lesion was found at screening, biopsy was performed at the same time or the patient was recalled for work-up examinations that involved endoscopy with biopsy. Although endoscopic screening has been performed in clinical settings, the results have been judged based on monitor screen review by the local committee, including experienced endoscopists, in each city.

Target group

The target population was selected as shown in Figure 1. There were 56,676 screenings for gastric cancer using radiography and endoscopy from April 2002 to March 2007 in Yonago, Japan. The target age group was from 40 to 79 years, and the total number screened was 50,988. Individuals with a history of gastric cancer, irregular participants and participants whose screening method was unclear were excluded. Screening history was investigated within 2 years from index screening at the individual level based on the screening participant lists from 2000 to 2007. Based on the screening history, these were divided into two groups (prevalence screening and incidence screening). The prevalence screening group was defined as including persons who had no screening over 2 years earlier and those who were being screened for the first time. The incidence screening group was defined as including persons who were screened by the same method 1 year earlier. In both groups, the participants were divided into endoscopic screening and radiographic screening.

Data collection

In the screening programs, the final diagnosis was determined based on endoscopy with biopsy as a work-up examination and confirmed histologically. Clinical cases including interval cancer were diagnosed by various methods, and the results were obtained by the Tottori Cancer Registry database reflecting incidence cases through December 2009. Linkage was based on three independent identifiers as follows: sex, date of birth and name. All linked records were further checked manually to eliminate mismatches. Screen-detected cases were defined as true-positive cases regardless of the time between the date of screening and the date of diagnosis. All gastric cancers diagnosed within 1 year after a negative

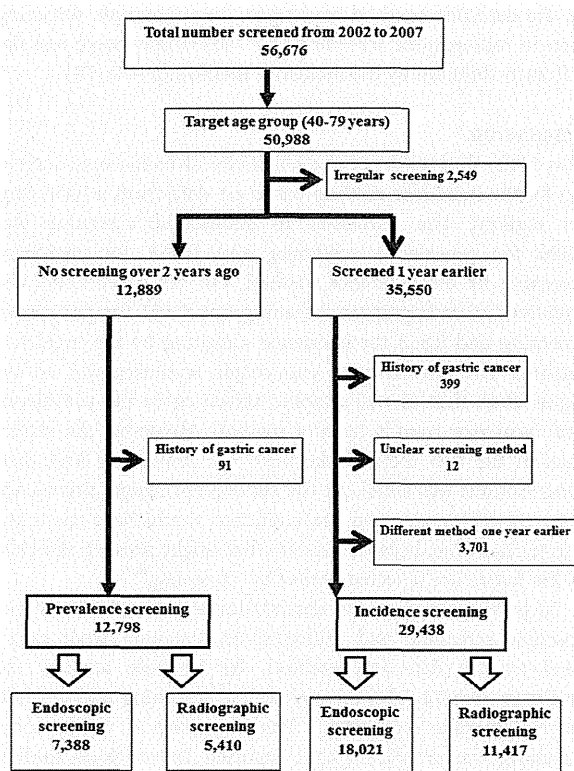


Figure 1. Selection process for the target population. The target population was selected. There were 56,676 screenings for gastric cancer using radiography and endoscopy from April 2002 to March 2007 in Yonago, Japan. The target age group was from 40 to 79 years, and the total number screened was 50,988. Individuals with a history of gastric cancer, irregular participants and participants whose screening method was unclear were excluded. Prevalence screenings included 7,388 endoscopic screenings and 5,410 radiographic screenings, whereas incidence screenings included 18,021 endoscopic screenings and 11,417 radiographic screenings.

screen were considered interval cancers. The location, histological type and stage of all gastric cancers were studied. Tumor location was recorded using the Japanese Classification of Gastric Carcinoma,¹⁶ in which the stomach is anatomically divided into three portions: upper, middle and lower. Clinical stage was also used for the determination of the clinical stage based on the Japanese Classification of Gastric Carcinoma.¹⁶

Our study was approved by the Institutional Review Board of the National Cancer Center of Japan.

Statistical analysis

First, the sensitivity and specificity of endoscopic and radiographic screenings were calculated by the detection method for incidence and prevalence screening. Sensitivity is the ability of a test to correctly identify cancer as positive [true positive/(true positive + false negative)]. Specificity is

the ability of a test to correctly identify no cancer as negative [true negative/(true negative + false positive)]. Second, the sensitivities of endoscopic and radiographic screenings were also calculated for the incidence and prevalence screenings by the incidence method using the following approximate formula¹⁷:

$$\text{Sensitivity} = 1 - [I(t)/I],$$

where $I(t)$ is the observed number of interval cancer cases during time t , and I is the expected number of cases in the absence of screening.

The expected number for the target population (P) in the absence of screening was assumed to be equal to the incidence of gastric cancer, and it could be found by the next screening. In incidence screening, the screening interval was 1 year, and the expected number of gastric cancers was calculated as follows: $I = (\text{Incidence rate}/100,000) \times P$. In prevalence screening, the expected number was calculated as the 2-year cumulative incidence, and the expected number of gastric cancers was calculated as follows: $I = (\text{Incidence rate}/100,000) \times 2 \text{ (years)} \times P$. The age-specific incidence for gastric cancer was based on estimates from monitoring of the 15 population-based cancer registries in Japan.² Age-specific gastric cancer incidences of 2006 were 20.5, 47.1, 82.4, 156.3, 232.4, 348.7, 477.0 and 576.9 (per 100,000) for males, and 15.8, 25.3, 37.3, 55.0, 72.7, 103.3, 150.8 and 181.1 (per 100,000) for females, for age groups 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74 and ≥ 75 years, respectively.

The differences in sensitivity and specificity were tested by the χ^2 test. Analyses were carried out with STATA 11.0 (STATA, College Station, TX).

Results

Prevalence screenings included 7,388 endoscopic screenings and 5,410 radiographic screenings, whereas incidence screenings included 18,021 endoscopic screenings and 11,417 radiographic screenings (Table 1). Most participants in the prevalence and incidence screenings were females. The age distributions differed between the endoscopic and radiographic screenings for the prevalence and incidence rounds. Although the positive rates were similar in both screenings, the detection rate of endoscopic screening was around twice that of radiographic screening in both rounds (Table 2). The positive predictive value was also higher with endoscopic screening than with radiographic screening.

In prevalence screening, 64 cases were found by endoscopic screening and 25 cases were found by radiographic screening. In incidence screening, 86 cases were found by endoscopic screening and 23 cases were found by radiographic screening. Six cases from prevalence screening and five cases from incidence screening were confirmed as interval cancer by the Tottori Cancer Registry (Table 3). All interval cancers were finally diagnosed by endoscopy with biopsy. All cases were aged above 60 years. The histological types were mainly

Table 1. Number of screening tests performed by sex and age group for preference and incidence screening

	Endoscopic screening		Radiographic screening		p-value
	Total numbers	%	Total numbers	%	
Prevalence screening					
Total number	7,388		5,410		
Sex					
Male	2,849	38.6	1,993	36.8	0.047
Female	4,539	61.4	3,417	63.2	
Age (years)					
40–49	851	11.5	747	13.8	
50–59	1,593	21.6	1,252	23.1	<0.001
60–69	2,788	37.7	1,984	36.7	
70–79	2,156	29.2	1,427	26.4	
Incidence screening					
Total number	18,021		11,417		
Sex					
Male	6,511	36.1	3,562	31.2	
Female	11,510	63.9	7,855	68.8	<0.001
Age (years)					
40–49	551	3.1	813	7.1	
50–59	1,999	11.1	2,231	19.5	<0.001
60–69	6,651	36.9	4,101	35.9	
70–79	8,820	48.9	4,772	41.8	

tubular adenocarcinoma, and the clinical stages were mainly IA and IB.

The sensitivity and specificity of endoscopy and radiography for gastric cancer in prevalence screening and incidence screening are shown in Table 4. In prevalence screening, by the detection method, the sensitivity of prevalence screening was 0.955 (95% CI = 0.875–0.991) for endoscopic screening and 0.893 (95% CI = 0.718–0.977) for radiographic screening; however, the difference was not significant ($p = 0.255$). The specificity of endoscopic screening was nearly equal to that of radiographic screening ($p = 0.408$). By the incidence method, the sensitivity of prevalence screening was 0.886 (95% CI = 0.698–0.976) for endoscopic screening and 0.831 (95% CI = 0.586–0.964) for radiographic screening; however, the difference was not significant ($p = 0.626$). The sensitivity and specificity for incidence screening were similar to those for prevalence screening. By the detection method, the sensitivity of incidence screening was 0.977 (95% CI = 0.919–0.997) for endoscopic screening and 0.885 (95% CI = 0.664–0.972) for radiographic screening. The specificities of both screenings were similar ($p = 0.362$). By the incidence method, the sensitivity of incidence screening was 0.954 (95% CI = 0.842–0.994) for endoscopic screening and 0.855 (95% CI = 0.637–0.970) for radiographic screening. Although the sensitivity calculated

by the detection method was higher in endoscopic screening than in radiographic screening ($p = 0.043$), they were not significantly different by the incidence method ($p = 0.177$).

Discussion

This is the first report of the sensitivity of endoscopic screening by the incidence method based on data from a local cancer registry. The sensitivity of endoscopic screening was 0.886 for prevalence screening and 0.954 for incidence screening by the incidence method. On the other hand, the sensitivity of radiographic screening was 0.831 for prevalence screening and 0.855 for incidence screening by the incidence method. The sensitivity of endoscopic screening was always higher than that of radiographic screening in the prevalence and incidence rounds by any method. However, the difference in the two methods between the prevalence and incidence rounds was small. At the subsequent round, prevalence cases might remain, and the incidence would have increased due to lead time, because cancers that might present clinically in the future are detected earlier by screening.⁸

In previous studies, the sensitivities and specificities of endoscopic screening and radiographic screening were calculated by the detection method. In Japanese studies, the sensitivity was 74–84% for endoscopic screening and 57–91% for radiographic screening.¹⁰ The sensitivity of radiographic screening was similar to that reported by previous studies. However, the sensitivities of endoscopic and radiographic screenings were higher in Japan than in Korea. In the National Cancer Screening in Korea, the sensitivity of endoscopic screening was 69.4% in the first round and 66.8% in the subsequent round.¹¹ Sensitivities of radiographic screening were also lower in Korean than in Japanese studies. In our study, both endoscopic and radiographic screenings were performed every year in Yonago. The difference in the sensitivities and specificities between Korea and Japan was affected by the different screening interval: every 2 years in Korea and every year in Japan. The specificities of endoscopic screening in Korea were 96.12% in the first round and 96.30% in the second round,¹¹ higher than those in Japan. The specificity of radiographic screening in Korea was 89.8%,¹² similar to our results and previous studies in Japan.

Although the detection method is simple and widely used, it is affected by overdiagnosis or length bias because cancers with a long preclinical detectable phase are included in the denominator. The incidence method, which is not affected by overdiagnosis bias and length bias, is used to obtain the correct evaluation. The sensitivity of screening for breast, colorectal and lung cancer has been evaluated using the incidence method.^{13–15} In our study, most interval cancers detected by endoscopy were early cancer and might have included slow-growing cancers. The definition of overdiagnosis is cancer detected by screening and histologically confirmed that would never have surfaced in the lifetime of the subjects.⁸ However, it is impossible to identify early diagnosis and overdiagnosis cases in excess of incidence. The sensitivity of the prevalence

Table 2. Basic results of endoscopic and radiographic screening for gastric cancer

	Endoscopic screening Total numbers	Radiographic screening Total numbers
Prevalence screening		
Total number	7,388	5,410
Positive case	1,154	798
Positive rate (%)	15.6 (14.8–16.5)	14.8 (13.8–15.7)
No. of detected cancer by screening	64	25
Detection rate (/1,000)	8.7 (6.7–11.0)	4.6 (3.0–6.8)
Positive predictive value	5.5 (4.3–7.0)	3.1 (2.0–4.6)
No. of interval cancer	3	3
Incidence screening		
Total number	18,021	11,417
Positive case	2,020	1,251
Positive rate (%)	11.2 (10.8–11.7)	11.0 (10.4–11.5)
No. of detected cancer by screening	86	23
Detection rate (/1,000)	4.8 (3.8–5.9)	2.0 (1.3–3.0)
PPV	4.3 (3.4–5.2)	1.8 (1.2–2.7)
No. of interval cancer	2	3

The 95% confidential intervals are given in parentheses. Abbreviation: PPV: positive predictive value.

Table 3. Interval cancer cases on endoscopic and radiographic screening

Type of screening	Screening method	Sex	Age at diagnosis (years)	Location	Pathology	Clinical stage
Prevalence screening	Endoscopy	Female	68.8	L	Tub	IA
	Endoscopy	Female	70.7	M	Tub	IA
	Endoscopy	Male	61.1	M	Tub	IB
	Radiography	Male	69.8	U	Tub	IV
	Radiography	Male	71.7	L	Tub	IB
	Radiography	Female	72.6	L	Tub	IA
Incidence screening	Endoscopy	Male	78.0	U	Sig	IB
	Endoscopy	Male	69.0	L	Tub	IA
	Radiography	Male	77.2	U	Tub	IV
	Radiography	Male	78.1	U	Tub	IA
	Radiography	Female	72.7	M	Por	IA

The location, histological type and stage of all gastric cancers were studied. Tumor location was recorded using the Japanese Classification of Gastric Carcinoma,¹⁶ in which the stomach is anatomically divided into three portions: upper, middle and lower. Clinical stage was also used for the determination of the clinical stage based on the Japanese Classification of Gastric Carcinoma.¹⁶ Abbreviations: U: upper body; M: middle body; L: lower body; Tub: tubular adenoma; Sig: signet-ring cell carcinoma; Por: poorly differentiated adenocarcinoma.

screening was affected by length bias and overestimation, because gastric cancers with a long preclinical detectable phase were prevalent. As most interval cancers were of low stage, it remained possible to save the patients' lives through the cancer being detected at the next screening. Based on the report of the natural history of nonresected cancers, half of early cancer cases remained in their early stages for more than 44 months.¹⁸ Although the high detection rate of endoscopic screening might suggest a lead time effect, mortality reduction by endoscopic screening is still unclear.

It is anticipated that endoscopy will become a new screening method because of its high detection rate. However, lead-time effects and overdiagnosis were included among screen-detected cancers. Overdiagnosis of breast cancer screening was estimated by the cumulative incidence method based on the observational studies in European countries that defined upper age limit.⁷ However, the absence of an upper age limit for screening in Japanese programs increases the probability that early diagnosis converts into overdiagnosis. In such circumstances, to evaluate the sensitivity of the