参考文献

- 厚生労働省.平成25年度地域保健・健康増進事業報告
- Nakama H, Yamamoto M, Kamijo NH, et al. Colonoscopic evaluation of immunochemical fecal occult blood test for detection of colorectal neoplasia. Hepatogastroentelorogy. 1999; 46(25):228-231.
- 船越和博. 大腸がん検診の現状 - 早期発見・早期治療にむけた戦略. 新潟癌センター病院医誌. 2015; 54(1):16-23
- 公益財団法人がん研究振興財団. がんの統計 '05 http://ganjoho.jp/reg_stat/statistics/brochure/backnumber/2005_jp.html
- 大腸癌治療ガイドライン医師用2014年版 金原出版. 2014年
- 厚生労働省.平成26年簡易生命表. http://www.mhlw.go.jp/toukei/saikin/hw/seimei/list54-57-02.html
- Kobayashi H, Mochizuki H, Sugihara K, et al. Characteristics of recurrence and surveillance tools after curative resection for colorectal cancer: a multicenter study. Surgery. 2007; Jan;141(1):67-75.
- Stryker SJ, Wolff BG, Culp CE, Libbe SD, Ilstrup DM, MacCarty RL.. Natural history of untreated colonic polyps. Gastroenterology. 1987 Nov;93(5):1009-13.
- 地域がん登録全国協議会. 大腸良性ポリープとポリープ切除によるがん発生の抑制効果の検証. http://www.jacr.info/about/yakudatsu-detail.php?no=26

厚生労働科学研究費補助金（がん対策推進総合研究事業）
分担研究報告書

大腸がん検診の費用対効果推計モデル構築に関する研究

研究分担者　五十嵐中　　東京大学大学院薬学系研究科
研究分担者　池田俊也　　国際医療福祉大学薬学部

研究要旨

大腸がん検診に関して、真のエンドポイント(QALYや大腸がん死亡)を評価でき、なおかつより実態に即した動的な検診戦略を再現できる費用対効果評価モデルを構築した。検診なし・内視鏡(TCS)中心戦略・便潜血検査(FIT)中心戦略・混合戦略の4戦略を比較したところ、費用対効果の観点からは、便潜血検査(FIT)中心の戦略が最も優れるという結果になった。また検診なしと比較すると、いずれの検診戦略もdominantになった。今後他のがん検診プログラムに関しても、同様の自然史モデルを構築した上で、死亡回避やQALYをアウトカムにした費用対効果の評価が望まれる。

A．研究目的

がん検診領域の費用対効果評価に際して、単なる「がん発見増加」をアウトカムにとることは、過剰診断バイアスの問題がある。また、単純に発見後の生存期間を比較すると、検診で発見されるがんは自覚症状を経て発見されるがんよりも早期である可能性が高いため、見かけの生存期間は検診経由の方が長くなる(リードタイムバイアス)。

それゆえ、正しい費用対効果評価のためには、癌進行の自然死モデルを構築した上で、検診を導入した場合としない場合の期待費用・期待アウトカムを比較する必要がある。なおかつ、アウトカムとしてはがん死亡や生存年数・QALYなどを用いるべきである。

以上を踏まえて、分担研究者らの過去の研究で使用したポリープ発生から大腸がん発症(さらにはがん死亡)に至るまでの大腸がん進行を再現できるモデルを改良し、自由度の高いモデルを構築した。あわせて、種々の検診戦略の費用対効果の評価を行った。

B．研究方法

過去の研究で、ポリープ発生から大腸がん発症・がん死亡に至るマルコフモデルを構築している(Hashimoto et al., 2014)。しかしこのモデルは、状態間の推移確率に関して海外のデータのみを用いていることに加え、マルコフモデルの元々の特性である無記憶性(n+1サイクル時点での状態は、nサイクル時点でどの健康状態にいるかのみによって決定される。n-1サイクル以前の状態は考慮できない)ゆえに、より現実に近い形で検診戦略を評価することはやや困難であった。

具体的には、検診の結果によって再検診までの間隔を変化させること(陽性ならば2年後再検診・陰性ならば5年後再検診など)の再現が不可能であった。

そこで、既存の自然史モデルに関し、以下の2点の変更を加えた新モデルを構築した。

1) ポリープ状態の移行確率の修正と、状態数の変更

従前のモデルはポリープに関し、「低リスクポリープ(1-9mm)」「高リスクポリープ(10mm以上)」の2状態に分割し、なおかつ状態間の移行確率は海外文献のデータを援用していた。これを日本の診療実態にあわせ、「低リスクポリープ(1-4mm)」「中リスクポリープ(5-9mm)」「高リスクポリープ(10mm以上)」の3状態に再設定した。あわせて状態間の移行確率について、がんセンターの検診データをもとに、低・中・高リスクポリープ間の遷移確率を年齢階級別に算出した。

2) モンテカルロシミュレーションによる過去の検診結果を参照した動的な検診戦略の再現

マルコフモデルの無記憶性の問題を克服すべく、モンテカルロシミュレーションによる動的な分析モデルを構築した。モンテ

カルロシミュレーションの導入により、検診の結果によって再検診までの間隔を変化させること（陽性ならば2年後再検診・陰性ならば5年後再検診など)が可能になる。

構築したモデルを用いて、以下の3つの戦略(および検診なし)に関して期待費用および期待QALYを推計した。分析期間は生涯に設定した。

＜戦略1: 便潜血(FIT)ベースの戦略＞
原則として毎年FITを受診する。FITで陽性の場合、内視鏡検査(TCS)を実施する。TCSで陰性の場合は、5年後にFITを行う。TCSで陽性の場合は、切除した上で3年後に再度TCSを実施する。それ以降も、「TCS陰性→5年後にFIT, TCS陽性→3年後再度TCS」の戦略を維持する。
＜戦略2: 内視鏡検査(TCS)ベースの戦略＞
一定の年齢で(初期状態では45歳)、全員がTCSを受診する。TCS陰性の場合、10年後に再度TCSを受診する。TCS陽性の場合は、切除した上で3年後に再度TCSを受診する。
それ以降も、「陽性ならば3年後、陰性ならば10年後」の戦略を維持する。
＜戦略3: 混合戦略＞
戦略1をベースにしつつ、40歳代で一度もTCSを受診しなかった人に対して、50歳時点で一斉にTCS検診を実施する。

（倫理面への配慮）
既存の文献から得られた数値と、統計処理されたデータのみを用いるため、倫理面の問題はない。

C．研究結果

表1に、4戦略の期待費用・期待QALYの推計結果と、10万人あたりのTCS実施件数の推計値を示す。検診を全く行わない場合と比較すると、どの戦略も費用は削減され、獲得QALYは増大するdominantの状態になった。
3戦略相互間の比較では、戦略1は戦略3よりも「高くて効かない」状態にあるため、除外された。残った戦略2と戦略3に関して、戦略2が99,930円・23.0178QALY, 戦略3が93,523円・23.0096円となった。戦略2は戦略3を比較対照としたとき、期待費用は6,407円増大するものの、期待QALYは0.082QALY増大する。1QALY獲得あたりのICERは78.1万円/QALYで、一般的な閾値である500-600万円を十分に下回る。
費用対効果の観点からは、FIT中心の戦略2が最も優れるという結果になった。ただしTCSの施行件数は他の戦略と比較して倍以上(戦略1: 10.0万件, 戦略2: 29.4万件, 戦略3: 12.6万件)になった。

D．考察

大腸がん検診に関して、真のエンドポイント(QALYや大腸がん死亡)を評価でき、なおかつより実態に即した動的な検診戦略を再現できる費用対効果評価モデルを構築した。元々の自然史モデルでも、検診まわりの既知のバイアスを可能な限り最小化すべく、ポリープから進行(Dukes 4)大腸がんに至る自然経過を再現しつつ、検診もしくは自覚症状によって発見された時点で処置を行う(処置の有効率は、検診経由でも自覚症状経由でも不変)ことを仮定している。バイアスを最小化した状態で各種の検診戦略の比較ができることは、検診の真の有用性を評価できる点で意義深いものと考える。
大腸がんは、発見時の進行状況がその後の生存率に大きく影響している点で、検診による早期発見・早期介入のメリットを享受しやすいがんとも考えられる。今後他のがん検診プログラムに関しても、同様の自然史モデルを構築した上で、死亡回避やQALYをアウトカムにした費用対効果の評価が望まれる。
予防や検診は「一般的に費用対効果に優れる」と定性的に議論されることも多いが、低リスク集団に対して網羅的に予防・検診を実施することは、過剰診断のリスクが大きいことやそもそもの罹患率が低い可能性を勘案すると、必ずしも効率的ではない一面もある。他の介入との比較可能性を保ちつつ検診の有用性を判断し、なおかつ公費助成や検診プログラム拡充の優先順位付けを際には、このような分析の果たすべき役割は大きい。

E．結論

大腸がん検診に関して、真のエンドポイント(QALYや大腸がん死亡)を評価でき、なおかつより実態に即した動的な検診戦略を再現できる費用対効果評価モデルを構築した。費用対効果の観点からは、便潜血検査(FIT)中心の戦略が最も優れるという結果になった。また検診なしと比較すると、いずれの検診戦略もdominantになった。今後他のがん検診プログラムに関しても、同様の自然史モデルを構築した上で、死亡回避やQALYをアウトカムにした費用対効果の評価が望まれる。

F．健康危険情報

なし

G．研究発表

1. 論文発表

研究分担者　池田俊也

1) Shiroiwa T, Fukuda T, Ikeda S, Igarashi A, Noto S, Saito S, Shimozuma K. Japanese population norms for preference-based measures: EQ-5D-3L, EQ-5D-5L, and SF-6D. Qual Life Res. 2015.

2)Ito K, Ikeda S, Muto M. A Review of Clinical Studies of Brand-name and Generic Drugs Used in Arrhythmia. Iryo To Shakai. 2015; 25(4): 417-429.

研究分担者　五十嵐　中

1) Shiroiwa T, Fukuda T, Ikeda S, Igarashi A, Noto S, Saito S, Shimozuma K. Japanese population norms for preference-based measures: EQ-5D-3L, EQ-5D-5L, and SF-6D. Qual Life Res. 2015.

2) Kaitani T, Nakagami G, Iizaka S, Fukuda T, Oe M, Igarashi A, Mori T, Takemura Y, Mizokami Y, Sugama J, Sanada H. Cost-utility analysis of an advanced pressure ulcer management protocol followed by trained wound, ostomy, and continence nurses. Wound Repair Regen. doi: 10.1111/wrr.12350: 2015.

3) Sekiguchi M, Igarashi A, Matsuda T, Matsumoto M, Sakamoto T, Nakajima T, Kakugawa Y, Yamamoto S, Saito H, Saito Y. Optimal use of colonoscopy and fecal immunochemical test for population-based colorectal cancer screening: a cost-effectiveness analysis using Japanese data. Jpn J Clin Oncol 2016; 46(2): 116-125.

2. 学会発表

なし

（発表誌名巻号・頁・発行年等も記入）

H．知的財産権の出願・登録状況
（予定を含む。）

1. 特許取得

なし

2. 実用新案登録

なし

3.その他

なし

図１．４戦略の費用対効果平面

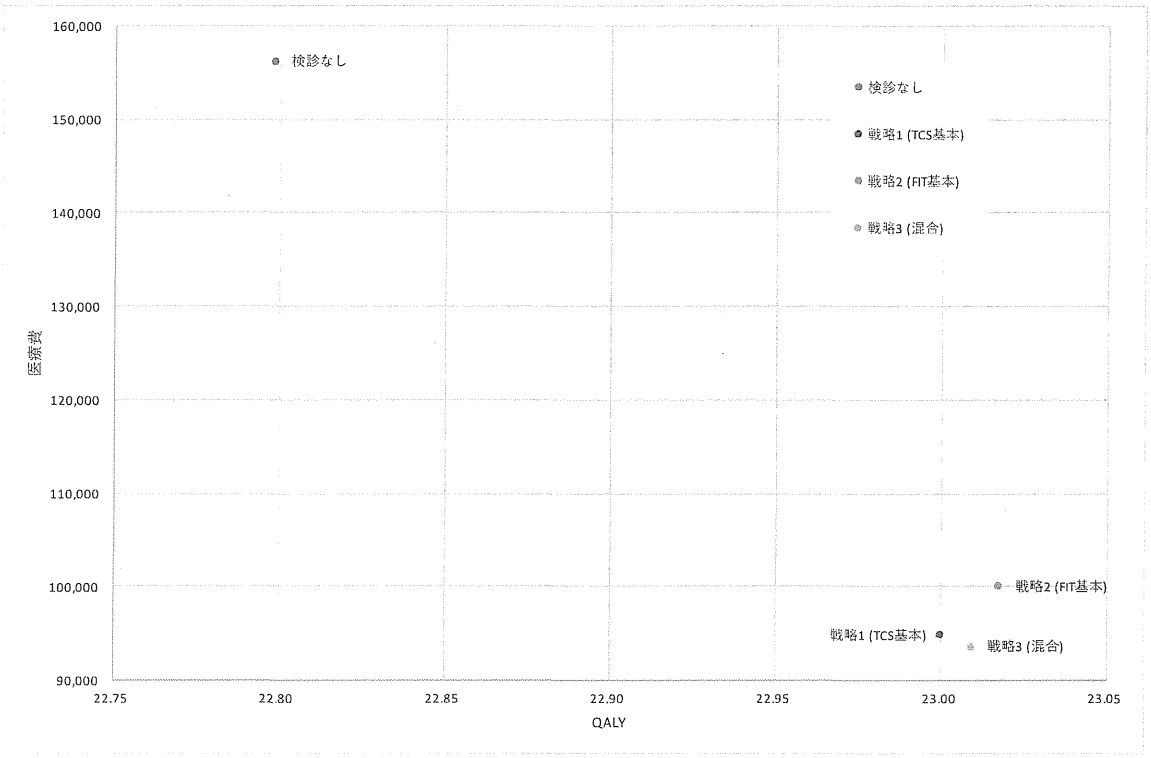

表 1.　４戦略の期待費用・期待 QALY・10 万人あたりの内視鏡件数

	cost	QALY	TCS 件数 (10 万人あたり)
検診なし	156,125	22.7986	0
戦略 1 (TCS 基本)	94,733	23.0001	100,740
戦略 2 (FIT 基本)	99,930	23.0178	294,322
戦略 3 (混合)	93,523	23.0096	126,171

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(分担).	2. がんの検診.	日本臨床腫瘍学会	[4]がんの予防と検診. II 臨床腫瘍学の基礎、新臨床腫瘍学ーがん薬物療法専門医のためにー改訂第4版	南江堂	東京	2015.7	109-112 (総頁数738pp)
濱島ちさと, 斎藤博(分担).	1. 有効性評価に基づく乳がん検診ガイドライン2013年度版の解説. 第1章「検診・診断」	監修: 園尾博司, 編集: 福田護, 池田正, 佐伯俊昭, 鹿間直人	これからの乳癌診療2015-2016	金原出版	東京	2015.7	2-6 (総頁数161pp)

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
Hamashima C, Shabana M, Okada K, Okamoto M, Osaki Y.	Mortality reduction from gastric cancer by endoscopic and radiographic screening.	Cancer Sci.	106 (12)	1744-1749	2015
Hamashima C, Ohta K, Kasahara Y, Katayama T, Nakayama T, Honjo S, Ohnuki K.	A meta-analysis of mammographic screening with and without clinical breast examination.	Cancer Sci.	106 (7)	812-818	2015
Lauby-Secretan B, Scoccianti C, Loomis D, Benbrahim-Tallaa L, Bouvard V, Bianchini F, Straif K; International Agency for Research on Cancer Handbook Working Group: [Armstrong B, Anttila A, de Koning HJ, Smith RA, Thomas DB, Weiderpass E, Anderson BO, Badwe RA, da Silva TCF, de Bock GH, Duffy SW, Ellis I, Hamashima C, Houssami N, Kristensen V, Miller AB, Murillo R, Paci E, Patnick J, Qiao YL, Rogel A, Segnan N, Shastri SS, Solbjor M, Heyyang-Kobrunner SH, Yaffe MJ, Forman D, von Karsa Lawrence, Sankaranarayanan R].	Breast-cancer screening--viewpoint of the IARC Working Group.	N Engl J Med.	372 (24)	2353-2358	2015

Hamashima C, Shabana M, Okamoto M, Osaki Y, Kishimoto T.	Survival analysis of patients with interval cancer undergoing gastric cancer screening by endoscopy.	PLoS One.	10 (5)	e0126796	2015
Hamashima C.	Have we Comprehensively Evaluated the Effectiveness of Endoscopic Screening for Gastric Cancer?	Asian Pac J Cancer Prev.	16 (8)	3591-3592	2015
Hamashima C.	The Japanese Guidelines for Breast Cancer Screening.	Jpn J Clin Oncol.	46 (5)	482-492	2016
濱島 ちさと.	【有効性評価に基づく胃がん検診ガイドライン-内視鏡検診時代の新たなる幕開け】 ガイドライン改訂に当たっての変更点と課題.	臨床消化器内科	31 (2)	125-132	2016
Shiroiwa T, Fukuda T, Ikeda S, Igarashi A, Noto S, Saito S, Shimozuma K.	Japanese population norms for preference-based measures: EQ-5D-3L, EQ-5D-5L, and SF-6D.	Qual Life Res.	25 (3)	707-719	2016
Ito K, Ikeda S, Muto M.	A Review of Clinical Studies of Brand-name and Generic Drugs Used in Arrhythmia.	Iryo To Shakai	25 (4)	417-429	2015
Kaitani T, Nakagami G, Iizaka S, Fukuda T, Oe M, Igarashi A, Mori T, Takemura Y, Mizokami Y, Sugama J, Sanada H.	Cost-utility analysis of an advanced pressure ulcer management protocol followed by trained wound, ostomy, and continence nurses.	Wound Repair Regen.	23 (6)	915-921	2015
Sekiguchi M, Igarashi A, Matsuda T, Matsumoto M, Sakamoto T, Nakajima T, Kakugawa Y, Yamamoto S, Saito H, Saito Y.	Optimal use of colonoscopy and fecal immunochemical test for population-based colorectal cancer screening: a cost-effectiveness analysis using Japanese data.	Jpn J Clin Oncol.	46 (2)	116-125	2016
Narita Y, Matsushima Y, Shiroiwa T, Chiba K, Nakanishi Y, Kurokawa T, Urushihara H.	Cost-effectiveness analysis of EGFR mutation testing and gefitinib as first-line therapy for non-small cell lung cancer.	Lung Cancer.	90 (1)	71-77	2015
Igarashi A, Goto R, Suwa K, Yoshikawa R, Ward AJ, Moller J.	Cost-Effectiveness Analysis of Smoking Cessation Interventions in Japan Using a Discrete-Event Simulation.	Appl Health Econ Health Policy.	14 (1)	77-87	2016

Cancer Science
Japanese Cancer Association JCA
Open Access

Mortality reduction from gastric cancer by endoscopic and radiographic screening

Chisato Hamashima,[1] Michiko Shabana,[2] Katsuo Okada,[3] Mikizo Okamoto[4] and Yoneatsu Osaki[5]

[1]Cancer Screening Assessment and Management Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo; [2]Department of Internal Medicine, San-in Rosai Hospital, Yonago; [3]Tottori Prefecture Health Promoting Council, Tottori; [4]Cancer Center, Tottori University Hospital, Yonago; [5]Division of Environmental and Preventive Medicine, Department of Social Medicine, Faculty of Medicine, Tottori University, Yonago, Japan

Key words

Cohort study, gastric cancer screening, mortality reduction, upper gastrointestinal endoscopy, upper gastrointestinal X-ray

Correspondence

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

Funding Information

Ministry of Health, Labor and Welfare of Japan.

Received August 20, 2015; Revised September 24, 2015; Accepted September 26, 2015

Cancer Sci **106** (2015) 1744–1749

doi: 10.1111/cas.12829

To evaluate mortality reduction from gastric cancer by endoscopic screening, we undertook a population-based cohort study in which both radiographic and endoscopic screenings for gastric cancer have been carried out. The subjects were selected from the participants of gastric cancer screening in two cities in Japan, Tottori and Yonago, from 2007 to 2008. The subjects were defined as participants aged 40–79 years who had no gastric cancer screening in the previous year. Follow-up of mortality was continued from the date of the first screening to the date of death or up to December 31, 2013. A Cox proportional hazards model was used to estimate the relative risk (RR) of gastric cancer incidence, gastric cancer death, all cancer deaths except gastric cancer death, and all-causes death except gastric cancer death. The number of subjects selected for endoscopic screening was 9950 and that for radiographic screening was 4324. The subjects screened by endoscopy showed a 67% reduction of gastric cancer compared with the subjects screened by radiography (adjusted RR by sex, age group, and resident city = 0.327; 95% confidence interval [CI], 0.118–0.908). The adjusted RR of endoscopic screening was 0.968 (95%CI, 0.675–1.387) for all cancer deaths except gastric cancer death, and 0.929 (95%CI, 0.740–1.168) for all-causes death except gastric cancer death. This study indicates that endoscopic screening can reduce gastric cancer mortality by 67% compared with radiographic screening. This is consistent with previous studies showing that endoscopic screening reduces gastric cancer mortality.

In 2012, approximately 1 million new cases of gastric cancer were recorded worldwide, and half of these cases occurred in Eastern Asian countries.[1] The mortality rates from gastric cancers in Eastern Asian countries were also higher than those in other countries, with rates of 24 per 100 000 men and 9.8 per 100 000 women. Clearly, the burden of gastric cancer cannot be ignored in Eastern Asian countries; this also holds true in Eastern European countries and South America, which also have high incidences of gastric cancer.

Recently, upper gastrointestinal endoscopy has been increasingly used in clinical practice and as a standardized examination procedure for gastrointestinal diseases. In some Asian countries, opportunistic cancer screening for gastric cancer using upper gastrointestinal endoscopy (i.e., endoscopic screening) has gradually increased.[2] In fact, high detection rates of gastric cancer have been reported with endoscopic screening in local areas of Eastern Asian countries.[3,4] Although endoscopic screening for gastric cancer has already been introduced in Korean national programs,[5] evidence for mortality reduction from gastric cancer screening using endoscopy was unclear when endoscopic screening was introduced in the early 2000s.[6] In Japan, gastric cancer screening using upper gastrointestinal X-ray with barium meal (i.e., radiographic screening) has been carried out as a national program since 1983.[7] Several case–control and cohort studies have reported consistent results showing mortality reduction from gastric cancer by radiographic screening in Japan.[6] Recently, several municipalities have introduced endoscopic screening as an option for gastric cancer screening. In fact, the possibility of reducing mortality from gastric cancer by endoscopic screening was shown by several studies.[8–12] However, discussions regarding the effectiveness of endoscopic screening continue. To effectively introduce endoscopic screening for gastric cancer in communities, evidence regarding its effectiveness must be accumulated.[13]

We undertook a population-based cohort study in Tottori and Yonago cities in Japan, where radiographic and endoscopic screenings for gastric cancer have been carried out for 15 years, to evaluate mortality reduction from gastric cancer by endoscopic screening.

Methods

Screening programs. Endoscopic screening for gastric cancer has been carried out in Tottori and Yonago since 2000. Local governments have performed radiographic screening and endoscopic screening for gastric cancer in both cities. All individuals aged 40 years and above 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. Although the introduction of endoscopic screening has increased, the participation rate in gastric cancer screening involving both methods has remained at approximately 25%.[14]

Physicians who carried out the endoscopic screening were approved by the local committee for gastric cancer screening based on certain requirements.[14] 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 study subjects were selected from the participants of gastric cancer screening in Tottori and Yonago between 2007 and 2008. There were 28 782 participants in Tottori and 23 753 participants in Yonago. The subjects were defined as participants aged 40–79 years who had no gastric cancer screening in the previous year. The following cases were excluded: (i) subjects who had registry duplication; and (ii) subjects who had a history of gastric cancer. The selected subjects were divided into two groups, the endoscopic screening group and radiographic screening group, according to the first screening method used from 2007 to 2008.

Outcomes. The primary outcome of the study was gastric cancer mortality. All cancer deaths except gastric cancer death and all-causes deaths except gastric cancer death were assessed to ensure comparability between the two groups. Mortality data were obtained by linkage to the residential registrations of each city and the Tottori Cancer Registry (Tottori, Japan). The incidence of gastric cancer was identified from the Tottori Cancer Registry. Follow-up of gastric cancer incidence and mortality was continued from the date of the first screening to the date of gastric cancer diagnosis or up to December 31, 2013.

Statistical analysis. Differences in the proportion of both screening groups were compared using the χ^2-test and Student's *t*-test. A Cox proportional hazards model was used to estimate the relative risk (RR) of incident gastric cancer, gastric cancer death, all cancer deaths except gastric cancer death, and all-causes deaths except gastric cancer death. Unadjusted and adjusted RRs by sex, age group, and resident city were calculated. The cumulative hazard values of gastric cancer incidence and mortality were estimated by the Nelson–Aalen method and plotted on graphs. All test statistics were two-tailed, and *P*-values of <0.05 were considered to indicate a statically significant difference. Analyses were carried out using STATA 13.0 (STATA, College Station, Texas, USA).

This study was approved by the Institutional Review Board of the National Cancer Center of Japan (Tokyo, Japan).

Results

The procedure used for the selection of the target population is shown in Figure 1. A total of 52 535 subjects participated in gastric cancer screening in Tottori and Yonago from 2007 to 2008. Of these subjects, 5720 were not within the target age group for the analysis. Those subjects excluded from the target group were more than 80 years old at the first screening, which was not the actual target for cancer screening. A total of 14 394 subjects were selected as they had no gastric cancer screening history in the previous year. Three patients who had duplication on the participant list for gastric cancer screening were excluded from the target group for the analysis. There were 117 subjects who were identified as having a history of gastric cancer by linkage to a local cancer registry, and they were also excluded from the target group. The remaining 14 274 subjects were finally divided into two groups according to the first screening procedure as follows: endoscopic screening group (n = 9950), and radiographic screening group (n = 4324).

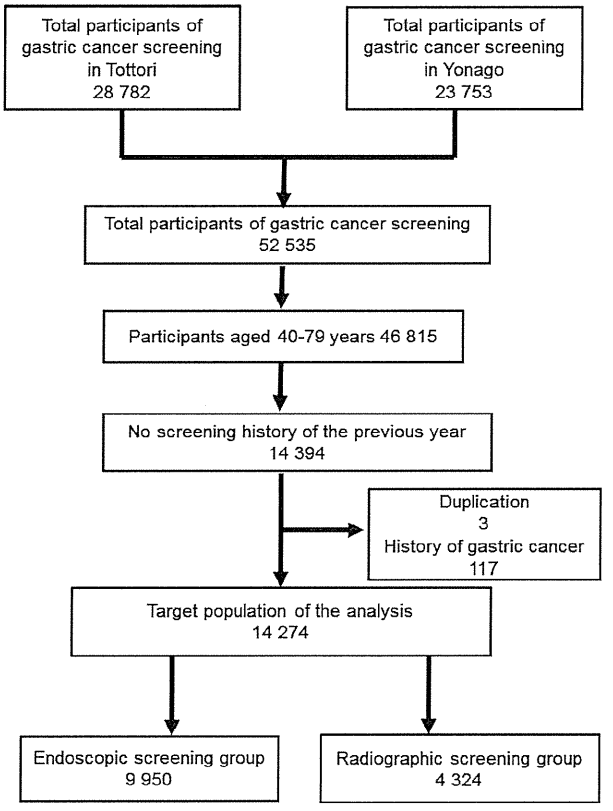

Fig. 1. Flowchart of the selection process for the study target group to compare endoscopic and radiographic screening for gastric cancer. A total of 52 535 subjects participated in gastric cancer screening in Tottori and Yonago (Japan) from 2007 to 2008, of which 5720 participants were not within the target age for the analysis (aged more than 80 years at the time of first screening). A total of 14 394 subjects were selected as they had no gastric screening history of the previous year. Three patients who had duplication on the participant list of gastric cancer screening were excluded from 2007 to 2008 the target group of the analysis. There were 117 subjects who were identified as having a history of gastric cancer by linkage to a local cancer registry and they were also excluded from the target group. The remaining 14 274 subjects were divided into two groups according to the first screening procedure: endoscopic screening group (n = 9950), and radiographic screening group (n = 4324).

The results of the comparison of the basic characteristics of the endoscopic screening group and radiographic screening group are shown in Table 1. The sex and age distributions were significantly different between the two groups. The proportion of female subjects was significantly higher than that of male subjects in both groups. The proportion of the ≥70 years age group was significantly lower in the radiographic screening group than in the endoscopic screening group ($P < 0.001$). During the 6-year follow-up period, the screening frequency was 2.3 for the endoscopic screening group and 2.2 for the radiographic screening group ($P = 0.988$). During the follow-up period, very few subjects of the endoscopic screening group

Table 1. Comparison of participants between endoscopic screening and radiographic screening for gastric cancer

	Endoscopic screening		Radiographic screening		*P*-value
	n	(%)	*n*	(%)	
Total	9950		4324		
Sex					
Male	3589	(36.1)	1454	(33.6)	0.005
Female	6361	(63.9)	2870	(66.4)	
Age, years					
40–49	1174	(11.8)	593	(13.7)	
50–59	1959	(19.7)	1086	(25.1)	<0.001
60–69	3793	(38.1)	1551	(35.9)	
70–79	3024	(30.4)	1094	(25.3)	
City					
Tottori	5564	(55.9)	2945	(68.1)	<0.001
Yonago	4386	(44.1)	1379	(31.9)	
Screening frequency during follow-up period, average					
Total	2.3		2.2		0.988
Endoscopy	2.2		0.9		<0.001
Radiography	0.1		1.3		<0.001

had also been screened by radiography. In contrast, subjects in the radiographic screening group had two screenings on average, one radiographic and one endoscopic screening.

During the 6-year follow-up period, 127 gastric cancers were diagnosed in the endoscopic screening group and 41 gastric cancers in the radiographic screening group (Table 2). Approximately half of the subjects were aged 70–79 years and the proportions of the age group were nearly equal in both screening groups ($P = 0.365$). Although the proportion of localized cancers was higher in the endoscopic screening group than in the radiographic screening group, the stage distribution was similar in both groups ($P = 0.276$).

The mean follow-up period was 66.6 ± 0.9 months (95% confidence interval [CI], 66.4–66.7). The gastric cancer incidence was 233.7 per 100 000 person-years in the endoscopic screening group and 172.1 per 100 000 person-years in the radiographic screening group (Table 3). Although the gastric cancer incidence of the endoscopic screening group was higher than that of the radiographic screening group, it was not significantly different (unadjusted RR = 1.168, 95%CI, 0.804–1.695; adjusted RR = 0.988, 95%CI, 0.679–1.438). During the follow-up years, cumulative hazard values of gastric cancer incidence were nearly equal between the radiographic screening group and the endoscopic screening group (Fig. 2a).

After the 6-year follow-up period, seven subjects from the endoscopic screening group and eight from the radiographic screening group died of gastric cancer. The gastric cancer death rate was 33.1 per 100 000 person-years in the endoscopic screening group and 12.7 per 100 000 person-years in the radiographic screening group (Table 3). Although the unadjusted RR was not statistically significant (unadjusted RR = 0.384, 95%CI, 0.139–1.060), the subjects screened by endoscopy showed a 67% mortality reduction from gastric cancer compared with the subjects screened by radiography when the RR was adjusted by sex, age group, and resident city (adjusted RR = 0.327, 95%CI, 0.118–0.908). The cumulative hazard of gastric cancer mortality became nearly similar in both screening groups until 3 years of follow-up, but the difference subsequently widened (Fig. 2b).

Table 2. Comparison of detected gastric cancers between endoscopic screening and radiographic screening

	Endoscopic group		Radiographic group		*P*-value
	n	(%)	*n*	(%)	
Total number of detected cancer	127		41		
Sex					
Male	87	(68.5)	25	(61.0)	0.374
Female	40	(31.5)	16	(39.0)	
Age group, years					
40–49	3	(2.4)	1	(2.4)	
50–59	9	(7.1)	4	(9.8)	0.365
60–69	57	(44.9)	12	(29.3)	
70–79	58	(45.7)	24	(58.5)	
City					
Tottori	55	(43.3)	19	(46.3)	0.734
Yonago	72	(56.7)	22	(53.7)	
Stage					
Localized	98	(77.2)	30	(73.2)	0.276
Regional	8	(6.3)	6	(14.6)	
Distant	4	(3.1)	2	(4.9)	
Unknown	17	(13.4)	3	(7.3)	
Pathology					
Intestine	99	(78.0)	27	(65.9)	0.158
Diffuse	20	(15.7)	12	(29.3)	
Others and unknown	8	(6.3)	2	(4.9)	

After the 6-year follow-up period, 111 subjects of the endoscopic screening group and 41 subjects of the radiographic screening group died from all cancer deaths excluding gastric cancer death. The all cancer deaths excluding gastric cancer death were 201.8 per 100 000 person-years in the endoscopic screening group and 169.5 per 100 000 person-years in the radiographic screening group (Table 3). A total of 264 subjects of the endoscopic screening group and 104 subjects of the radiographic screening group died from all-causes deaths excluding gastric cancer death. The all-causes deaths excluding gastric cancer death was 480.0 per 100 000 person-years in the endoscopic screening group and 430.1 per 100 000 person-years in the radiographic screening group (Table 3). The adjusted RR of the endoscopic screening group was 0.968 (95%CI, 0.675–1.387) for all cancer deaths except gastric cancer death and 0.929 (95%CI, 0.740–1.168) for all-causes deaths except gastric cancer death.

Discussion

The present results suggest that endoscopic screening can reduce mortality from gastric cancer by 67% compared with radiographic screening. Although upper gastrointestinal endoscopy has been commonly used for diagnostic examinations in clinical settings, evidence for cancer screening has remained controversial. This has limited its use to opportunistic screening in clinical settings even if high detection rates of gastric cancer can be expected.[2] We have recently published the results of our community-based case–control study evaluating the effectiveness of endoscopic screening for gastric cancer. The findings of our previous study suggest a 30% reduction in

Table 3. Relative risks (RR) and 95% confidence intervals (CI) of endoscopic screenings

Outcome	Screening method	No. of cases	Person-years	Rate (per 100 000 person-years)	Unadjusted RR	(95%CI)	Adjusted RR†	(95%CI)
Gastric cancer incidence								
	Radiographic screening	41	23 824	172.1	1.000		1.000	
	Endoscopic screening	127	54 353	233.7	1.168	(0.804–1.695)	0.988	(0.679–1.438)
Gastric cancer death								
	Radiographic screening	8	24 183	33.1	1.000		1.000	
	Endoscopic screening	7	55 002	12.7	0.384	(0.139–1.060)	0.327	(0.118–0.908)
All cancer deaths‡								
	Radiographic screening	41	24 183	169.5	1.000		1.000	
	Endoscopic screening	111	55 002	201.8	1.197	(0.837–1.713)	0.968	(0.675–1.387)
All-causes deaths§								
	Radiographic screening	104	24 183	430.1	1.000		1.000	
	Endoscopic screening	264	55 002	480.0	1.121	(0.893–1.407)	0.929	(0.740–1.168)

†Adjusted by sex, age group (40–59 years, 60–69 years, and 70–79 years), and resident city. ‡All cancer deaths excluding gastric cancer death. §All-causes deaths excluding gastric cancer death.

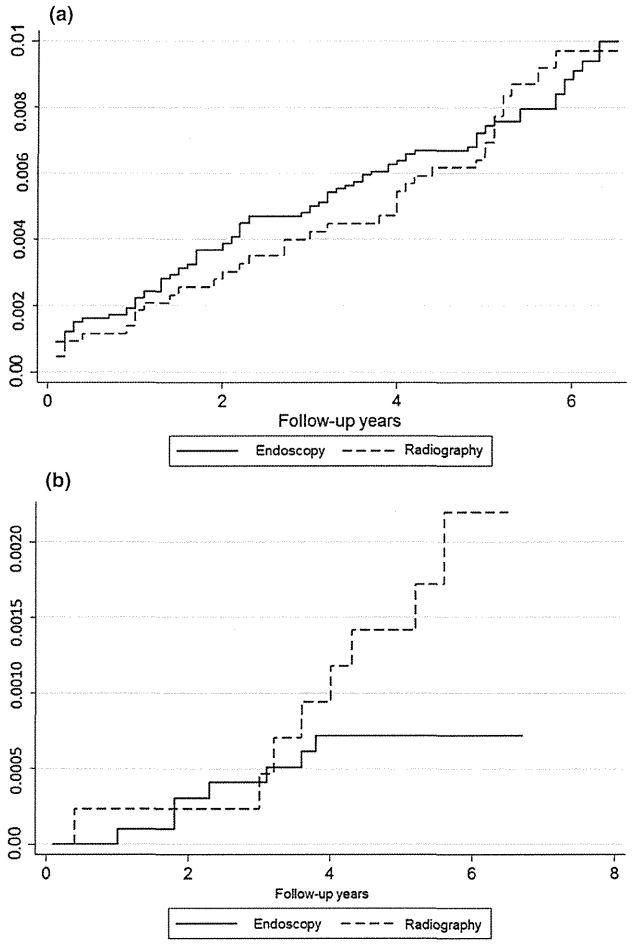

Fig. 2. Cumulative hazard values of gastric cancer incidence (a) and mortality (b) in follow-up years, estimated by the Nelson–Aalen method. Cumulative hazard values were compared between the endoscopic and radiographic screening groups.

gastric cancer mortality by endoscopic screening within 36 months before the date of gastric cancer diagnosis.[10] A nested case–control study from Korea reported a 57% mortality reduction by endoscopic screening based on the national database.[11] Hosokawa *et al.*[15] reported a 78% mortality reduction from gastric cancer by endoscopic screening compared with radiographic screening based on a 5-year follow-up period. The age distribution of the target population was younger in the endoscopic screening group than in the radiographic screening group. Although the present study has a different study design or background from these previous studies, the results consistently demonstrate mortality reduction from gastric cancer by endoscopic screening.

The possibility of reducing mortality from gastric cancer by radiographic screening has been mainly reported in Japan.[6] Although radiographic equipment for the upper gastrointestinal series has been improved, the sensitivity range of radiographic screening has remained from 80% to 90%.[16–19] To evaluate mortality reduction from gastric cancer by radiographic screening, case–control studies were mostly carried out until 1995, and then cohort studies were started for follow-up from the early 1990s. The subjects compared in these studies were individuals who had no screening history and had been treated by the usual care as needed. In 1996, the total number of upper gastrointestinal endoscopy procedures carried out was 73 879 in hospitals and 149 848 in outpatient clinics per month.[20] However, the total number of upper gastrointestinal endoscopic examinations carried out in 2011 increased to 521 936 in hospitals and 392 773 in outpatient clinics per month,[20] with endoscopic examination becoming a more common technique in medical services in Japan. The Japanese health insurance system covers most of the medical services except screening programs. However, the opportunity to be examined by endoscopy has rapidly increased according to the increase in the total number of upper gastrointestinal endoscopy procedures conducted. A recent case–control study particularly showed that mortality reduction could not be obtained by radiographic screening.[10] The impact of radiographic screening may be decreased depending on the periods when the evaluation studies were carried out. Therefore, to evaluate the effectiveness of endoscopic screening for gastric cancer, radiographic screening can be used for comparison.

Although the gastric cancer mortality in the endoscopic screening group was found to be lower than that in the radiographic screening group, the gastric cancer incidence and the stage distribution of diagnosed cancer were similar in both screening groups. As the proportion of the unknown stage of

the endoscopic screening group was higher than that of the radiographic screening group, there might be more patients with early stage cancer included in the endoscopic screening group than in the radiographic screening group. In Japanese studies, the proportion of early stage cancer, which constitutes tumor showing invasion within the gastric submucosa, based on the definition of the Japanese Gastric Cancer Association,[21] was usually approximately 70% in the radiographic screening group[22] and more than 80% in the endoscopic screening group.[23] Hosokawa *et al.*[15] previously reported that the detection rate of early cancer was higher in the endoscopic screening group than in the radiographic screening group, and the stage distribution was different in both groups. Endoscopy can diagnose more early stage cancers that can be treated by endoscopic surgical dissection. In fact, endoscopic surgical dissection has been carried out for approximately half of early stage cancers detected by endoscopic screening.[23] The difference in the cumulative hazard of gastric cancer mortality widened after 3 years from the first screening. This indicates that the detection of early stage cancer was initially achieved and then the gap of cumulative hazard of gastric cancer mortality widened between endoscopic screening and radiographic screening. Early stage gastric cancer takes approximately 44 months to become advanced stage gastric cancer.[24] This fact has to be taken into consideration when aiming for mortality reduction from gastric cancer by endoscopic screening. Although detecting more early stage gastric cancer is advantageous for endoscopic screening, cases of overdiagnosis might also be included. Currently, there are no reports of overdiagnosis by gastric cancer screening using radiography and endoscopy. However, the numbers of cancers detected by endoscopic screening have reportedly been twice the expected numbers.[25] These excess cases include overdiagnosis cases and early stage cancers that progress to advanced stage cancers. To further validate evidence of the effectiveness of endoscopic screening for gastric cancer, additional studies to evaluate mortality reduction from gastric cancer by endoscopic screening are warranted.

The relative risks of all cancer mortality excluding gastric cancer death and all-cause mortality excluding gastric cancer death were nearly equal between the endoscopic screening group and the radiographic screening group. However, to compare mortality reduction from gastric cancer between endoscopic screening and radiographic screening, the background difference should be considered between the endoscopic screening group and the radiographic screening group. Endoscopic screening has been carried out in clinical practice in Tottori prefecture. The age of the participants in the endoscopic screening group was more advanced than that of the participants in the radiographic screening group.[10] Individuals aged more than 70 years could be screened by physicians using endoscopy in their own private practice. As the number of younger people with family physicians was fewer than older people with family physicians, there was little opportunity for the younger people to be tested in clinical practice. *Helicobacter pylori* infection is a major cause of gastric cancer,[26] and the difference of the age group also affects the *H. pylori* infection rate. Although the *H. pylori* infection rate has decreased in Japan, the rate has remained higher in individuals aged 70 years and over than in individuals aged 40–69 years.[27] As the proportion of individuals aged ≥70 years was higher in the endoscopic screening group than in the radiographic screening group, the risk for gastric cancer might be higher in endoscopic screening than in radiographic screening. However, we could not obtain the *H. pylori* infection rates at the first screening in both screening groups. Lifestyle behaviors could also be a risk factor for gastric cancer; in particular, high salt intake and smoking are associated with gastric cancer.[28–30] The smoking rate is reportedly higher in Tottori prefecture than the national average and the rates decrease according to age in men and women.[31] Salt intake in Tottori prefecture is reportedly similar to the national average and the differences of the age group are small.[31] Although Fukao *et al.*[32] reported differences in family history and smoking between participants and non-participants in gastric cancer screening, the difference in the backgrounds between the endoscopic and radiographic screening groups is unclear. We could not use the results of the questionnaire survey at the screening participation because there were no questions regarding salt intake or smoking.

This study has additional limitations. First, the quality of the Tottori Cancer Registry was not optimal as the percentage of death-certification-only cases was 15.1% in 2007, which was lower than the national average.[33] In Japan, cancer registries have not yet been prepared at the national level, and the registry method, as of 2014, has not yet been standardized.[34,35] As the registration of gastric cancers remains insufficient, differences in the detected cancers by each screening group might not have been fully clarified. Second, there was no information as to whether or not the patients participated in opportunistic screenings. Third, the subjects of the radiographic screening group had been screened by endoscopy once during the follow-up period. In the study areas, people could choose either endoscopy or radiography as the screening method at the individual level. It was difficult to divide the screening method completely during the follow-up period. Therefore, the results might suggest a comparison between higher intensive and lower intensive endoscopic screening. Finally, subgroup analysis could not be adequately carried out because of the small sample size.

The incidence of gastric cancer has been decreasing and a predicted additional decrease is anticipated because of a decrease in the *H. pylori* infection rate,[27,36,37] However, as the participation rate in gastric cancer screening has decreased, its impact on mortality reduction has become limited. Although the participation rate in radiographic screening for gastric cancer has sunk below 10%,[38] there is a possibility of improving the participation rate by the introduction of endoscopic screening as an option for gastric cancer screening. Notably, the participation rate is reportedly approximately 25% in municipalities that have already introduced endoscopic screening.[22,39] However, according to the change in the incidence of gastric cancer, the possibility of a new screening system should be investigated considering the risk factors for gastric cancer.

In conclusion, the present study suggests that endoscopic screening can reduce mortality from gastric cancer by 67% compared with radiographic screening. The results consistently support mortality reduction from gastric cancer by endoscopic screening described by previous studies. Although this indicates the effectiveness of endoscopic screening for gastric cancer, several limitations, including self-selection bias, remain, and prudent interpretation of the finding is needed. Thus far, endoscopic screening for gastric cancer has shown promising results. Endoscopic screening therefore deserves further comprehensive evaluation to reliably confirm its effectiveness and how its optimal use can be strategically promoted.

Acknowledgments

This study was supported solely by a Grant-in-Aid for Research for Promotion of Cancer Control Programs from the Japanese Ministry of Health, Labour and Welfare (H27-Toku-Shitei-005). We thank the Tottori Cancer Registry office, and the local governments of Tottori and Yonago for their cooperation with the study. We are grateful to Dr. Edward F. Barroga, Associate Professor and Senior Medical Editor of Tokyo Medical University, for editing the English manuscript. We also thank Ms. Kanoko Matsushima, Ms. Junko Asai, and Ms. Mayumi Kobayashi for research assistance.

Disclosure Statement

The authors have no conflict of interest.

References

1 International Agency for Research on Cancer. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012, 2012. [Cited 10 Jul 2015.] Available from URL: http://globocan.iarc.fr/.
2 Leung WK, Wu MS, Kakugawa Y *et al.* Screening for gastric cancer in Asia: current evidence and practice. *Lancet Oncol* 2008; **9**: 279–87.
3 Tashiro A, Sano M, Kinameri K *et al.* Comparing mass screening techniques for gastric cancer in Japan. *World J Gastroenterol* 2006; **12**: 4873–4.
4 Lu YF, Liu ZC, Li ZH *et al.* Esophageal/gastric cancer screening in high-risk populations in Henan Province, China. *Asian Pac J Cancer Prev* 2014; **5**: 1419–22.
5 Kim Y, Jun JK, Choi KS *et al.* Overview of the national cancer screening programme and the cancer screening status in Korea. *Asian Pac J Cancer Prev* 2011; **12**: 725–30.
6 Hamashima C, Shibuya D, Yamazaki H *et al.* The Japanese guidelines for gastric cancer screening. *Jpn J Clin Oncol* 2008; **38**: 259–67.
7 Oshima A. A critical review of cancer screening programs in Japan. *Int J Technol Assess Health Care* 1994; **10**: 346–58.
8 Matsumoto S, Yamasaki K, Tsuji K *et al.* Results of mass endoscopic examination for gastric cancer in Kamigoto Hospital, Nagasaki Prefecture. *World J Gastroenterol* 2007; **13**: 4316–20.
9 Hosokawa O, Miyanaga T, Kaizaki Y *et al.* Decreased death from gastric cancer by endoscopic screening: association with a population-based cancer registry. *Scand J Gastroenterol* 2008; **43**: 1112–5.
10 Hamashima C, Ogoshi K, Okamoto M *et al.* A community-based, case–control study evaluating mortality reduction from gastric cancer by endoscopic screening in Japan. *PLoS ONE* 2013; **8**: e79088.
11 Cho BY. Evaluation of the validity of current national health screening programs and plans to improve the system. Seoul: Seoul University, 2014; 741–58 (in Korean).
12 Hamashima C, Ogoshi K, Narisawa R *et al.* Impact of endoscopic screening on mortality reduction from gastric cancer. *World J Gantroenterol* 2015; **21**: 2460–6.
13 Hamashima C. Have we comprehensively evaluated the effectiveness of endoscopic screening for gastric cancer? *Asian Pac J Cancer Prev* 2015; **16**: 3591–2.
14 Shabana M, Hamashima C, Nishida M *et al.* Current status and evaluation of endoscopic screening for gastric cancer. *Jpn J Cancer Det Diag* 2010; **17**: 229–35. (In Japanese).
15 Hosokawa O, Shinbo T, Matsuda K *et al.* Impact of opportunistic endoscopic screening on the decrease of mortality from gastric cancer. *J Gatsroenterol Cancer Screen* 2011; **49**: 401–9. (In Japanese).
16 Hamashima C, Okamoto M, Shabana M *et al.* Sensitivity of endoscopic screening for gastric cancer by the incidence method. *Int J Cancer* 2013; **133**: 653–9.
17 Murakami R, Tsukuma H, Ubukata T *et al.* Estimation of validity of mass screening program for gastric cancer in Osaka, Japan. *Cancer* 1990; **65**: 1255–60.
18 Abe S, Shibuya D, Noguchi T *et al.* An estimate of the false-negative rate of mass-screening for gastric carcinoma. *J Gatsroenterol Cancer Screen* 2000; **38**: 475–82. (In Japanese).
19 Yamamoto K, Yamazaki H, Kuroda C *et al.* Diagnostic validity of high-density barium sulfate in gastric cancer screening: follow-up of screenees by record linkage with the Osaka Cancer Registry. *J Epidemiol* 2010; **20**: 287–94.
20 Ministry of Health, Labour and Welfare. Medical Institute Survey, 2011, 2012. [Cited 10 Jul 2015.] Available from URL: http://www.e-stat.go.jp/SG1/estat/GL08020101.do?_toGL08020101_&tstatCode=000001030908&requestSender=dsearch.
21 Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011; **14**: 101–12.
22 Kitagawa S, Miyagawa K, Iriguchi Y *et al.* The report of gastroenterological screening in 2012. *J Gatsroenterol Cancer Screen* 2015; **53**: 60–86. (In Japanese).
23 Ogoshi K, Narisawa R, Kato T *et al.* Evaluation of endoscopic screening for gastric cancer in Niigata City: the reduction of the mortality rate. *J Gatsroenterol Cancer Screen* 2009; **47**: 531–41. (In Japanese).
24 Tsukuma H, Oshima A, Narahara H *et al.* Natural history of early gastric cancer: a non-concurrent, long term, follow up study. *Gut* 2000; **47**: 618–21.
25 Hamashima C, Sobue T, Muramatsu Y *et al.* Comparison of observed and expected numbers of detected cancers in the research center for cancer prevention and screening program. *Jpn J Clin Oncol* 2006; **36**: 301–8.
26 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans Helicobacter pylori. In: International Agency for Research on Cancer, eds. *IARC Monographs on the Evaluation of Carcinogenic Risk to Humans. Biological Agents. Volume 100b. A Review of Human Cartinogeogens*. Lyon: IARC press, 2012; 385–436.
27 Hirayama Y, Kawai T, Otaki J, Kawakami K, Harada Y. Prevalence of *Helicobacter pylori* infection with healthy subjects in Japan. *J Gastroenterol Hepatol* 2014; **29**(Suppl 4): 16–9.
28 Tsugane S, Sasazuki S. Diet and the risk of gastric cancer: review of epidemiological evidence. *Gastric Cancer* 2007; **10**: 75–83.
29 Nishino Y, Inoue M, Tsuji I *et al.* Tobacco smoking and gastric cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol* 2006; **36**: 800–7.
30 Charvat H, Sasazuki S, Inoue M *et al.* Prediction of the 10-year probability of gastric cancer occurrence in the Japanese population: the JPHC study cohort II. *Int J Cancer* 2015 (in press). doi:10.1002/ijc.29705.
31 Tottori prefecture government. Nutrition and health survey 2010. Tottori. 2011 25-130.
32 Fukao A, Hisamichi S, Komatsu S *et al.* Comparison of characteristics between frequent participants and non-participants in screening programs for stomach cancer. *Tohoku J Exp Med* 1995; **166**: 459–69.
33 Sobue T, Matsuda T, Shibata A *et al. Monitoring of Cancer Incidence in Japan 2007*. Tokyo: National Cancer Center, Center for Cancer Control and Information Services, 2012.
34 Matsuda T, Sobue T. Recent trends in population-based cancer registries in Japan: the Act on Promotion of Cancer Registries and drastic changes in the historical registry. *Int J Clin Oncol* 2015; **20**: 11–20.
35 Okamoto N. A history of the cancer registration system in Japan. *Int J Clin Oncol* 2008; **13**: 90–6.
36 National Cancer Center. Center for Cancer Control and Information Services. [Cited 1 Sep 2015.] Available from URL: http://ganjoho.ncc.go.jp/professional/statistics/index.html
37 Sobue T, ed. *White Paper Cancer Statistics 2012*. Tokyo: Shinohara Press, 2012.
38 Ministry of Health, Labour and Welfare. The Report of Health Promotion and Community Health 2013. [Cited 1 Sep 2015.] Available from URL: http://www.e-stat.go.jp/SG1/estat/GL08020101.do?_toGL08020101_&tstatCode=000001030884&requestSender=dsearch.
39 Shabana M, Hamashima C, Nishida M, Miura K, Kishimoto T. Current status and evaluation of endoscopic screening for gastric cancer. *Jpn J Cancer Det Diagn* 2010; **17**: 229–35. (In Japanese).

Cancer Science
Japanese Cancer Association JCA
Open Access

Review Article

A meta-analysis of mammographic screening with and without clinical breast examination

Chisato Hamashima,[1] Koji Ohta,[2] Yoshio Kasahara,[3] Takafumi Katayama,[4] Tomio Nakayama,[5] Satoshi Honjo[6] and Koji Ohnuki[7]

[1]Cancer Screening Assessment and Management Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo; [2]Department of Surgery, Fukui Prefecture Hospital, Fukui; [3]Division of Breast Surgery, Fukui-ken Saiseikai Hospital, Fukui; [4]College of Nursing Art and Science, University of Hyogo, Akashi; [5]Center of Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka; [6]Department of Pediatrics, National Hospital Organization Fukuoka National Hospital, Fukuoka; [7]Division of Breast Surgery, Iwate Prefectural Central Hospital, Morioka, Japan

Key words

Breast cancer, cancer screening, mammography, meta-analysis, review

Correspondence

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

Funding Information

National Cancer Center, Japan.

Received March 10, 2015; Revised April 19, 2015; Accepted May 2, 2015

Cancer Sci **106** (2015) 812–818

doi: 10.1111/cas.12693

Mammographic screening with clinical breast examination has been recommended in Japan since 2000. Although mammographic screening without clinical breast examination has not been recommended, its introduction is anticipated. The efficacies of mammographic screening with and without clinical breast examination were evaluated based on the results of randomized controlled trials. PubMed and other databases for studies published between 1985 and 2014 were searched. The study design was limited to randomized controlled trials to evaluate mortality reduction from breast cancer. Five studies were eligible for meta-analysis of mammographic screening without clinical breast examination. The relative risk for women aged 40–74 years was 0.75 (95% confidence interval, 0.67–0.83). Three studies evaluated the efficacy of mammographic screening with clinical breast examination. The relative risk for women aged 40–64 years was 0.87 (95% confidence interval, 0.77–0.98). The number needed to invite was always lower in mammographic screening without clinical breast examination than in mammographic screening with clinical breast examination. In both screening methods, the number needed to invite was higher in women aged 40–49 years than in women aged 50–70 years. These results suggest that mammographic screening without clinical breast examination can afford higher benefits to women aged 50 years and over. Although evidence of the efficacy of mammographic screening without clinical breast examination was confirmed based on the results of the randomized controlled trials, a Japanese study is needed to resolve local problems.

Breast cancer is currently the most common cancer in Japan and accounts for 19.0% of all new cancers.[1] The age-standardized rate has been reported to be 51.5 per 100 000 women. The incidence rate of breast cancer initially increased gradually between 1975 and 1999 and has risen steeply since 2000 when mammography was introduced for breast cancer screening. In North America and Europe, the incidence of breast cancer has increased according to age. In Japan, the highest incidence rate of breast cancer has been observed in women aged 45–49 years.[1]

Japan is the first among East Asian countries to introduce breast cancer screening, and it has a unique program for population-based screening. In 1987, the Japanese government approved the introduction of breast cancer screening in Japan.[2] The first screening method was clinical breast examination with women aged 30 years and over as the target population. In 2000, mammographic screening was added for women aged 50 years and over, but clinical breast examination was used for women aged 30–49 years. Since 2004, a combination of mammography and clinical breast examination has been recommended for women aged 40 years and over as population-based screening. However, in most developed countries, mammographic screening without clinical breast examination has been the standard method for breast cancer screening. In the previous evidence report for cancer screening in Japan, it was not clearly specified why mammographic screening without clinical breast examination is not recommended.[3] Although mammographic screening without clinical breast examination has not been recommended, its introduction to local communities is anticipated owing to limitations in specialists who can carry out clinical breast examination. To successfully introduce mammographic screening without clinical breast examination, the efficacy of mammography must be evaluated with and without clinical breast examination. However, most guidelines and evidence reports have combined the results of a meta-analysis for mammographic screening with and without clinical breast examina-

tion.[4,5] There has been a lengthy discussion regarding the appropriateness of including women aged 40–49 years in the target population for breast cancer screening.[4,5] In most European countries, the target age group is 50–69 years, excluding the 40–49 years age group.[6]

To confirm evidence of the effectiveness of the Japanese screening program and to identify the best available method for breast cancer screening in Japan, we carried out a systematic review and meta-analysis of randomized controlled trials (RCTs) with and without mammographic screening. The results of the systematic review and meta-analysis were used for the development of comprehensive guidelines for breast cancer screening published by the National Cancer Center, Japan.

Methods

Systematic review of published reports. To identify the individual efficacy of mammographic screening with and without clinical breast examination, we searched PubMed, Web of Science, Igaku-Cyuo zasshi, and J Dream databases for studies using search terms such as "breast cancer", "mammography", "clinical breast examination", "physical breast examination", or "mortality reduction", published between January 1985 and April 2012. Additional references recommended were identified and included as needed. If the result from a branch of a large-scale RCT was published, the study was included. In addition, we searched for articles with revised results based on an extended follow-up and other RCTs regarding mammographic screening to evaluate mortality reduction from breast cancer from April 2012 to December 2014. The searches were limited to English language or Japanese language publications. Original articles published after peer review were included, whereas guidelines and evidence reports were excluded. The study design was limited to RCTs to evaluate mortality reduction from breast cancer. Modeling studies were not included. The RCTs for mammographic screening with and without clinical breast examination compared with a no screening group with the usual care were selected.

To select appropriate evidence for our research questions, we carried out a two-stage review: the title and abstract were initially checked and the full papers were subsequently reviewed. For the initial step, articles without an abstract were also excluded. Two reviewers screened the abstracts individually and subsequently reviewed the full papers of potentially relevant studies. To select appropriate evidence, a systematic review of the retrieved articles was carried out using the checklist according to the study design and the quality of the studies was defined.[7] If the decision for the full paper review was inconsistent, the appropriateness of these studies was carefully discussed. Finally, adequate studies were selected and included in a meta-analysis.

Meta-analysis. Based on the results of the systematic review, we carried out a meta-analysis. Although the follow-up years were different among the studies, we cited the results of 13 years follow-up from the Cochrane review[8] and original data from selected articles. Meta-analysis for RCTs of mammography with and without clinical breast examination was carried out for women of different age groups as follows: women aged 40–74 years (all age group), women aged 40–49 years, and women aged 50 years and over. For studies that reported cumulative count data, we carried out a Mantel–Haenszel fixed-effects meta-analysis to obtain the relative risk with the corresponding 95% confidence interval (CI). Statistical analyses were carried out using StatsDirect3 (StatsDirect, Altrincham, UK).

Comparison of benefit and harm. To compare benefit and harm, the number needed to invite (NNI) was calculated on the basis of the mortality risk from breast cancer in Japanese women. The NNI refers to the number needed to avoid one breast cancer death. The NNI can show the impact of the benefits of cancer screening, as well as suggest harms because unnecessary examinations increase with increasing number. To estimate the NNI in Japan, we used the prediction results for Japanese women[9] and the meta-analysis results.

A high recall rate for diagnostic examination can also be considered as harm for mammographic screening participants owing to an increase in unnecessary examinations. We also calculated the number needed for diagnostic examination to avoid one breast cancer death on the basis of the recall rate of mammographic screening in communities.[10] These results were compared between mammographic screening with and without clinical breast examination divided into different age groups from 40 to 70 years.

Results

Search of published works. The number of articles identified from the search using PubMed and other databases was 5270. After a two-stage review, 110 English articles were selected. From these 110 articles, six RCTs for mammographic screening without clinical breast examination were identified: Malmö study,[11,12] Canadian study II,[13–15] Swedish Two-County study,[16–22] Stockholm study,[23,24] Gothenburg study,[25,26] and the UK Age trial.[27] Three RCTs for mammographic screening with clinical breast examination were also identified as follows: New York HIP study,[28] Edinburgh study,[29] and Canadian study I.[30,31] The Canadian studies consisted of two groups with different targets: women aged 50–59 years for Canadian study II,[13–15] and women aged 40–49 years for Canadian study I.[30,31] In Canadian study II, the screening method for the intervention group was mammography with clinical breast examination; clinical breast examination was also provided for the control group with the same frequency as that for the intervention group.[13–15] In Canadian study I, the screening method for the intervention group was mammography with clinical breast examination; clinical breast examination was provided for the control group only at the first screening.[30,31] Based on the inclusion criteria related to a comparator, we excluded Canadian study II from the evidence of mammography without clinical breast examination, and included Canadian study I as the evidence of mammography with clinical breast examination. From April 2012 to December 2014, although the revised results were reported in a Canadian study, there were no additional studies to evaluate mortality reduction from breast cancer.[15]

Evidence of mammographic screening with and without clinical breast examination. *Mammographic screening without clinical breast examination.* Five RCTs of mammographic screening without clinical breast examination were identified for mortality reduction from breast cancer (Table 1).[11–27] Each of these studies began in the 1980s, except the UK Age trial which started in 1991. Randomized allocation was performed at individual base except the Swedish Two-County study. Although the screening method was the same in these studies, the target age group, screening interval, and follow-up periods were different (Table 1). Although the target age group was different among the five RCTs, all of these studies included women aged in their

Table 1. Randomized controlled trials for evaluation of mammographic screening without clinical breast examination

	Malmö I and II	Swedish Two-County	Stockholm	Gothenburg	UK Age trial
Starting year of the study	1976	1977	1981	1982	1991
Randomization	Individual	Cluster	Birthday	Birthday	Individual
Number	60 076	133 065	60 800	52 222	160 921
Target age	45–69 years/43–49 years	38–75 years	39–65 years	39–59 years	39–41 years
Screening method	MMG	MMG+SBE	MMG	MMG	MMG
View	First, two-view Subsequent, one-view or two-view	One-view	One-view	First, two-view Subsequent, one-view or two-view	First, two-view Subsequent, one-view or two-view
Screening interval, months	18–24	24 (40s)–33 (50s)	24–28	18	12
Screening frequency	6–8	2–4	2	4–5	8–10
Screening periods, years	12	7	4	7	8
Participation rate, %	74	85	82	84	81
Relative risk (95%CI)	0.81 (0.61–1.07)	0.68 (0.57–0.81)	0.73 (0.50–1.06)	0.75 (0.58–0.97)	0.83 (0.66–1.04)

Relative risk was based on the results of 13 years of follow-up based on the references 8 (Gøtzsche & Jørgensen, 2013) and 16 (Tabar *et al.*, 1995). CI, confidence interval; MMG, mammography; SBE; self-breast examination.

40s as their target age group. In the UK Age trial, the study targets were limited to women aged 39–41 years years because the aim of the trial was evaluation of the efficacy of mammography for women aged in their 40s.[27] The screening view was mainly one-view, but two-view was used at the first screening in the Malmö study, Gothenburg study, and UK Age trial. The screening interval for women aged 50 years and over was from 18 to 33 months. The results were analyzed using the intention to treat method in all studies.

Based on the outcome of 13 years of follow-up, the results suggest mortality reduction from breast cancer by mammographic screening without clinical breast examination, although significant results were also obtained in the Swedish Two-County study (0.68; 95%CI, 0.57–0.81) and Gothenburg study (0.75; 95%CI, 0.58–0.97).[10] When the targets of these studies were limited to women aged in their 40s, significant results in terms of mortality reduction from breast cancer could not be obtained in all the studies.

Mammographic screening with clinical breast examination. Three RCTs of mammographic screening with clinical breast examination served as eligible evidence for mortality reduction from breast cancer (Table 2).[28–31] Compared with the studies related to mammographic screening without clinical breast examination, the starting years of these studies were early and detailed information was insufficient. The New York HIP study was the first RCT of this kind. It started in 1963 with the aim of evaluating the efficacy of mammographic screening.[28] The other studies commenced around the 1980s. In the Edinburgh study, inappropriate randomization was suggested because of the different socio-economic classes between the intervention group and the control group.[29] Although the screening method was the same in these studies, the control group in Canadian study I was initially provided clinical breast screening.[30,31] Although the target age group was different among the three RCTs, all of these studies included women aged 40s as their target. Although two-view mammography was used for all the studies, the screening interval was different, that is, 12 months for the New York HIP study[28] and Canadian study I,[30,31] and 24 months for the Edinburgh study.[29] The results were analyzed using the intention to treat method. The results of 13 years of follow-up for the New York HIP study and Canadian study I were obtained from the Cochrane review.[8] The results of 14 years of follow-up for

Table 2. Randomized controlled trials for evaluation of mammographic screening with physical examination

	New York HIP	Canada I	Edinburgh
Starting year of study	1963	1980	1978
Randomization Subjects	Individual	Individual	Cluster
Number	62 000	89 835	54 654
Target age	40–64 years	40–49 years	45–64 years
Screening method	MMG+CBE	MMG+CBE+SBE	MMG+CBE
Mammography View	Two-view	Two-view	First, two-view Subsequent, one-view or two-view
Screening interval, months	12	12	24
Screening frequency	4	4–5	2–4
Screening periods, years	3	5	6
Participation rate, %	65	88	65
Relative risk (95%CI)	0.83 (0.70–0.99)	0.97 (0.74–1.27)	0.85 (0.68–1.05)

Relative risk was based on the results of 13 years of follow-up for the New York HIP and Canada I studies (Gøtzsche & Jørgensen, 2013), and 14 years of follow-up for the Edinburgh study (Alexander *et al.*, 1999). CBE, clinical breast examination; CI, confidence interval; MMG, mammography; SBE, self breast examination.

the Edinburgh study[29] were directly obtained from the article. Although not statistically significant, these results suggest mortality reduction from breast cancer by mammographic screening with clinical breast examination. Similar results were suggested when the targets of these studies were limited to women aged 40–49 years.

Meta-analysis. *Mammographic screening without clinical breast examination.* Five studies were eligible for the meta-analysis of mammographic screening without clinical breast examination programs (Table 1). The overall relative risk for all the age groups was 0.75 (95%CI, 0.67–0.83) (Fig. 1a). When the target age group was divided into two groups, the relative risks were 0.81 (95%CI, 0.68–0.96) for women aged 40–49 years and 0.71 (95%CI, 0.62–0.81) for women aged 50–74 years (Fig. 1b,c).

Mammographic screening with clinical breast examination. Three studies were selected to evaluate the efficacy of mammographic screening with clinical breast examination (Table 2). The overall relative risk for all the age groups was 0.87 (95%CI, 0.77–0.98) (Fig. 2a). When the target age group was divided into two groups, the relative risks were 0.87 (95% CI, 0.72–1.04) for women aged 40–49 years and 0.83 (95%CI, 0.70–0.99) for women aged 50–64 years (Fig. 2b,c).

Comparison of benefit and harm. The NNI and the number needed for diagnostic examination to avoid one breast cancer death were calculated for mammographic screening with and without clinical breast examination for women aged 40–70 years (Table 3). The NNI was consistently lower in mammographic screening without clinical breast examination than in mammographic screening with clinical breast examination. In both screening methods, the NNI was higher in women aged 40–49 years than in women aged 50–70 years. Similar results were obtained for the number needed for recall of diagnostic examination to avoid one breast cancer death. These results suggest that mammographic screening without clinical breast examination could provide higher benefits for women aged 50 years and over.

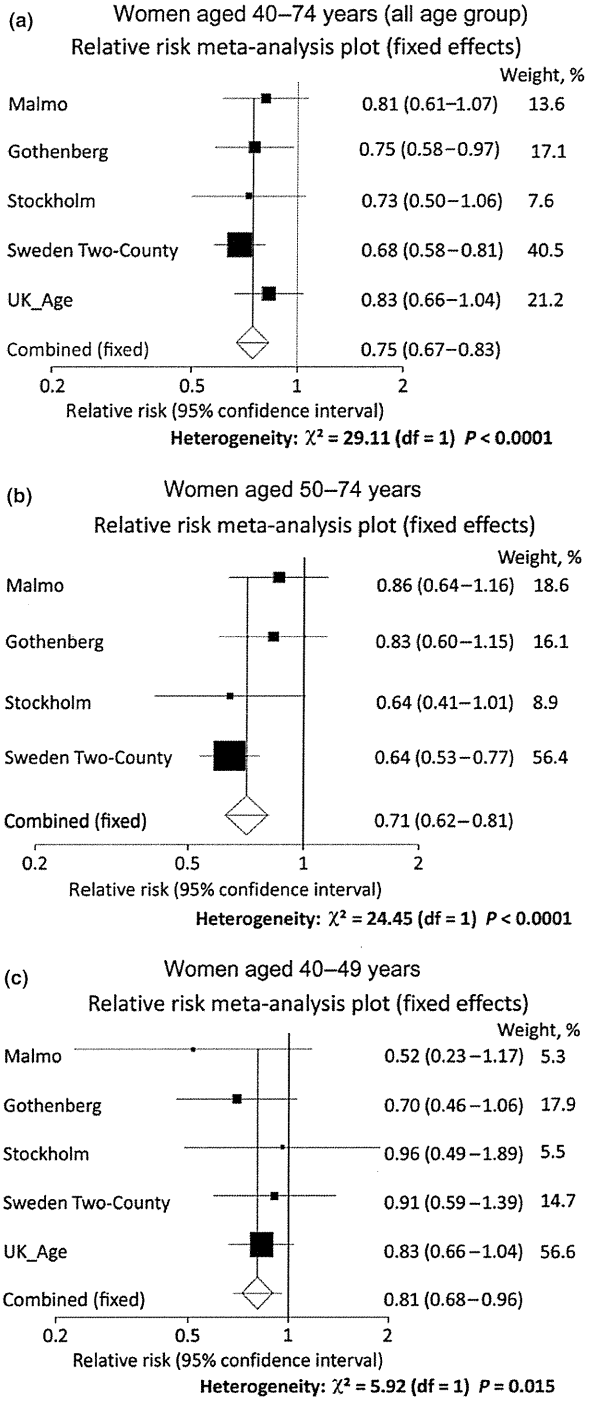

Fig. 1. Meta-analysis of mammography without clinical breast examination. Five studies were eligible for the meta-analysis of mammographic screening without clinical breast examination programs: Malmö study,[11,12] Swedish Two-County study,[16–22] Stockholm study,[23,24] Gothenburg study,[25,26] and UK Age trial.[27] Women were divided into three target age groups: 40–74 years (all age group) (a); 50–74 years (b); 40–49 years (c).

Discussion

Although it has been 15 years since the Japanese government has recommended mammographic screening with clinical breast examination, mammographic screening without clinical breast examination has not yet been introduced. In the present study, individual efficacy could be confirmed for mammographic screening with and without clinical examination. The impacts of mortality reduction were different between both methods. The NNIs of mammographic screening without clinical breast examination were consistently lower than those of mammographic screening with clinical breast examination among women aged 40–70 years. In addition, the recall rate for diagnostic examinations was higher in mammographic screening with clinical breast examination than in mammographic screening without clinical breast examination.[10] Compared with mammographic screening with clinical breast examination, mammographic screening without clinical breast examination could reduce harm. However, the NNIs were always higher in women aged 40–49 years than in women aged 50 years and over for both methods.

Clinical breast examination was introduced as the first screening method for breast cancer and it has been carried out with mammographic screening in Japan.[2] In Japan, physicians perform clinical breast examinations, whereas in some countries, nurses can undertake that role. In the Canadian I and II studies, clinical breast examinations were carried out by trained nurses.[13–15,30,31] The Edinburgh study also recommended clinical breast examinations be carried out by nurses.[29] Although clinical breast examination alone was not

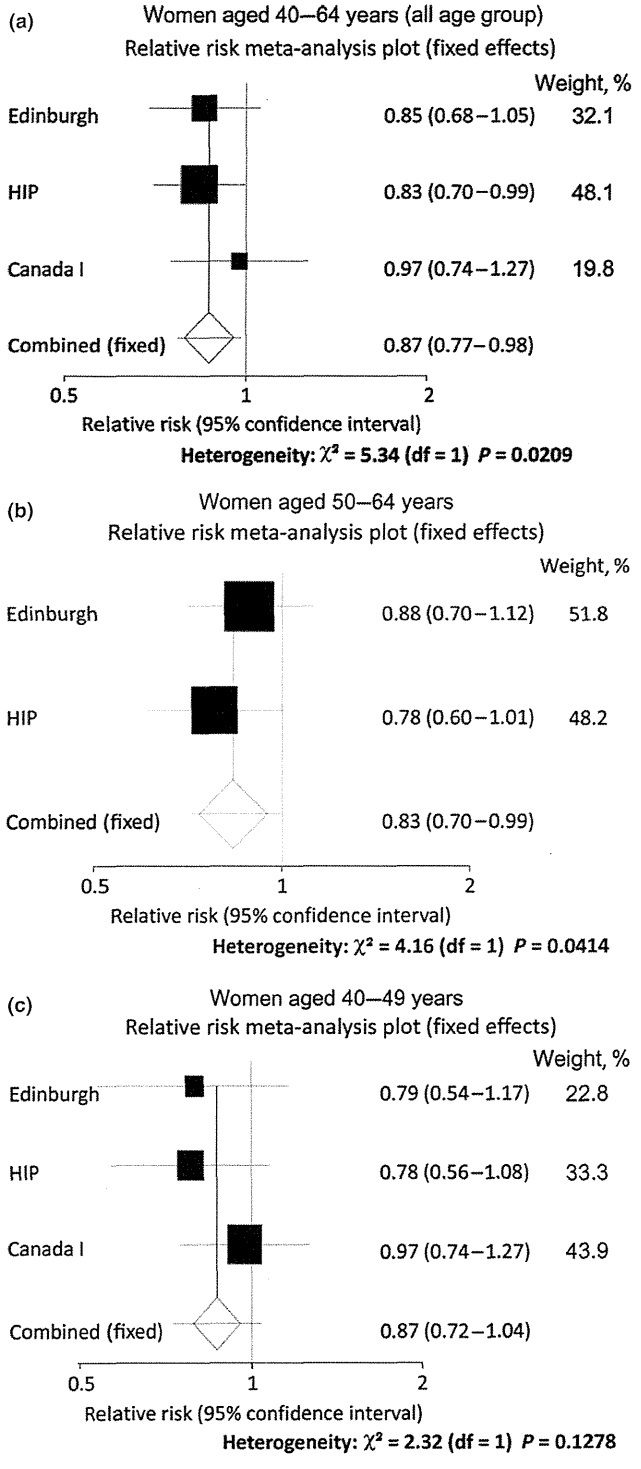

Fig. 2. Meta-analysis of mammographic screening with clinical breast examination. Three randomized controlled trials were identified as eligible: New York HIP study,[28] Edinburgh study,[29] and Canadian study I.[30,31] Women were divided into three target age groups: 40–64 years (all age group) (a); 50–64 years (b); 40–49 years (c).

recommended in developed countries, this method has been commonly used in developing countries.[32] The positive efficacy of clinical breast examination has been suggested by the results of a previous RCT in India.[33] Randomized controlled trials have been performed to evaluate the efficacy of clinical breast examination.[33,34] The sensitivity of clinical breast examination was found to be higher in Japanese studies (50–70%) than in Indian studies.[33,35–37] The results of a Japanese case–control study suggested mortality reduction when symptomatic women were excluded.[38] Despite its advantages, there are serious problems with the continued use of clinical breast examination. Although several studies have reported that training programs could improve the accuracy of clinical breast examination,[39,40] it is difficult to standardize the method because of a lack of an educational system at the national level. Moreover, insufficient human resources can also be a barrier for improving the participation rates of mammographic screening with clinical breast examination in communities. Because of the low accuracy of clinical breast examination, breast ultrasonography has been anticipated as an alternative method that can be combined with mammographic screening. The efficacy of a combination of mammography and ultrasonography in Japan has been evaluated.[41]

There has been significant discussion whether or not to include women aged 40–49 years in the target population of mammographic screening. In 2009, the US Preventive Services Task Force changed its policy for women aged in their 40s and stopped its recommendation of routine screening.[4] The Task Force suggested that women aged in their 40s should have the individual autonomy to choose whether or not to participate in mammographic screening based on shared decision-making with their family physicians. In most European countries, women aged in their 40s have not been included in the target population for breast cancer screening.[6] After the publication of the new guidelines of the US Preventive Services Task Force, the appropriateness of the target age group was carefully examined in previous studies.[5,8,42,43] The results of these studies were similar with regard to women aged in their 40s, that is, not to include them in the target population. However, as the distribution of breast cancer incidence is different in East Asian countries, the same conclusion could not be easily obtained. Although the benefit of mammographic screening is lower in women aged in their 40s, the data for NNI calculation was based on the results of RCTs conducted in Western countries. The proportion of dense breast in women aged in their 40s is higher in Japan than in Western countries[42] and this leads to a lower accuracy of mammographic screening. To resolve the local problem in Japan, a study evaluating mortality reduction from breast cancer among women aged in their 40s is required.

To effectively introduce population-based screening, the balance of benefits and harms of cancer screening must be considered.[6] However, measurement methods for quantitative assessment have not yet been standardized to date. Although NNI is commonly used, the appropriate threshold for the balance of benefits and harms remains unclear. Even if the threshold can be defined, it can be changed considering the local context in terms of disease burden and medical resources. From previous studies, we attempted to evaluate the benefits and harms using the results of meta-analysis of RCTs and available Japanese data. In the Japanese situation, the benefits were always higher in women aged 50 years and over. As there is still no standard established in Japan, the appropriateness of including women aged in their 40s in the NNI cannot be ascertained.

There are additional limitations of this study. First, since most of the RCTs assessed were started before 1990, mammographic equipment use during that time might have been dif-

Table 3. Comparison of benefit and harm between mammographic screening with and without clinical breast examination (CBE)

Screening method	Target age						
	40 years	45 years	50 years	55 years	60 years	65 years	70 years
Mammographic screening without CBE							
Per 1000 women screened							
Number of recalls	77	77	67	67	53	53	53
Per single death prevented							
Number needed to invite	2530	1713	864	777	782	807	833
Number of recalls	195	132	58	52	41	43	44
Mammographic screening with CBE							
Per 1000 women screened							
Number of recalls	99	99	76	76	62	62	62
Per single death prevented							
Number needed to invite	3698	2504	1474	1325	1334	1376	1420
Number of recalls	366	248	112	101	83	85	88

Numbers needed to invite are expressed per 1000 women invited for 13-year follow-up.

ferent from contemporary equipment. At present, even if clinical breast examination is not added, benefits can be obtained, especially with mammography alone. Second, to resolve our research questions, all RCTs using mammography with and without clinical breast examination were included in our analysis. The Edinburgh study is often excluded from the set of evidence because of its inadequate randomization. When this study was excluded, we could not obtain significant results for mammographic screening with clinical breast examination (relative risk = 0.87; 95%CI, 0.75–1.01). Third, Canadian study II was not included in a meta-analysis of mammographic screening without clinical breast examination because the control group underwent clinical breast examination for breast cancer screening. Most guidelines include mammographic screening with clinical breast examination for evaluating the efficacy of mammographic screening.[4,5,8,43,44] The results of our study may show an overestimation of the efficacy of mammographic screening without clinical breast examination. Finally, although the efficacy of mammographic screening without clinical breast examination could be identified for women aged 40–74 years, the efficacy of mammographic screening with clinical breast examination was unclear for women aged 65–74 years because there was no study that included this age group for the target population.

In conclusion, the results of our analysis suggest that mammographic screening without clinical breast examination may afford higher benefits to women aged 50 years and over. Although evidence regarding the effectiveness of mammographic screening without clinical breast examination could be confirmed based on previous RCTs, a Japanese study is needed to resolve local problems, including identification of the appropriate target age group for Japanese women and taking into consideration the balance of benefits and harms.

Acknowledgments

We thank Ms. Kanoko Matsushima, Ms. Junko Asai, and Ms. Hiromi Sugiyama for secretarial work. We are also grateful to Dr. Edward F. Barroga, Associate Professor and Senior Medical Editor of Tokyo Medical University for the editorial review of the manuscript. This study was supported by the National Cancer Center, Tokyo, Japan (grant no. 26-A-30).

Disclosure Statement

The authors have no conflict of interest.

References

1 National Cancer Center. Center for Cancer Control and Information Services. Estimation of cancer incidence. [Cited 26 Feb 2015.] Available from URL: http://ganjoho.ncc.go.jp/professional/statistics/index.html
2 Oshima A. A critical review of cancer screening programs in Japan. *Int J Technol Assess Health Care* 1994; **10**: 346–58.
3 Hisamichi S. *Guidelines for cancer screening programs*. Tokyo: Japan Public Health Association, 2000; (in Japanese.).
4 Nelson HD, Tyne K, Naik A, Bougatsos C, Chan BK, Humphrey L. Screening for breast cancer: an update for the U.S. Preventive Services Task Force. *Ann Intern Med* 2009; **151**: 727–37.
5 The Canadian Task Force on Preventive Health Care. Recommendations on screening for breast cancer in average-risk women aged 40–74 years. *CMAJ* 2011; **183**: 1991–2001.
6 International Agency for Research on Cancer. Cancer screening in the European Union: report on the implementation of the Council Recommendation on cancer screening. Lyon. 2008.
7 Hamashima C, Saito H, Nakayama T, Nakayama T, Sobue T. The standardized development method of the Japanese guidelines for cancer screening. *Jpn J Clin Oncol* 2008; **38**: 288–95.
8 Gøtzsche PC, Jorgensen KJ. Screening for breast cancer with mammography. *Cochrane Database Syst Rev* 2013; (6): CD001877.
9 National Cancer Center. Center for Cancer Control and Information Services. Cancer Statistics 2012. [Cited26 Feb 2015.] Available from URL: http://ganjoho.jp/data/professional/statistics/backnumber/2012/cancer_statistics_2012.pdf
10 Kasahara Y, Tsuji I, Ichimura M *et al.* Anuual Report 2011 on Breast Cancer Screening in Japan. *J Jpn Assoc Breast Cancer Screening* 2012; **21**: 48–58.
11 Andersson I, Janzon L. Reduced breast cancer mortality in women under age 50: updated results from the Malmö Mammographic Screening Program. *J Natl Cancer Inst Monogr* 1997; **22**: 63–7.
12 Nyström L, Andersson I, Bjurstam N, Frisell J, Nordenskjöld B, Rutqvist LE. Long-term effects of mammography screening: updated overview of the Swedish randomized trials. *Lancet* 2002; **359**: 909–19.
13 Miller AB, Baines CJ, To T, Wall C. Canadian National Breast Screening Study: 2. Breast cancer detection and death rates among women aged 50 to 59 years. *CMAJ* 1992; **147**: 1477–88.
14 Miller AB, To T, Baines CJ, Wall C. Canadian National Breast Screening Study-2: 13-year results of a randomized trial in women aged 50–59 years. *J Natl Cancer Inst* 2000; **92**: 1490–9.

15 Miller AB, Wall C, Baines CJ, Sun P, To T, Narod SA. Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial. *BMJ* 2014; **348**: g366.
16 Tabar L, Fagerberg G, Chen HH *et al.* Efficacy of breast-cancer screening by age – New results from the Swedish Two-County Trial. *Cancer* 1995; **75**: 2507–17.
17 Tabár L, Fagerberg CJ, Gad A *et al.* Reduction in mortality from breast cancer after mass screening with mammography. Randomized trial from the Breast Cancer Screening Working Group of the Swedish National Board of Health and Welfare. *Lancet* 1985; **1**: 829–32.
18 Duffy SW, Tabar L, Vitak B *et al.* The Swedish Two-County Trial of mammographic screening: cluster randomization and end point evaluation. *Ann Oncol* 2003; **14**: 1196–8.
19 Tabar L, Vitak B, Chen HH, Prevost TC, Duffy SW. Update of the Swedish Two-County Trial of breast cancer screening: histologic grade-specific and age-specific results. *Swiss Surg* 1999; **5**: 199–204.
20 Tabar L, Duffy SW, Yen MF *et al.* All-cause mortality among breast cancer patients in a screening trial: support for breast cancer mortality as an end point. *J Med Screen* 2002; **9**: 159–62.
21 Tabár L, Vitak B, Chen HH, Yen MF, Duffy SW, Smith RA. Beyond randomized controlled trials: organized mammographic screening substantially reduces breast carcinoma mortality. *Cancer* 2001; **91**: 1724–31.
22 Duffy SW, Tabar L, Olsen AH *et al.* Absolute numbers of lives saved and overdiagnosis in breast cancer screening, from a randomized trial and from the Breast Screening Programme in England. *J Med Screen* 2010; **17**: 25–30.
23 Frisell J, Eklund G, Hellström L, Lidbrink E, Rutqvist LE, Somell A. Randomized study of mammography screening-preliminary report on mortality in the Stockholm trial. *Breast Cancer Res Treat* 1991; **18**: 49–56.
24 Frisell J, Lidbrink E, Hellström L, Rutqvist LE. Follow-up after 11 years – update of mortality results in the Stockholm mammographic screening trial. *Breast Cancer Res Treat* 1997; **45**: 263–70.
25 Bjurstam N, Björneld L, Duffy SW *et al.* The Gothenburg Breast Screening Trial – first results on mortality, incidence, and mode of detection for women ages 39–49 years at randomization. *Cancer* 1997; **80**: 2091–9.
26 Bjurstam N, Björneld L, Warwick J *et al.* The Gothenburg Breast Screening Trial. *Cancer* 2003; **97**: 2387–96.
27 Moss SM, Cuckle H, Evans A, Johns L, Waller M, Bobrow L, Trial Management Group. Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomized controlled trial. *Lancet* 2006; **368**: 2053–60.
28 Habbema JD, van Oortmarssen GJ, van Putten DJ, Lubbe JT, van der Maas PJ. Age-specific reduction in breast cancer mortality by screening: an analysis of the results of the Health Insurance Plan of Greater New York study. *J Natl Cancer Inst* 1986; **77**: 317–20.
29 Alexander FE, Anderson TJ, Brown HK *et al.* 14 years of follow-up from the Edinburgh randomized trial of breast-cancer screening. *Lancet* 1999; **353**: 1903–8.
30 Miller AB, Baines CJ, To T, Wall C. Canadian National Breast Screening Study: 1. Breast cancer detection and death rates among women aged 40 to 49 years. *CMAJ* 1992; **147**: 1459–76.
31 Miller AB, To T, Baines CJ, Wall C. The Canadian National Breast Screening Study-1: breast cancer mortality after 11 to 16 years of follow-up. A randomized screening trial of mammography in women age 40 to 49 years. *Ann Intern Med* 2002; **137**: 305–12.
32 International Agency for Research on Cancer. *IARC Handbooks of Cancer Prevention. Breast Cancer Screening*. Lyon: IARC Press, 2002; 64–72.
33 Sankaranarayanan R, Ramadas K, Thara S *et al.* Clinical breast examination: preliminary results from a cluster randomized controlled trial in India. *J Natl Cancer Inst* 2011; **103**: 1476–80.
34 Boulos S, Gadallah M, Neguib S *et al.* Breast screening in the emerging world: high prevalence of breast cancer in Cairo. *Breast* 2005; **14**: 340–6.
35 Shibata A, Takahashi T, Ohuchi N, Fukao A. Evaluation of service screening for breast cancer by clinical breast examination using regional cancer registry data. *Jpn J Public Health* 2005; **52**: 128–36.
36 Honjo S, Ando J, Tsukioka T *et al.* Relative and combined performance of mammography and ultrasonography for breast cancer screening in the general population: a pilot study in Tochigi Prefecture, Japan. *Jpn J Clin Oncol* 2007; **37**: 715–20.
37 Uchida K, Yamashita A, Kawase K, Kamiya K. Screening ultrasonography revealed 15% of mammographically occult breast cancers. *Breast Cancer* 2008; **15**: 165–8.
38 Kanemura S, Tsuji I, Ohuchi N *et al.* A case control study on the effectiveness of breast cancer screening by clinical breast examination in Japan. *Jpn J Cancer Res* 1999; **90**: 607–13.
39 Sloan DA, Donnelly MB, Plymale MA *et al.* Improving residents' clinical skills with the structured clinical instruction module for breast cancer: results of a multiinstitutional study. Breast Cancer Education Working Group. *Surgery* 1997; **122**: 324–33.
40 Lee KC, Dunlop D, Dolan NC. Do clinical breast examination skills improve during medical school? *Acad Med* 1998; **73**: 1013–9.
41 Ishida T, Suzuki A, Kawai M *et al.* A randomized controlled trial to verify the efficacy of the use of ultrasonography in breast cancerscreening aged 40–49 (J-START): 76 196 women registered. *Jpn J Clin Oncol* 2014; **44**: 134–40.
42 Morimoto T, Sasa M, Yamaguchi T, Kondo H, Akaiwa H, Sagara Y. Breast cancer screening by mammography in women aged under 50 years in Japan. *Anticancer Res* 2000; **20**: 3689–94.
43 Marmot MG, Altman DG, Cameron DA, Dewar JA, Thompson SG, Wilcox M. The benefits and harms of breast cancer screening: an independent review. *Br J Cancer* 2013; **108**: 2205–40.
44 Paci E1, EUROSCREEN Working Group. Summary of the evidence of breast cancer service screening outcomes in Europe and first estimate of the benefit and harm balance sheet. *J Med Screen* 2012; **19**: S5–13.