Sensitivity and specificity of mammography and adjunctive ultrasonography to screen for breast cancer in the Japan Strategic Anti-cancer Randomized Trial (J-START): a randomised controlled trial

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Summary

Background **Mammography is the only proven method for breast cancer screening that reduces mortality, although it is inaccurate in young women or women with dense breasts. We investigated the efficacy of adjunctive ultrasonography.**

Methods **Between July, 2007, and March, 2011, we enrolled asymptomatic women aged 40–49 years at 42 study sites in 23 prefectures into the Japan Strategic Anti-cancer Randomized Trial (J-START). Eligible women had no history of any cancer in the previous 5 years and were expected to live for more than 5 years. Randomisation was done centrally by the Japan Clinical Research Support Unit. Participants were randomly assigned in 1:1 ratio to undergo mammography and ultrasonography (intervention group) or mammography alone (control group) twice in 2 years. The primary outcome was sensitivity, specificity, cancer detection rate, and stage distribution at the first round of screening. Analysis was by intention to treat. This study is registered, number UMIN000000757.**

Findings **Of 72 998 women enrolled, 36 859 were assigned to the intervention group and 36 139 to the control group. Sensitivity was significantly higher in the intervention group than in the control group (91·1%, 95% CI 87·2–95·0 *vs* 77·0%, 70·3–83·7; p=0·0004), whereas specificity was significantly lower (87·7%, 87·3–88·0 *vs* 91·4%, 91·1–91·7; p<0·0001). More cancers were detected in the intervention group than in the control group (184 [0·50%] *vs* 117 [0·32%], p=0·0003) and were more frequently stage 0 and I (144 [71·3%] *vs* 79 [52·0%], p=0·0194). 18 (0·05%) interval cancers were detected in the intervention group compared with 35 (0·10%) in the control group (p=0·034).**

Interpretation **Adjunctive ultrasonography increases sensitivity and detection rate of early cancers.**

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See **Comment** page 313

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Introduction

The incidence of breast cancer continues to increase worldwide. Incidence remains highest in the USA and Europe, but has been increasing substantially in Japan and other Asian countries over the past three decades.[1–4] Early detection and access to optimum treatment are crucial to reduce mortality associated with breast cancer. Many countries have adopted national mammography screening programmes based on the results of randomised controlled trials (RCTs) done in developed countries. Although mammography is the only method that has evidence supporting mortality reduction for breast cancer, accuracy is reduced in women with high-density breast tissue and in young women.[5–7] Asian women characteristically have higher-density breasts than do women from other ethnic groups.[8–10] Consequently high accuracy is difficult to achieve with mammography screening alone. Furthermore, the age-specific incidence of female breast cancer in Asia peaks at age 40–49 years, whereas in western countries the peak is at age 60–70 years.[2] Asian countries must, therefore, take measures to address the accuracy of breast cancer screening in women aged 40–49 years.

Ultrasonography is one candidate to improve examination sensitivity because it can detect breast cancer at an early stage on the basis of the mass shape, even in the dense parenchyma of premenopausal women. Some clinical trials and observational studies have shown that mammography with adjunctive ultrasonography increased screening sensitivity and detection rates and lowered the frequency of interval cancers in women with dense breasts.[11–18] However, the addition of ultrasonography to mammography has substantially increased the number of false-positive findings.[17,19] Breast cancer screening including ultrasonography has not been assessed in RCTs in specified groups or for population screening and, therefore, its effect on detection of interval cancers cannot be estimated from published studies.[20–22] We did the Japan Strategic Anti-cancer Randomized Trial (J-START) to assess the efficacy of adjunctive ultrasonography in screening for breast cancer in Japanese women aged 40–49 years.

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Methods

Participants

The design, standardisation of screening examinations, and study enrolment have been described in detail previously.[23,24] Briefly, between July, 2007, and March, 2011, we enrolled asymptomatic women in 42 study sites in 23 of 47 prefectures in Japan.[8,23] Eligible women were aged 40–49 years without a history of breast cancer, including in-situ cancer, or other cancers in the previous 5 years, and who had life expectancy of more than 5 years.

Trained clinical research coordinators or research staff obtained written informed consent from all women at each study site.[24] The study protocol was developed in accordance with the principles of the Declaration of Helsinki. We adhered strictly to the ethics guidelines for clinical studies issued by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare of Japan. Ethics approval was obtained from Tohoku University School of Medicine Research Ethics Committee and the Japan Anticancer Society.[23]

Randomisation and masking

We asked each study site to choose its method of allocation—individual RCT, cluster RCT, or non-RCT—on the basis of feasibility. According to the study protocol, sites that chose non-RCT would be excluded from the analysis. At cluster randomisation sites the clusters were balanced for numbers of participants. Deviations were defined in the statistical analysis plan (appendix).

See Online for appendix

Randomisation was done centrally by the Japan Clinical Research Support Unit, which was responsible for data management and trial operations, independently of Tohoku University. Women were randomised in a 1:1 ratio to receive screening by mammography plus ultrasonography, with or without clinical breast examination (intervention group) or mammography with or without clinical breast examination (control group) twice within a 2-year period. Allocation codes were kept in sealed envelopes that were sent to the principal investigators at each study site before randmisation. Screening allocations could not be masked for participants and study coordinators, but an independent panel that assessed outcomes was unaware of group assignment.

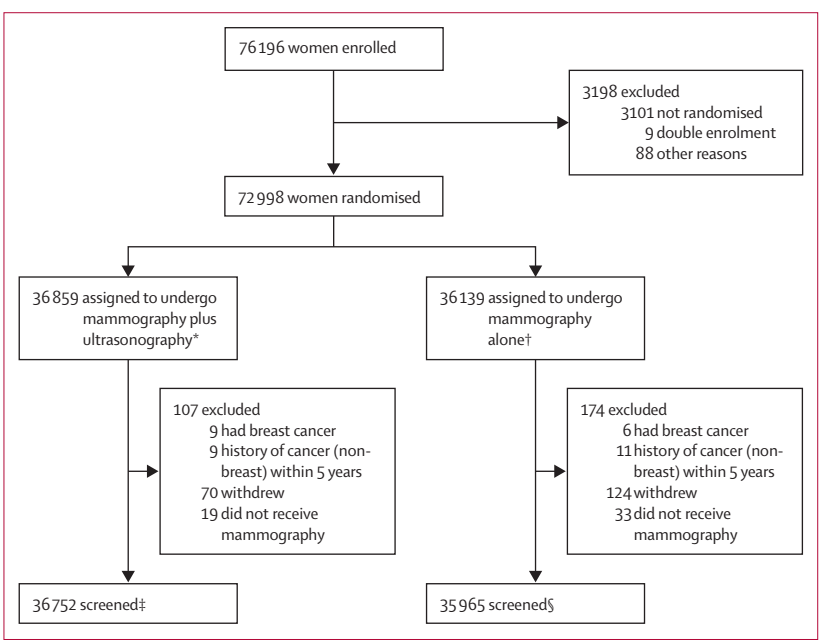

Figure: **Trial profile**
*26 434 enrolled in individual and 10 245 in cluster randomised controlled trials. †26 411 enrolled in individual 9278 in cluster randomised controlled trials. ‡Four women did not undergo ultrasonography. §Five women underwent ultrasonography.

Screening

Standard mammography and ultrasonography techniques were used at all participating facilities[23,24] and images were interpreted at each study site with double reading by two authorised physicians. Clinical examination was performed by physicians. Ultrasonography was done at each study site by trained clinical examiners, mostly clinical technologists, who had participated in a 2-day educational programme before screening started. The results were reassessed by physicians at the study sites, including radiologists and breast surgeons.

The independently assessed findings of mammography, ultrasonography, and clinical examination were classified into five categories that are used locally and internationally: 1, no findings; 2, benign; 3, probably benign but further assessment needed; 4, probably malignant; 5, malignant.[23,25–27] If further assessments were deemed necessary, results were taken to be positive if scores of 3 or higher were assigned. Mammography acquisition, practice, apparatus, and interpretation were certified by the Japan Central Organization on Quality Assurance of Breast Cancer Screening. Ultrasonography acquisition, practice, apparatus, and interpretation were certified by the Japan Association of Breast and Thyroid Sonology (JABTS).[24,28] Further details of screening methods are provided in the study protocol and in the appendix.

Follow-up

Breast cancers were diagnosed by assessment of first-round and second-round screening results or by a postal survey at the time of the second-round screening for women who did not attend. If data were incomplete, we used the Japan Clinical Research Support Unit to look up women's vital status from residential registers. To calculate the sensitivity of first-round screening, we defined screen-detected breast cancers as those categorised as 3–5 at the first round and interval cancers as those diagnosed between the first round and the second round of screening for which the initial category had been 1 or 2. All participants without breast cancer at either screening were followed up by assessment of screening records, questionnaire, and official cancer registry. Cases diagnosed after the second round of screening were not counted. Tumour stage was classified

with the Union for International Cancer Control Tumour Node Metastatic classification at referral hospitals and reported with histopathological findings.[29] A data and safety monitoring board was established to monitor the progress of the study every 6 months.

Statistical analysis

The primary outcome was sensitivity, specificity, cancer detection rate, and distribution of cancer stage at the first round of screening. The secondary outcome was rate of advanced breast cancers after the initial screening, but these data are not reported here. The sample size was calculated according to the hypothesis that adjunctive ultrasonography would improve screening sensitivity. We had shown previously that sensitivity of mammography screening was 71% in women aged 40–49 years, 85% in those aged 50–59 years, and 86% in those aged 60–69 years.[6] Therefore, we assumed that the sensitivity would increase from 71% to 86% by adding ultrasonography. We calculated that 130 confirmed cases of breast cancer would be needed to show this difference with 5% significance (two-sided) and 80% power and, therefore, that 42 500 women would need to be assigned to each group, based on prevalence of 0·003% among women aged 40–49 years.[6] We recruited 76 196 women, which, on the basis of the original calculation, would provide 75% statistical power to test the hypothesis. However, the incidence of breast cancer was expected to be higher than originally calculated, since the incidence in Japan is continuously increasing. Therefore, we estimated that the study would still have sufficient power to assess the primary endpoint, which was confirmed by the data monitoring committee after the second round of screening.

Analyses were done by intention to treat (appendix). There was no heterogeneity in the results between participants enrolled in individual and cluster RCTs (appendix), and the results are presented for all included women. First-round screening performance outcomes were assessed with generalised estimating equations with an exchangeable working correlation matrix and robust SEs. All tests were two-sided and significance was set at 5%. All statistical analyses were done with SAS version 9.2. This trial is registered, number UMIN000000757.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to most datasets and all summary estimates from each dataset, and had final responsibility for the decision to submit for publication.

Results

72 998 participants were randomised, of whom 36 859 were assigned to the intervention group and 36 139 to the control group (figure). 36 752 (99·7%) and 35 965 (99·5%), respectively, underwent screening. Data were unavailable for 1538 (2·1%) women at June 30, 2014. Baseline characteristics were similar in the two groups (table 1).

	All participants (n=72 717)	Intervention group (n=36 752)	Control group (n=35 965)
Age at randomisation (years)	44 (3·0)	44 (3·0)	44 (3·0)
Ever undergone breast cancer screening			
No	16 867 (23·2%)	8432 (22·9%)	8435 (23·5%)
Yes	55 838 (76·8%)	28 310 (77·0)	27 528 (76·5%)
Unknown or data missing	12 (<0·1%)	10 (<0·1%)	2 (<0·1%)
Time since most recent breast cancer screening (months)			
<12	11 460 (15·8%)	5882 (16·0%)	5578 (15·5%)
12–24	18 213 (25·1%)	9184 (25·0%)	9029 (25·1%)
25–36	14 096 (19·4%)	7128 (19·4%)	6968 (19·4%)
>36	10 802 (14·9%)	5531 (15·1%)	5271 (14·7%)
Unknown or data missing	18 146 (25·0%)	9027 (24·6%)	9119 (25·4%)
Method of most recent breast cancer screening			
Mammography			
No	16 303 (22·4%)	8285 (22·5%)	8018 (22·3%)
Yes	39 525 (54·4%)	20 023 (54·5%)	19 502 (54·2%)
Unknown or data missing	16 889 (23·2%)	8444 (23·0%)	8445 (23·5%)
Ultrasonography			
No	45 264 (62·3%)	22 849 (62·2%)	22 415 (62·3%)
Yes	10 564 (14·5%)	5459 (14·9%)	5105 (14·2%)
Unknown or data missing	16 889 (23·2%)	8444 (23·0%)	8445 (23·5%)
Clinical breast examination			
No	5247 (7·2%)	2635 (7·2%)	2612 (7·3%)
Yes	50 581 (69·6%)	25 673 (69·9%)	24 908 (69·3%)
Unknown or data missing	16 889 (23·2%)	8444 (23·0%)	8445 (23·5%)
Age at menarche (years)			
7–11	15 269 (21·0%)	7661 (20·9%)	7608 (21·2%)
12–13	41 682 (57·3%)	21 090 (57·4%)	20 592 (57·3%)
≥14	15 671 (21·6%)	7950 (21·6%)	7721 (21·5%)
Unknown or data missing	95 (0·1%)	51 (0·1%)	44 (0·1%)
Menopausal status			
Premenopausal	55 007 (75·7%)	27 742 (75·5%)	27 265 (75·8%)
Perimenopausal	13 394 (18·4%)	6775 (18·4%)	6619 (18·4%)
Postmenopausal	4272 (5·8%)	2208 (6·0%)	2064 (5·7%)
Unknown or data missing	44 (0·1%)	27 (0·1%)	17 (0·1%)
Number of preganancies			
0	8749 (12·0%)	4429 (12·0%)	4320 (12·1%)
1	8814 (12·1%)	4507 (12·0%)	4307 (12·3%)
2	25 225 (34·7%)	12 659 (34·9%)	12 566 (34·4%)
3–4	24 091 (33·1%)	12 237 (33·0%)	11 854 (33·3%)
5–10	3422 (4·7%)	1752 (4·6%)	1670 (4·8%)
Unknown or data missing	2416 (3·3%)	1168 (3·5%)	1248 (3·2%)
Number of pregnancies delivered			
Nulliparous	9506 (13·1%)	4858 (13·2%)	4648 (12·9%)
1	11 020 (15·2%)	5564 (15·1%)	5456 (15·2%)
2	32 142 (44·2%)	16 174 (44·0%)	15 968 (44·4%)
3	14 973 (20·6%)	7638 (20·8%)	7335 (20·4%)
4–8	2155 (3·0%)	1090 (3·0%)	1065 (3·0%)
Unknown or data missing	2921 (4·0%)	1428 (3·9%)	1493 (4·2%)

(Table 1 continues on next page)

	All participants (n=72 717)	Intervention group (n=36 752)	Control group (n=35 965)
(Continued from previous page)			
Age at first birth (years)			
<20	675 (0·9%)	354 (1·0%)	321 (0·9%)
20–24	9186 (12·6%)	4717 (12·8%)	4469 (12·4%)
25–29	23 365 (32·1%)	11 817 (32·2%)	11 548 (32·1%)
30–39	15 441 (21·2%)	7702 (21·0%)	7739 (21·5%)
40–49	430 (0·6%)	222 (0·6%)	208 (0·6%)
Unknown or data missing	23 620 (32·5%)	11 940 (32·5%)	11 680 (32·5%)
Ever breastfed children			
Yes	56 215 (77·3%)	28 432 (77·4%)	27 783 (77·3%)
No	14 974 (20·6%)	7587 (20·6%)	7387 (20·5%)
Unknown or data missing	1528 (2·1%)	733 (2·0%)	795 (2·2%)
Number of first-degree female relatives with breast cancer			
0	69 304 (95·3%)	34 988 (95·2%)	34 316 (95·4%)
1	3344 (4·6%)	1727 (4·7%)	1617 (4·5%)
>1	69 (0·1%)	37 (0·1%)	32 (0·1%)
Ever had breast surgery	1462 (2·0%)	754 (2·1%)	708 (2·0%)
Ever had benign neoplasm	917 (1·3%)	489 (1·3%)	428 (1·2%)
Ever had breast inflammation	538 (0·7%)	264 (0·7%)	274 (0·8%)

Data are mean (SD) or number (%).

Table 1: **Baseline characteristics**

The mean age of participants was 44·0 (SD 3·0) years. 3344 (4·6%) participants reported a history of breast cancer in first-degree female relatives and 917 (1·3%) reported having ever had one or more benign breast diseases.

Attendance at both screening visits was high (75%), and the proportion of participants not covered was 2%. The sensitivity of screening was higher in the intervention group than in the control group (p=0·0004), but specificity was lower (p<0·0001, table 2). Mammography alone detected notably more cancers in the control group than in the intervention group, but ultrasonography alone detected 67 cases (table 2).

Screening-detected cancers were more frequently clinical stage 0 and I in the intervention group than in the control group (144 [71·3%] *vs* 79 [52·0%], p=0·0194; table 3). The frequency of breast cancers of clinical stage II or worse did not differ significantly between groups. 48 (78%) of 61 cancers detected by ultrasonography alone were stage 0–I. The screening detection rate overall was increased by 0·17% (95% CI 0·08–0·27) in the intervention group (p=0·0003).

18 interval cancers (0·05%, 95% CI 0·03–0·07) were diagnosed in the intervention group, compared with 35 (0·10%, 0·07–0·13) in the control group. Thus ultrasonography was associated with a decrease of 0·05% in interval cancers (appendix). 128 (70%) of 184 cancers

	Confirmed breast cancer		No breast cancer		Status unknown	Total
	Number of participants	Sensitivity (95% CI)*	Number of participants	Specificity (95% CI)†		
Intervention group (n=36 752)						
MG+, US–, CBE+/–	41	..	1876	..	11	1928 (5·2%)
MG+, US+, CBE+/–	76	..	424	..	5	505 (1·4%)
MG–, US+, CBE+/–	67	..	1865	..	18	1950 (5·3%)
Total MG+	117	57·9% (51·0–64·8)	..	..	0	117 (<0·01%)
Total US+	143	70·8% (64·0–77·0)	..	..	0	143 (<0·01%)
Total CBE+	46	22·8% (17·2–29·2)	..	..	0	46 (<0·01%)
Only MG+	34	16·8% (11·7–22·0)	..	..	0	34 (<0·01%)
Only US+	61	30·2% (23·9–36·5)	1765	..	0	61 (<0·01%)
Only CBE+	0	NA	262	..	2	264 (0·7%)
Any positive	184‡	91·1% (87·2–95·0)	4427§	..	36	4647 (12·6%)
All negative	18¶	..	31 420‖	87·7% (87·3–88·0)	667	32 105 (87·4%)
Control group (n=35 965)						
MG+, CBE+/–	109	71·7% (63·8–78·7)	2576	..	17	2702 (7·5%)
MG–, CBE+	8	5·3% (2·3–10·1)	439	..	4	451 (1·3%)
Only MG+	72	47·4% (39·4–55·3)	..	..	0	72 (<0·01%)
Total CBE+	45	29·6% (22·4–36·9)	..	..	0	45 (<0·01%)
Either positive	117‡	77·0% (70·3–83·7)	3015§	..	21	3153 (8·8%)
Both negative	35¶	..	31 963‖	91·4% (91·1–91·7)	814	32 812 (91·2%)

Percentages might not total 100% due to rounding. MG=mammography. US=ultrasonography. CBE=clinical breast examination. NA=not applicable. *p=0·0004 for proportion difference between groups. †p<0·0001 for proportion difference between groups. ‡Screening-detected breast cancers. §False positive. ¶Interval breast cancers. ‖True negative.

Table 2: **Results of first round of screening**

	Clinical stage*					Total	Stage 0–I	Stage II or worse
	0	I	II	III or IV	Data missing			
Intervention group (n=36 752)								
MG+, US–, CBE+	3 (1·5%)	2 (1·0%)	2 (1·0%)	0	0	7 (3·5%)	5 (2·5%)	2 (1·0%)
MG+, US–, CBE+/–	20 (10·0%)	10 (5·0%)	3 (1·5%)	0	1 (0·5%)	34 (16·8%)	30 (14·9%)	3 (1·5%)
MG+, US+, CBE+	5 (2·5%)	16 (7·9%)	10 (5·0%)	2 (1·0%)	0	33 (16·3%)	21 (10·4%)	12 (5·9%)
MG+, US+, CBE–	15 (7·4%)	21 (10·4%)	5 (2·5%)	2 (1·0%)	0	43 (21·3%)	35 (17·3%)	8 (4·0%)
MG–, US+, CBE+	2 (1·0%)	3 (1·5%)	1 (0·5%)	0	0	6 (3·0%)	5 (2·5%)	1 (0·5%)
MG–, US+, CBE–	9 (4·5%)	39 (19·3%)	10 (5·0%)	1 (0·5%)	2 (1·0%)	61 (30·2%)	48 (23·8%)	13 (6·4%)
MG–, US–, CBE+	0	0	0	0	0	0	0	0
MG–, US–, CBE–	1 (0·5%)	8 (4·0%)	8 (4·0%)	1 (0·5%)	0	18 (8·9%)	9 (4·5%)	9 (4·5%)
Only MG+	40 (19·8%)	51 (25·3%)	21 (10·4%)	4 (2·0%)	1 (0·5%)	117 (57·9%)	91 (45·1%)	25 (12·4%)
Only US+	28 (13·8%)	81 (40·1%)	27 (13·4%)	5 (2·5%)	2 (1·0%)	143 (70·8%)	109 (54·0%)	32 (15·8%)
Only CBE+	10 (4·9%)	21 (10·4%)	13 (6·4%)	2 (1·0%)	0	46 (22·8%)	31 (15·4%)	15 (7·4%)
Any positive	51 (25·2%)	93 (46·0%)	32 (15·8%)	5 (2·5%)	3 (1·5%)	184 (91·1%)	144 (71·3%)	37 (18·3%)
Relative sensitivity (US/MG)	0·70	1·59	1·29	1·25	2·00	1·22	..	..
Control group (n=35 965)								
MG+, CBE+	2 (1·3%)	14 (9·2%)	19 (12·5%)	2 (1·3%)	0	37 (24·3%)	16 (10·5%)	21 (13·8%)
MG+, CBE–	28 (18·4%)	28 (18·4%)	15 (9·9%)	1 (0·7%)	0	72 (47·4%)	56 (36·8%)	16 (10·3%)
MG, CBE+	1 (0·7%)	6 (4·0%)	1 (0·7%)	0	0	8 (5·3%)	7 (4·6%)	1 (0·7%)
Both negative	8 (5·3%)	17 (11·2%)	9 (5·9%)	1 (0·7%)	0	35 (23·0%)	25 (16·5%)	10 (6·6%)
MG+	30 (2·0%)	42 (27·6%)	34 (22·4%)	3 (2·0%)	0	109 (71·7%)	72 (47·4%)	37 (24·3%)
CBE+	3 (1·3%)	20 (13·2%)	20 (13·2%)	2 (1·3%)	0	45 (29·6%)	23 (15·1%)	22 (14·5%)
Either positive	31 (2·0%)	48 (31·6%)	35 (23·0%)	3 (2·0%)	0	117 (77·0%)	79 (52·0%)	38 (25·0%)
Relative sensitivity (CBE/MG)	0·1	0·48	0·59	0·67	0	0·41	..	..

Data are number (%), unless otherwise indicated. MG=mammography. US=ultrasonography. CBE=clinical breast examination. *Based on the Union for International Cancer Control Tumour Node Metastases classification, seventh edition.

***Table 3*: Distribution of clinical stages of breast cancer**

detected in the intervention group were invasive, compared with 86 (74%) of 117 in the control group; 16 (89%) of 18 and 27 (77%) of 35 of interval cancers, respectively, were invasive (table 4).

Further assessment was recommended for 4647 particpants in the intervention group compared with 3153 in the control group (table 5). The number of biopsies done owing to the first round of screening was higher in the intervention group than in the control group. There were no complications or adverse events associated with mammography and ultrasonography throughout the screening period.

Discussion

Mammography with adjunctive ultrasonography was associated with a significantly higher detection rate of breast cancer than mammography alone. The main strength of this study is that it differed from previous studies in several important ways (panel). Our study design enabled recruitment at multiple centres to ensure a large study population with good adherence and a follow-up rate of 98%, which was sufficient quality compared with the populations in previous studies.[17] Attendance at both screening visits was high and surgical outcomes after recall were independently reviewed. Our original target sample size was 85 000 for the overall study population, based on the number of cases needed to detect a difference between groups and expected prevalence. Our final results are based on a sample of 72 717 women, but, because the number of cases of breast cancer was 354, the study had sufficient power to detect a clinically meaningful difference in sensitivity.

Sensitivity was higher in the intervention group than in the control group because of a lower number of interval cancers (18 *vs* 35) and because 67 additional cases were detected by ultrasonography. In the intervention group, 78% of breast cancers detected by ultrasonography alone were clinical stage 0–I, and most were invasive and node negative. These findings are similar to those in previous studies where ultrasonography detected breast cancers at early and preclinical stages.[11,13,14,17] The difference between the intervention and control groups in the total number of breast cancers detected (202 *vs* 152) might be explained by the ability of ultrasonography to depict additional cancers, which is supported by our finding of fewer interval cancers in the intervention group (18 *vs* 35). No breast cancers were detected by clinical examination alone in the intervention group. By contrast, eight breast

	Intervention group (n=36 752)						Control group (n=35 965)			
	Screen-detected cancers					Interval cancers (n=18)	Screen-detected cancers			Interval cancers (n=35)
	Total (n=184)	MG+ and US+ (n=76)	Only MG+ (n=41)	Only US+ (n=67)	Only CBE+ (n=0)		Total (n=117)	Only MG+ (n=109)	Only CBE+ (n=8)	
Time since initial screening (months)										
≤12	169 (92%)	70 (92%)	37 (90%)	62 (93%)	0	5 (28%)	109 (93%)	102 (94%)	7 (88%)	7 (20%)
>12	15 (8%)	6 (8%)	4 (10%)	5 (8%)	0	13 (72%)	8 (7%)	7 (6%)	1 (13%)	28 (80%)
Histopathological cancer type*										
Non-invasive†	53 (29%)	20 (26%)	23 (56%)	10 (15%)	0	2 (11%)	31 (27%)	30 (28%)	1 (13%)	8 (23%)
Invasive‡	128 (70%)	56 (74%)	17 (42%)	55 (82%)	0	16 (89%)	86 (74%)	79 (73%)	7 (88%)	27 (77%)
Unknown or data missing	3 (2%)	0	1 (2%)	2 (3%)	0	0	0	0	0	0
Size of invasive tumours on histology (mm)										
Mean (SD)	15·3 (12·6)	17·5 (14·3)	11·4 (8·9)	14·2 (11·5)	0	15·3 (8·1)	15·1 (8·7)	15·2 (8·9)	14·3 (5·9)	17·7 (8·0)
25th percentile	9·0	10·0	6·0	9·0	0	10·0	9·0	8·0	9·0	12·0
75th percentile	16·0	18·0	14·0	16·0	0	21·0	20·0	21·0	17·0	21·0
Node status of invasive cancers										
Negative	101 (79%)	41 (73%)	13 (77%)	47 (86%)	0	10 (63%)	54 (63%)	47 (60%)	7 (100%)	17 (63%)
Positive	23 (18%)	13 (23%)	2 (12%)	8 (15%)	0	6 (38%)	29 (34%)	29 (37%)	0	10 (37%)
Unknown or data missing	4 (3%)	2 (4%)	2 (12%)	0	0	0	3 (4%)	3 (4%)	0	0

Data are number (%), unless otherwise indicated. MG=mammography. US=ultrasonography. CBE=clinical breast examination. Percentages might not total 100% due to rounding. *Based on the International Classification of Diseases, tenth edition. †Including ductal carcinoma in situ and lobular carcinoma in situ. ‡Including invasive ductal carcinoma and special type.

Table 4: **Histological findings**

	Total (n=72 717)	Intervention group (n=36 752)	Control group (n=35 965)
Recalled after first-round screening	7800 (10·7%)	4647 (12·6%)	3153 (8·8%)
Biopsy done*	2320 (3·2%)	1665 (4·5%)	655 (1·8%)
Fine-needle aspiration	1662 (2·3%)	1227 (3·3%)	435 (1·2%)
Core needle biopsy	583 (0·8%)	407 (1·1%)	176 (0·5%)
Vacuum-assisted biopsy	225 (0·3%)	137 (0·4%)	88 (0·2%)
Surgical biopsy†	66 (0·1%)	42 (0·1%)	24 (0·1%)

Data are number (%). *When clinically indicated, participants might have undergone two or more types of biopsy. †14 (33%) in the intervention group and four (17%) in the control group had breast cancers diagnosed.

Table 5: **Need for biopsy on the basis of first-round screening**

cancers were detected by this method in the control group, which suggests that ultrasonography could replace clinical examination.

The use of adjunctive ultrasonography was associated with a 0·17% overall increase in the screening detection rate. This difference seems to be in accordance with the conclusions of a review which showed that ultrasonography detected an additional 0·03–0·77% of cancers.[17] Of note, though, is that the studies assessed were of heterogeneous design and that particpants were mostly mammography negative, had heterogeneously or extremely dense breasts, and that family history was mixed: some included only first-degree relatives, some included broader family members, one separated *BRCA* mutations from other family history, and some combined family and personal history of breast cancer.[17] Our study design enabled comparison of incidence of interval cancers, which was lower in the intervention group than in the control group. Berg and colleagues[12] and Corsetti and colleagues[13,14] had previously shown low interval cancer rates in women screened with adjunctive ultrasonography. All women in those studies, however, underwent ultrasonography screening and the effect could not be quantified. Our results, therefore, extend these findings.

Specificity was lower in the intervention group than in the control group. This finding is disadvantageous for young women. The first reason for low specificity was the separate categorisation of the mammographic and ultrasound images, which inevitably led to an increased recall rate and reduced specificity. Combined assessment might improve specificity. The JABTS and Japan Association of Breast Cancer Screening (JABCS) have proposed guidelines for combined categorisation from mammographic and ultrasound images.[30] If these guidelines are verified, the recall rate is likely to decrease in routine breast cancer screening programmes. Another reason for low specificity is that ultrasonography can detect some lesions that are not visible on mammography in women with dense breasts. A study in Japan reported that the recall rate of mammography screening among 33 924 women aged 40–49 years was 9·9%.[31] The recall rate in our study, however, was lower (8·8%) and within

Panel: Research in context

Systematic review

In 2013, Gartlehner and colleagues[20] reported the results of a systematic review and meta-analysis of mammography plus breast ultrasonography versus mammography alone for breast cancer screening in women at average risk. We searched MEDLINE (OVID), the Cochrane database (CCTR, DARE, and CDSR), and Embase from September, 1977, to November, 2014. The last search was done on Nov 22, 2014. We modified the search strategy of Gartlehner and colleagues, using the keywords "breast neoplasms", "breast cancer", "screening", "mammography", "ultrasound", and "randomised controlled trial" to identify whether any additional randomised controlled trials had been done since this review. Except for J-START reports, we did not identify any appropriate, completed studies. Houssami and Ciatto[21] had reviewed the use of adjunctive ultrasonography for breast screening, but the studies were restricted to women with dense breasts, and no study had used a randomised controlled design. Therefore, we decided to do a randomised controlled trial to compare screening approaches.

Interpretation

Adjunctive ultrasonography was associated with a significantly higher detection rate of breast cancer than mammography alone. Thus, ultrasonography could offer a low-cost way to increase sensitivity and detection rates of early cancers in women with dense breast tissue. Additionally, because stage I breast cancers are more likely to be correctly diagnosed than stage 0 cancers and have better survival than more advanced tumours, this distribution supports the potential for reduction of mortality or incidence of advanced breast cancer. Long-term studies are needed to assess these outcomes.

the target range of routine screening mammography (less than 11%).

To keep screening-associated harm to a minimum is very important.[19,32,33] Kasahara and colleagues[31] reviewed harm associated with screening mammography in 144 848 women in the general population in Japan, and compared the data with those from the Breast Cancer Surveillance Consortium (BCSC) and the JABCS in 2013.[31] Fine-needle aspiration cytology was used in 1·61% of cases in JABCS (no data are available from BCSC) and biopsies, including core needle, vacuum-assisted, and open surgical methods, were used in 0·93% of cases in the BCSC and 0·69% in the JABCS. In our study, the rates for both these assessments were about twice as high, at 3·34% for fine-needle aspiration and 1·59% for biopsies, but the detection rate was also around twice as high (0·50% in our intervention group *vs* 0·26% in BCSC and 0·28% in JABCS). Ultrasonography-guided histological examination is easier, more accurate, and more reliable than clinical observation of the lesions alone, and is the main reason for the increased biopsy rate. In Japan, fine-needle aspiration cytology is preferred to core needle biopsy for lesions thought to be benign, and lesions are histologically assessed when aspiration cytology is negative. Fine-needle aspiration is less harmful than core needle biopsy or surgery, and an increase in biopsy rate might raise the cancer yield, which means that harm overall might be almost equal to that with mammography screening alone.

An important limitation of this study is that sensitivity and specificity were calculated with the data from the first round of screening. Since characteristics of breast cancer, such as distribution of tumour size or sojourn time, would differ between the first and later rounds of screening, our findings cannot be extended beyond the first round.

Irrespective of ethnic origin and Asian versus non-Asian countries, about 60% of women in their 40s are estimated to have dense breasts.[8–10,19] In this study, 57·7% of the women were classified as having dense breasts (scores of 3 or 4 in the American College of Radiology Breast Imaging Reporting and Data System[34]) and will be reported in more detail in the future. Our study makes an important contribution to understanding of the efficacy of adjunctive ultrasonography in breast cancer screening of women aged 40–49 years and provides generalisable data. Ultrasonography could offer a low-cost way to increase sensitivity and detection rates of early cancers in women with dense breasts. Long-term follow-up is needed to assess whether the combined approach could reduce the frequency of advanced breast cancers at detection and breast cancer mortality.

Contributors

NO, TS, SY, and IT designed this study. NO, AS, TS, HS, ET, TE, AF, IT, MF, and TI did the literature search. NO, AS, MK, Y-FZ, YNS, and TI collected the data from the study sites. NO, TS, SY, Y-FZ, SK, AF, IT, TY, and YO planned the statistical analysis and analysed and interpreted the data. NO, AS, TS, MK, SY, Y-FZ, YNS, HS, SK, ET, TE, YO, MF, and TI drafted the paper. MK and Y-FZ did the systematic review. All authors contributed data and reviewed the drafts of the report. NO is the guarantor.

Declaration of interests

We declare no competing interests.

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