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The Japanese Guidelines for Breast Cancer Screening

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Abstract

Objective: The incidence of breast cancer has progressively increased, making it the leading cause of cancer deaths in Japan. Breast cancer accounts for 20.4% of all new cancers with a reported age-standardized rate of 63.6 per 100 000 women.

Methods: The Japanese guidelines for breast cancer screening were developed based on a previously established method. The efficacies of mammography with and without clinical breast examination, clinical breast examination and ultrasonography with and without mammography were evaluated. Based on the balance of the benefits and harms, recommendations for population-based and opportunistic screenings were formulated.

Results: Five randomized controlled trials of mammographic screening without clinical breast examination were identified for mortality reduction from breast cancer. The overall relative risk for women aged 40–74 years was 0.75 (95% CI: 0.67–0.83). Three randomized controlled trials of mammographic screening with clinical breast examination served as eligible evidence for mortality reduction from breast cancer. The overall relative risk for women aged 40–64 years was 0.87 (95% confidence interval: 0.77–0.98). The major harms of mammographic screening were radiation exposure, false-positive cases and overdiagnosis. Although two case–control studies evaluating mortality reduction from breast cancer were found for clinical breast examination, there was no study assessing the effectiveness of ultrasonography for breast cancer screening.

Conclusions: Mammographic screening without clinical breast examination for women aged 40–74 years and with clinical breast examination for women aged 40–64 years is recommended for population-based and opportunistic screenings. Clinical breast examination and ultrasonography are not recommended for population-based screening because of insufficient evidence regarding their effectiveness.

Key words: breast cancer, cancer screening, mammography, clinical breast examination, ultrasonography, meta-analysis, systematic review, guideline

Introduction

The incidence of breast cancer has progressively increased in many countries and it has become one of the leading causes of cancer deaths in Japan. Breast cancer accounts for 20.4% of all new cancers in Japan with an age-standardized rate of 63.6 per 100 000 women (1).

Most developed countries have provided mammographic screening mainly for women aged 50–69 years (2). Interestingly, although the incidence of breast cancer in western countries has increased according to age (3), mammographic screening for women aged 40–49 years has not been provided because it remains unclear whether its benefits outweigh its harms in this particular age group (4–7). Compared with western countries, the age distribution of breast cancer is different in Japan, with the highest incidence rate observed in women aged 45–49 years (1). Therefore, the burden of breast cancer for this age group cannot be ignored in Japan despite the absence of studies evaluating mortality reduction using mammography for Japanese women aged 40–49 years. Admittedly, there has been insufficient discussion whether or not it is appropriate to include women in their 40s as a target group for breast cancer screening in the Japanese program, particularly from the perspective of the balance of benefits and harms.

In their evidence report in 2001, Hisamichi et al. (8) recommended the combination of mammography and clinical breast examination for breast cancer screening. However, their report did not clearly specify the reason for the non-recommendation of mammographic screening without clinical breast examination. Although clinical breast examination and ultrasonography have also been evaluated, these methods were not recommended because of insufficient evidence regarding their effectiveness. Since 2000, a combination of mammography and clinical breast examination has been recommended as population-based screening in Japanese communities. Notably, mammographic screening without clinical breast examination was not recommended as a breast cancer screening option even though it is the most common method used in developed countries.

Since the publication of the previous reports by Hisamichi et al., new studies on mammographic screening including women aged 40–49 years and ultrasonography for the breast have been reported worldwide. Nevertheless, evidence regarding the efficacy of mammographic screening has remained controversial, spurring ongoing discussion with regard to its application (3–6,9,10). Subsequently, a new Japanese research group has established a standardized method for developing the Japanese Guidelines for Cancer Screening (11). Based on this method, the efficacy and effectiveness of mammography with and without clinical breast examination, clinical breast examination alone and ultrasonography with and without mammography for breast cancer screening were evaluated, and new guidelines were developed.

Methods

The target audiences for the breast cancer screening guidelines include the public, health professionals working in cancer screening programs, providers of cancer screening programs and policy makers. The members of the Japanese Research Group for Development of Breast Cancer Screening Guidelines were selected from various specialties, including primary care physicians, breast surgeons, radiologists and epidemiologists. The breast cancer screening guidelines were developed using the standardized method which was defined as the development method for the Japanese guidelines for cancer screening (11).

Target screening methods

Mammography with and without clinical breast examination, clinical breast examination and ultrasonography with and without mammography were evaluated in terms of their efficacy and effectiveness for breast cancer screening. In most developed countries, mammographic screening without clinical breast examination has been the standard method for breast cancer screening (2). However, in Japan, mammographic screening with clinical breast examination has been the method recommended and performed since 2000. Clinical breast examination alone was used for breast cancer screening from 1987 to 2003 as population-based screening in Japan. Recently, ultrasonography with and without mammography has been performed in a clinical setting as opportunistic screening, particularly for women aged 40–49 years.

The primary issue regarding the guidelines was evaluation of the efficacy of mammographic screening with and without clinical breast examination. The secondary issue was evaluation of the efficacy of mammographic screening for women aged 40 years.

Analytic framework

The target population for breast cancer screening was defined as asymptomatic women with an average risk of breast cancer. To select appropriate evidence, an analytic framework for breast cancer screening was developed (Fig. 1). For each stage of the analytic framework, clinical questions based on the PICO (population, intervention, comparison and outcome) format were prepared. Direct evidence was defined as evidence provided by a study that evaluated the efficacy and effectiveness of cancer screening for reducing breast cancer incidence and mortality (Fig. 1, arrow 1). Other studies that provided indirect evidence were selected on the basis of clinical questions related to other stages of the analytic framework (Fig. 1, arrows 2–8).

Systematic literature review

To select appropriate evidence for our clinical questions, a two-stage review was performed: (i) the title and abstract were initially checked and (ii) the text of the potentially relevant full papers was subsequently reviewed (11). Two reviewers screened the abstracts individually. Subsequently, they reviewed the full papers of potentially relevant studies.

The inclusion criteria for article selection were original articles published after peer review (11). The study design and outcome were defined differently among the screening methods, and the detailed inclusion criteria were described in the screening method section. The common exclusion criteria among all the screening methods were as follows: (i) no abstract, (ii) study in which the target screening group was composed of symptomatic persons (patients), (iii) economic evaluation study, (iv) guidelines, evidence reports and reviews, and (v) official statistics, letters and personal communications.

To select appropriate evidence, a systematic review of the retrieved articles was conducted using the checklist according to the study design, and the quality of the studies was defined. If the decision regarding the full paper review was inconsistent, the appropriateness of these studies was carefully discussed. Finally, adequate studies were selected for evaluation of breast cancer screening.

The evidence for each screening method was summarized in an evidence table based on the analytic framework's clinical questions. The body of evidence for each screening modality was determined according to the level of evidence which was defined on the basis of the study design, quality and consistency among the study results (11).

Mammographic screening

To identify the efficacy of mammographic screening with and without clinical breast examination, PubMed, Web of Science, Igaku-Cyuo zasshi and J Dream were searched for studies using search terms such as ‘breast cancer’, ‘mammography’, ‘clinical breast examination’, ‘physical breast examination’ or ‘mortality reduction’, from January 1985 to April 2012. Additional references recommended were identified and included as needed. If the result from a new result of a large-scale randomized controlled trial (RCT) based on an extended

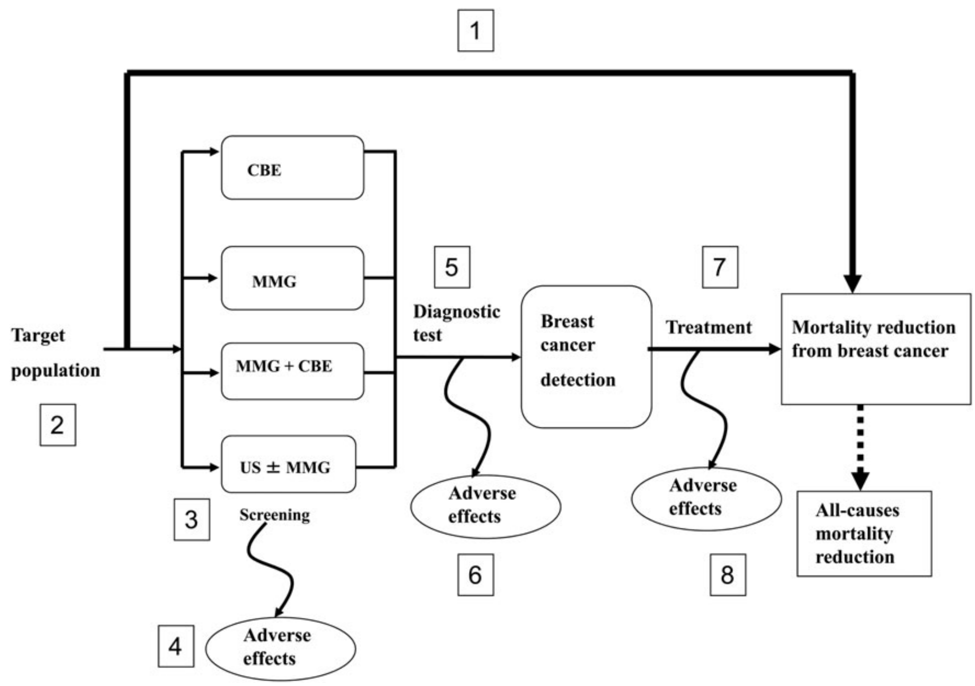

Figure 1. Analytic framework and key questions for breast cancer screening. The numbers in the analytic framework refer to the following clinical questions. (1) Compared with no screening (or other screening strategies), is there direct evidence that the mortality from breast cancer is reduced with the following screening methods? (a) Clinical breast examination (CBE). (b) Mammography (MMG). (c) Mammography with clinical breast examination (MMG + CBE). (d) Ultrasonography with and without mammography (US ± MMG). To appropriately determinate the level of evidence, the primary outcomes of mortality from breast cancer must be ascertained. (2) What age group was the preferable target for breast cancer screening? (3) Can the screening test accurately detect breast cancer? What are the sensitivity and specificity rates of the screening test? (4) What are the potential harms of screening tests, and how often do they occur? (5) Can the diagnostic test accurately detect the target women? (6) What are the potential harms of diagnostic tests, and how often do they occur? 7) (For breast cancer patients, how are the efficacy and effectiveness of treatment?

follow-up was published, the study was included. Articles with revised results based on an extended follow-up and other RCTs regarding mammographic screening were also searched from April 2012 to December 2014 to evaluate mortality reduction from breast cancer. The searches were limited to English-language or Japanese-language publications. The study design was limited to RCTs to evaluate mortality reduction from breast cancer. The RCTs for mammographic screening with and without clinical breast examination compared with a no screening group or the usual care were selected. Modeling studies were not included for evaluation of the studies to reduce mortality from breast cancer. The meta-analysis results were published in other articles and referred to for the guidelines development. In this article, we reported detailed information regarding the evaluation of study quality (11). Although the follow-up years varied among the studies, the results of 13 years follow-up from the Cochrane review (9) and original data from selected articles were cited. Meta-analysis for RCTs of mammographic screening with and without clinical breast examination was performed 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 (12). For studies that reported cumulative count data, we carried out a Mantel-Haenszel fixed-effects meta-analysis to obtain the relative risk and risk difference with the corresponding 95% confidence interval (CI). The results of the meta-analysis have been published in above-mentioned article.

Other methods and harms

To identify the effectiveness of clinical breast examination and ultrasonography, PubMed, Web of Science, Igaku-Cyuo zasshi and J Dream were searched for studies from January 1985 to April 2012 using search terms such as 'breast cancer', 'clinical breast examination', 'physical breast examination', 'ultrasonography' or 'mortality reduction'. Observational studies were included for the evaluation of clinical breast examination and ultrasonography. Studies that analyzed sensitivity and specificity were also included. Additional references recommended were identified and included as needed.

Articles related to overdiagnosis, false-positive cases, radiation exposure of mammographic screening and adverse effects of needle biopsy were also searched using the same method, and evidence from RCTs and observational studies was identified. Modeling studies were included for the evaluation of overdiagnosis, false-positive cases and radiation exposure.

Translation into recommendations

To compare the benefits and harms, number needed to invite (NNI) was calculated on the basis of the mortality rate from breast cancer in Japanese women. The results of NNI calculation published in other articles (12) were referred to for the guidelines development. NNI refers to the number needed to avoid one breast cancer death. NNI can show the impact of the benefits of cancer screening as well as harms, as unnecessary examinations increase with increasing NNI. A high recall rate for diagnostic examination can also be considered harms for mammographic screening participants owing to an increase in unnecessary examinations. The number needed for diagnostic examination to avoid one breast cancer death was also calculated on the basis of the recall rate of mammographic screening in communities (12). These results were compared between mammographic screening with and without clinical breast examination divided into different age groups from 40 to 70 years.

Considering the balance of benefits and harms, five grades of recommendations were determined for population-based and opportunistic screenings (10). As theses grades are supported by sufficient evidence and the benefits outweigh the harms, both Grades A and B recommendations could be conducted as both population-based and opportunistic screening programs. However, a method with a Grade D recommendation should not be used for either population-based or opportunistic screening programs because the harms outweigh the benefits. A grade C recommendation implies that the method should not be used for population-based screening. Even if there are benefits, we can give a Grade C recommendation when the benefits and harms are nearly equal. However, a Grade C recommendation implies that the method could be used in clinical settings if both adequate risk management and informed consent with respect to the harms were assured. Screening methods that have insufficient evidence related to mortality reduction from breast cancer are graded as I; such methods are not recommended for population-based screening or as routine screening methods in clinical settings, although the decision to undergo screening could be made at the individual level based on proper information provided by health professionals in clinical settings.

Formulating the guidelines

A draft of the guidelines has been written and uploaded on the 'Promoting Evidence-based Cancer Screening' website (http://canscreen.ncc.go.jp/). To improve and confirm the guidelines, comments from the public were collected. In addition, major issues identified during the review of the draft were discussed at a guidelines forum open to the public. Taking into account the comments received from external reviewers and the guidelines forum, the appropriateness of the recommendation and its language were re-discussed and the guidelines were refined. After the consultations were completed, the guidelines were approved by the National Cancer Center and published on the 'Promoting Evidence-based Cancer Screening' website (http://canscreen.ncc.go.jp/).

Findings

Evidence of the efficacy and effectiveness of breast cancer screening methods

There were 5270 articles identified from the literature search using PubMed and other databases. After a two-stage review, 110 English articles and 8 Japanese articles were selected (Fig. 2). From these 110 articles, 6 RCTs for mammographic screening without clinical breast examination were identified as follows: Malmö study (13,14), Canadian study II (15–17), Swedish Two-County study (18–24), Stockholm study (25,26), Göteborg study (27,28) and UK Age trial (29). Three RCTs for mammographic screening with clinical breast examination were also identified as follows: New York HIP study (30), Edinburgh study (31) and Canadian study I (32,33). The RCTs which evaluated mortality reduction from breast cancer were limited to eight studies worldwide. Although there were several problems in these studies, we adopted all the RCTs to resolve the primary issues for Japanese women. Canadian studies consisted of two groups with different targets: women aged 50–59 years for Canadian study II (15–17), and women aged 40–49 years for Canadian study I (32,33). 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 (15–17). 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 (32). Based on the inclusion criteria related to a comparator, Canadian study II was excluded from the evidence of mammography without clinical breast examination, and Canadian study I was included 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 evaluating mortality reduction from breast cancer (17).

Although two case–control studies evaluating mortality reduction from breast cancer were found for clinical breast examination, there was no study evaluating the effectiveness of ultrasonography for breast cancer.

Body of evidence related to mortality reduction from breast cancer

Mammographic screening without clinical breast examination (level of evidence: 1+)

Five RCTs of mammographic screening without clinical breast examination were identified for mortality reduction from breast cancer (Table 1) (13,14,18–29). The starting years of these studies were around the 1980s except the UK Age trial which commenced in 1991. Randomized allocation was individual-based except the Swedish Two-County study. Although the screening method was the same in these studies, the randomized allocation, target age group, screening interval, radiographic view and follow-up periods were different

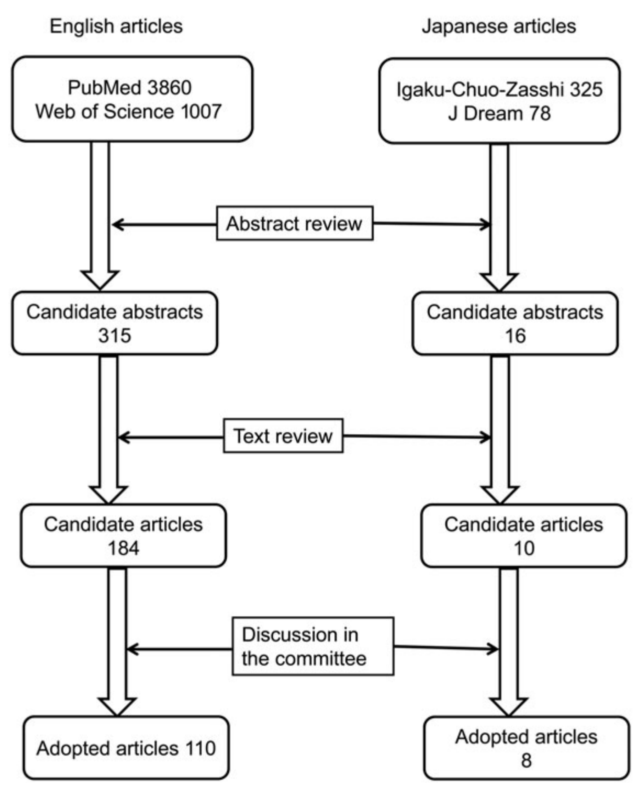

Figure 2. Flowchart of literature search. To identify evidence of breast cancer screening in the literature, PubMed, Web of Science, Igaku-Cyuo zasshi and J Dream were searched. A total of 5270 articles were identified from the literature search using PubMed and other databases. After a two-stage review, 110 English articles and 8 Japanese articles were selected.

Table 1. RCTs for evaluation of mammographic screening without clinical breast examination

	Malmö I and II	Swedish Two County	Stockholm	Göteborg	UK Age trial
Starting year of the study	1976	1977	1981	1982	1991
Randomization	Individual	Cluster	Birthday	Birthday	Individual
Number	60 076	133 065 (45)	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)

MMG, mammography; SBE, self-breast examination; CBE, clinical breast examination.
Reference (12).
The relative risk was based on the results of 13 years of follow-up based on the following references: (8) and (16).

(Table 1) (12). Based on the results of the meta-analysis for mammographic screening without clinical breast examination programs, the overall relative risk for all the age groups was 0.75 (95% CI: 0.67–0.83) (Table 2) (12). 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. Since the selected studies covered women aged 40–74 years, the efficacy of mammographic screening could be confirmed for women of this age group.

Mammographic screening with clinical breast examination (level of evidence: 1+)

Three RCTs of mammographic screening with clinical breast examination served as eligible evidence for mortality reduction from breast cancer (Table 3) (17, 30–33). 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 started in 1963 to evaluate the efficacy of mammographic screening (30). The other studies were commenced at 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 (31). Although the screening method was the same in these studies, the control group in Canadian study I was initially provided clinical breast examination (32,33). Three studies were selected to evaluate the efficacy of mammographic screening with clinical breast examination (Table 3). Based on the meta-analysis results, the overall relative risk for all the age groups was 0.87 (95% CI: 0.77–0.98) (Table 2) (12). 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. Since the selected studies covered women aged 40–64 years, the efficacy of mammographic screening could be confirmed for women of this age group.

Clinical breast examination (level of evidence: 2−)

In a previous Japanese study, the odds ratio of mortality reduction from breast cancer for women who have had at least one clinical breast examination within 1 year was 0.93 (95% CI: 0.48–1.79) and that for women who have had clinical breast examination within 5 years was 0.59 (95% CI: 0.48–1.79) (34). However, after excluding symptomatic women, the odds ratio for women who have had at least one clinical breast examination within 1 year was 0.56 (95% CI: 0.27–1.18) and that for women who have had clinical breast examination within 5 year was 0.45 (95% CI: 0.22–0.89). In a case–control study conducted in the USA, the odds ratio of mortality reduction from breast cancer for average-risk women who have had one clinical breast examination within 3 years was 0.94 (95% CI: 0.79–1.12) and that for high-risk women was 0.80 (95% CI: 0.59–1.08) (35). Similar odds ratios were obtained for mammographic screening in this study.

Although RCTs has been mainly conducted in some developing countries, intermediate results have been reported. In these studies, screening was provided annually and interval cancers were identified from follow-up studies and cancer registries. A study in India reported a sensitivity of 51.7% (95% CI: 38.2–65.0) and a specificity of 94.3% (95% CI: 94.1–94.5) for clinical breast examination (36). A study based on the Breast and Cervical Early Detection Program reported a sensitivity of 58.8% and a specificity of 93.4% (37). In the results of a meta-analysis that included an HIP New York study and a Canadian study, the sensitivity was 54.1% (38). Japanese studies reported similar results based on local cancer registries and the sensitivity was different among local areas (39–41). Since clinical breast cancer examination has been performed annually, interval cancer was defined as negative results at the first screening and diagnosed until the next year screening. In a study in Yamagata, Japan, Shibata et al. (39) reported a sensitivity of 46.6% (95% CI: 33.3–60.1) and a specificity of 97.3%. In a study in Miyagi, Japan, the differences in the sensitivities among the target age groups were as follows: 62.4% for women in their 40s, 59.1% for women in their 50s and 59.9% for women their 60s (40). However, the sensitivity was lower in a study conducted in Tochigi, Japan than in other studies based on follow-up using a local cancer registry (41). Based on these studies, although there was a difference among individual skills, clinical breast examination shows a sensitivity of 50% and a specificity of 95% and over.

There are only two studies that have evaluated mortality reduction from breast cancer and their study designs were case–control studies. In addition, the results of these studies were not same. Because of inconsistent results, a definitive confirmation as to whether or not clinical breast examination could reduce mortality from breast cancer could not be made

Table 2. Meta-analysis of mammographic screening with and without clinical breast examination

	Target age group of RCTs	Relative risk (95% CI)			Attribute risk difference (95% CI)		
		All age	40–49 years	≥50 years	All age	40–49 years	≥50 years
Mammography	40–74 years	0.75 (0.67–0.83)	0.81 (0.68–0.96)	0.71 (0.62–0.81)	−0.0010 (−0.0013– −0.0006)	−0.0005 (−0.0009– −0.0001)	−0.0015 (−0.0009– −0.0021)
Mammography with clinical breast examination	40–64 years	0.87 (0.77–0.98)	0.87 (0.72–1.04)	0.83 (0.70–0.99)	−0.0009 (−0.0016– −0.0001)	−0.0007 (−0.0015– −0.0002)	−0.0014 (−0.0027– −5.36E-5)

RCT, randomized controlled trial: CI, confidence interval.

Ultrasonography with and without mammography (level of evidence: 3)
Based on the results of systematic review, there is still no study evaluating mortality reduction from breast cancer using ultrasonography with and without mammography. Although several studies have reported on test accuracy, the sensitivity of ultrasonography was always higher in studies performed in Japan than in studies conducted in western countries (41–44). In a study conducted in Tochigi, Japan, the sensitivity was 53.8% and the specificity was 95.4% based on follow-up using a local cancer registry (41).

Harms of mammographic screening

The major harms of mammographic screening were radiation exposure, false-positive cases, and overdiagnosis (3–7). The risk of radiation exposure was calculated by modeling and this predicted the incidence and mortality of radiation-induced cancer (45–52).

False-positive cases

False-positive cases results in unnecessary diagnostic examinations and occasionally produce psychological effects including anxiety, fear and depression (53–61). Although cumulative false-positive rates were reported in several studies using the modeling approach, the results varied (62–66). In a US study using mammographic screening alone, the reported 10-year cumulative rates for biannual screening were 41.6% (95% CI: 40.6–42.5) for women who started cancer screening from 40 years of age and 42.0% (95% CI: 40.4–43.7) for women who started cancer screening from 50 years of age (63). Although there was no study which predicted the cumulative false-positive rate in Japan, the study in Tochigi, Japan reported a false-positive rate of 7.9% (41).

Despite the similar false-positive rates in the USA and Japan, the invasive biopsy rates for all age groups were lower in Japan (67).

Overdiagnosis

Although there is agreement regarding the basic concept of overdiagnosis, a method of estimating the rate of overdiagnosis has not been standardized to date (5). Therefore, the reported rates of overdiagnosis ranged from 5 to 50% and over (68–82). Pulti et al. (83) reviewed observational studies that provided an estimate of the rate of overdiagnosis in European countries, and reported a range of 1–10%. Although studies on calculating overdiagnosis are still lacking, the reported excess rate of mammographic screening was 141% (69). This rate included overdiagnosis cases, but early cancers that had the possibility of progressing into invasive cancers were also included.

The most reliable estimates of overdiagnosis come from RCTs. In the Malmö study, the rate of overdiagnosis was 10% based on 15 years of follow-up (82). A Canadian study reported an overdiagnosis rate of 22% based on 25 years of follow-up (17). An independent UK panel estimated the rate of overdiagnosis using four types of denominator based on the results of the Malmö study and Canadian studies (5). The panel considered that the data included overdiagnosis in the range of 5–15% from the population perspective and 15–25% from the individual woman's perspective.

Balance of benefits and harms of mammographic screening

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 4) (12). The NNI was consistently lower in mammographic screening without clinical breast examination than in

Table 3. RCTs for evaluation of mammographic screening with physical examination

	New York HIP	Canada I	Edinburgh
Starting year of the study	1963	1980	1978
Randomization	Individual	Individual	Cluster
Subjects			
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)

Reference (12).
The relative risk was based on the results of 13 years of follow-up for the NY HIP study and Canada I study, and 14 years of follow-up for the Edinburgh study. References (9) and (31).

Table 4. Comparison of benefits and harms between mammographic screening with and without clinical breast examination

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

Number needed to invite are expressed per thousand women invited for 13 years of follow-up.
CBE, clinical breast examination.
Reference (12).

Table 5. Recommendation of breast cancer screening

Screening method	Recommendation grade	Target age group	Recommendations language	
			Population-based screening	Opportunistic screening
Mammography	B	40–74 years	Recommend	Recommend
Mammography with clinical breast examination	B	40–64 years	Recommend	Recommend
Clinical breast examination (alone)	I		Not recommend[a]	Decision-making at the individual[b]
Ultrasonography with and without mammography	I		Not recommend[a]	Decision-making at the individual[b]

[a]There is insufficient evidence to recommend for or against.
[b]If required, the health professional should explain that the evidence regarding mortality and incidence reduction by cancer screening is unclear. In addition, information about the harms is required. In such situations, the decision regarding cancer screening should be made at the individual level.

mammographic screening with clinical breast examination. In both screening methods, the NNI was higher in women aged 40 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.

Discussion

In the Japanese guidelines, evidence pointing to the efficacy of mammographic screening with and without clinical breast examination was confirmed. In Japan, the combination method of mammography and clinical breast examination has been performed as the recommended procedure for breast cancer screening. Although mammographic screening without clinical breast examination has not been recommended in Japan, this procedure is the standard method for breast cancer screening in the USA and European countries (5). With the dissemination of only mammographic units, mammography alone has been anticipated to be introduced in Japanese communities because of the lack of physicians who can correctly perform clinical breast examination. The efficacy of mammography alone could be identified from the results of meta-analysis, and its impact was found to be higher than in the combination method of mammography and clinical breast examination (12). Since the accuracy of mammographic units has been continuously improved, mammography can therefore be used individually without clinical breast examination. In fact, the number of recall to avoid one breast cancer death was lower in mammography alone than in mammography with clinical breast examination (12). Based on the balance of benefits and harms, mammographic screening with and without clinical breast examination is recommended. In addition to improving the screening methods, more opportunities to improve access to mammographic screening in local municipalities should be provided.

However, the original issue remains as to whether Japanese women in their 40s should be included in the target group for mammographic screening. Although most RCTs have included women in their 40s in the target age group, it is insufficient to evaluate the efficacy of mammographic screening according to individual studies except the UK Age trial which targeted women in their 40s. The results of our meta-analysis to clarify the efficacy of mammographic screening without clinical breast cancer screening suggested a 19% mortality reduction from breast cancer (0.81, 95% CI; 0.68–0.96) (12). However, there were gaps in the number needed to invite women to avoid one death from breast cancer and the number needed to recall women to avoid one death from breast cancer between women in their 40s and 50s and above. The net benefits were smaller in women in their 40s than in women in their 50s and above. Ideally, it is preferable to make a recommendation based on evidence evaluated from the guideline developers' own countries because evidence obtained in other countries might not be adopted into other ethnic groups. As there are no RCTs and observational studies evaluating the efficacy and effectiveness of mammographic screening in Japan, a comprehensive assessment of the actual impact of mammographic screening in Japan could not be made. Nevertheless, despite the limited net benefits, we recommend mammographic screening with and without clinical breast examination considering the higher incidence of breast cancer in women in their 40s in Japan.

Although the peak incidence of breast cancer was observed in women aged 40–49 years (1), the sensitivity of mammography was lower in women in their 40s than in women in their 50s and above because of their dense breast (40). However, even if clinical breast examination is added in mammography, the sensitivity cannot always be improved owing to the technical gaps among physicians who have experience and physicians who have no experience. Ultrasonography has been shown to have a higher sensitivity than clinical breast examination (41), and it can detect small tumors in a dense breast without radiation exposure. To increase the magnitude of mortality reduction from breast cancer screening for women aged in their 40s, evaluation of the efficacy of mammographic screening with ultrasonography has been started (84). However, studies conducted in the US have reported a not so high sensitivity as well as the possibility of an increased false-positive rate (7,43,44). As studies evaluating mortality reduction from breast cancer by ultrasonography with and without mammography remain lacking, we could not accurately evaluate whether or not ultrasonography can be an alternative method for clinical breast examination.

To date, mammographic screening has been widely recommended and implemented in developed countries (5). In fact, most guidelines recommend mammographic screening for women aged 50–69 years every 2 or 3 years (3–7). Although the efficacy of mammographic screening has been evaluated by RCTs, there has been a long discussion regarding its efficacy since the publication of the Cochrane review in 2000. In the Cochrane review, questions about the efficacy of mammographic screening and the imbalance of benefits and harms have been raised (9). Moreover, the unconfirmed estimation method adds another layer of confusion in the evaluation of the net benefits of mammographic screening (5). Since the net benefits might be decreased in cases of overestimation, the range of overdiagnosis showed a large variation from 5 to 50% (68–84). In most influential guidelines and evidence reports, the efficacy of mammographic screening was re-evaluated on the basis of the results of RCTs and was reconfirmed. However, with much weight placed on the results of the Cochrane review, mammographic screening has not been recommended in some guidelines such as those of the Swiss Medical Association (10). For guidelines development, although the balance of benefits and harms based on valid evidence is a priority issue, the overall background should also be considered (85). To identify and confirm the best available method for breast cancer screening in Japan, original studies evaluating the actual impact of mammographic screening are warranted. We aim to revise and further improve the Japanese guidelines for breast cancer screening based on the results of new research studies after 5 years.

Recommendations

Based on the balance of benefits and harms, recommendations were formulated for population-based and opportunistic screenings (Table 5). Benefits were defined as evidence that mortality from a specific cancer was reduced by a cancer screening program.

Mammographic screening without clinical breast examination for women aged 40–74 years is recommended for population-based and opportunistic screenings as its benefits outweighs its harms (*Recommendation grade B*). Mammographic screening with clinical breast examination for women aged 40–64 years is recommended for population-based and opportunistic screenings as its benefit outweighs its harms (*Recommendation grade B*). As there remains insufficient evidence of mortality reduction from breast cancer, clinical breast examination and ultrasonography are not recommended for population-based screening (*Recommendation grade I*). With respect to opportunistic screening, if individuals request these screenings, they should be given appropriate information with the decision made at the individual level.

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Conflict of interest statement

None declared.

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Appendix

Japanese Research Group for Development of Breast Cancer Screening Guidelines

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