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BRIEF COMMUNICATION

Clinical Breast Examination: Preliminary Results from a Cluster Randomized Controlled Trial in India

Rengaswamy Sankaranarayanan, Kunnambath Ramadas, Somanathan Thara, Richard Muwonge, Jem Prabhakar, Paul Augustine, Muraleedharan Venugopal, Gopan Anju, Beela Sara Mathew

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Correspondence to: Rengaswamy Sankaranarayanan, MD, Screening Group, Early Detection and Prevention Section, International Agency for Research on Cancer, 150 cours Albert Thomas, Lyon 69008, France (e-mail: sankar@iarc.fr).

A cluster randomized controlled trial was initiated in the Trivandrum district (Kerala, India) on January 1, 2006, to evaluate whether three rounds of triennial clinical breast examination (CBE) can reduce the incidence rate of advanced disease incidence and breast cancer mortality. A total of 275 clusters that included 115 652 healthy women, aged 30–69 years, were randomly allocated to intervention (CBE; 133 clusters; 55 844 women) or control (no screening; 142 clusters; 59 808 women) groups. Performance characteristics (sensitivity, specificity, false-positive rate, and positive predictive value) of CBE were evaluated. An intention-to-treat analysis was performed for comparison of incidence rates between the intervention and control groups. Preliminary results for incidence are based on follow-up until May 31, 2009, when the first round of screening was completed. Of the 50 366 women who underwent CBE, 30 breast cancers were detected among 2880 women with suspicious findings in CBE screening that warranted further investigations. Sensitivity, specificity, false-positive rate, and positive predictive value of CBE were 51.7% (95% confidence interval [CI] = 38.2% to 65.0%), 94.3% (95% CI = 94.1% to 94.5%), 5.7% (95% CI = 5.5% to 5.9%), and 1.0% (95% CI = 0.7% to 1.5%), respectively. The age-standardized incidence rates for early-stage (stage IIA or lower) breast cancer were 18.8 and 8.1 per 100 000 women and for advanced-stage (stage IIB or higher) breast cancer were 19.6 and 21.7 per 100 000 women, in the intervention and control groups, respectively.

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Globally, 1 383 500 breast cancer cases and 458 400 breast cancer–specific deaths were recorded in 2008, half of which occurred in low- and middle-income countries (1). Breast cancer incidence and mortality are rising in low- and middle-income countries, and more than half of the breast cancer patients die of the disease because of limited access to early detection and treatment (1–8). Organized mammography screening is neither affordable nor feasible in low- and middle-income countries. Clinical breast examination (CBE) is an alternative screening option, but its effectiveness in reducing breast cancer mortality is not known. What we do know about the test performance and effectiveness of CBE is indirectly derived from studies in conjunction with mammography (9,10).

A cluster randomized controlled trial was initiated on January 1, 2006, to evaluate the effectiveness of CBE in reducing breast cancer mortality compared with no screening in Trivandrum district (Kerala, India). Breast cancer incidence and mortality rates are rising in India and account for one-fifth of cancer-related deaths among Indian women (1–3,11,12). The incidence and mortality rates among women aged 35–69 years range between 40–50 and 15–20 per 100 000 women, respectively (11,12).

In this study, we describe the methods and preliminary results of the trial based on follow-up through May 31, 2009, when the first round of CBE screening was completed. The study protocol was reviewed and approved by the institutional review boards of the International Agency for Research on Cancer (IARC) and Regional Cancer Center (RCC), Trivandrum. The study was designed to have 80% power at .05 level of statistical significance to assess whether CBE screening can reduce advanced breast cancer incidence and mortality rates by 30% and 20%, respectively. The aimed mortality reduction may be possible with early detection linked with adequate treatment in settings where two-thirds or more patients are diagnosed with advanced stages and one-third abandon or drop out from treatment (6,13,14).

Healthy women aged 30–69 years (115 652 women), with intact breasts and no history of breast cancer, were eligible to participate in this randomized trial that included 275 electoral wards (clusters) located in 17 suburban municipalities in Trivandrum district. Clusters were randomly assigned to two groups: 133 clusters (55 844 women) in the intervention group and 142 clusters (59 808 women) in the control group. Of the eligible women, 50 366 in the intervention group underwent CBE and 54 020 in the control group received education on cervical cancer prevention and advice on how to access cervical screening and treatment services (Figure 1). Women were identified through household surveys, and the purpose of the study was explained to them. After obtaining written informed consent from all participants, they were interviewed by 16 female health workers for sociodemographic and reproductive history.

All female health workers had a bachelor's degree. They were trained in creating breast awareness and CBE during a 3-week structured course at the RCC using silicone breast models followed by visual inspection and palpation of women with normal breasts, fibroadenosis, benign tumors and cancers, followed by periodic reorientation courses. The training included communication skills; visual inspection skills to assess breasts for asymmetry, visible lumps, skin changes, edema, nipple retraction, discharge

or axillary swellings; palpation of breast in a vertical grid pattern using pads of the middle three fingers with overlapping dime-sized circular movements while the woman is in a supine position with the ipsilateral arm overhead to flatten the breast; and palpation of axillary and clavicular regions in the sitting position. The trained female health workers provided CBE to women in their homes, a nearby health center, or a makeshift clinic in the locality. Silicone breast prostheses were used to familiarize women with tactile sensations of normal breast and breast lumps. Each CBE took 6–9 minutes, and the result reported as "CBE negative" when no abnormality was found and as "CBE positive" when suspicious findings warranted further investigations.

CBE-positive women were referred to a biweekly makeshift breast clinic set up at the screening project office, where they were clinically evaluated by a doctor, and those requiring further investigation were recommended for diagnostic mammography and/or ultrasonography and/or fine needle aspiration cytology or excision biopsy. Those confirmed with breast cancer were referred for further management.

The study subjects were followed for incident breast cancers and deaths by linkage with the Trivandrum district population-based cancer registry. Registry staff, unaware of study group assignments, collected data on the date of diagnosis, stage, treatment, and vital status of breast cancer patients by actively visiting hospitals and laboratories where breast cancers are diagnosed and treated (15) and assessed the cause of death using information collected from the municipal death registration offices, hospital records, and house visits. The screening project staff then matched the breast cancer cases and deaths with the study database.

An intention-to-treat analysis was performed for comparison of participant characteristics (with cluster as the unit of analysis and comparisons based on proportions or means within the cluster), intermediate outcomes, and incidence rates between the intervention and control groups. Participation (in screening, diagnosis, and treatment), screen-positivity rate, and performance characteristics (sensitivity, specificity, false-positive rate, and positive predictive value) of CBE were evaluated. Intermediate outcome measures included stage distribution of breast cancers based on Union for International Cancer Control (UICC) TNM stagings (16), primary tumor measuring 2 cm or less, negative axillary nodes, estrogen receptor-positive breast cancers, and breast conservation surgery The final outcome measure is breast cancer mortality, which is beyond the scope of this preliminary study. Comparisons of intermediate outcomes between the intervention and control groups were performed using the two-sided test on the equality of proportions using large sample statistics, which also gives exact *P* values. All *P* values less than .05 were considered statistically significant. Data were analyzed using STATA software package, version 11.0 (StataCorp, College Station, TX).

Preliminary results showed that household income, religion, education, age at menarche, proportion of postmenopausal women, parity, history of lactation, and contraceptive use were equally distributed in the intervention and control (data not shown) groups. Among the 2880 CBE-positive women, 1767 were judged to have a palpable lump and the remaining 1113 to have other abnormalities. Performance characteristics of CBE are shown in Table 1. CBE showed moderate sensitivity (51.7%, 95% confidence interval [CI] = 38.2% to 65.0%), high specificity (94.3%, 95% CI = 94.1% to 94.5%), high false-positive rate (5.7%, 95% CI = 5.5% to 5.9%), and low positive predictive value (1.0%, 95% CI = 0.7% to 1.5%) in our study. Our findings on sensitivity and specificity of CBE are consistent with a pooled analysis of six studies comprising of screening trials (17) and observational studies (18–20) (sensitivity 54.1%; specificity 94.0%) and randomized trials comparing CBE to no screening in Philippines and Mumbai, India (21,22). However, the Philippines trial (21) was closed after the first round because of low compliance with clinical follow-up and logistic barriers in ensuring diagnosis and treatment.

Among the intervention and control groups, 80 and 63 women, respectively, were diagnosed with breast cancer. Thirty breast cancers diagnosed in the intervention group were detected among the CBE-positive women. The distribution of early-stage (stage IIA or lower) breast cancer, advanced-stage (stage IIB or higher) breast cancer, tumor size 2 cm or less, lymph node–negative breast cancer, and breast conservation surgery in the intervention vs control groups were 43.8% (95% CI = 32.9% to 54.6%) vs 25.4% (95% CI = 14.6% to 36.1%) (*P* = .023), 45.0% (95% CI = 34.1% to 55.9%) vs 68.3% (95% CI = 56.8% to 79.7%) (*P* = .005), 18.8% (95% CI = 10.2% to 27.3%) vs 6.3% (95% CI = 0.3% to 12.4%) (*P* = .030), 50.0% (95% CI = 39.0% to 61.0%) vs 34.9% (95% CI = 23.1% to 46.7%) (*P* = .071), and 17.5% (95% CI = 9.2% to 25.8%) vs 4.8% (95% CI = −0.5% to

CONTEXT AND CAVEATS

Prior knowledge

Screening mammography is either not feasible or affordable in many low- and middle-income countries. It is not known whether screening by clinical breast examination (CBE) (visual inspection and palpation of breast by skilled health workers) can reduce breast cancer mortality.

Study design

A cluster randomized controlled trial was initiated in the Trivandrum district (India) on January 1, 2006, to evaluate whether three rounds of triennial CBE can reduce the incidence rate of advanced disease and breast cancer mortality. Incidence rates and intermediate outcomes in the intervention (underwent CBE screening) and control (no CBE screening) groups were analyzed by intent-to-treat analysis. Preliminary results are based on follow-up until May 31, 2009, when the first round of screening was completed.

Contribution

Of the 50366 CBE screened women, 30 among 2880 CBE-positive were diagnosed with breast cancer. Incidence rates of early-stage breast cancer were 18.8 and 8.1 per 100000 women in the intervention and control groups, respectively. Rates of advanced breast cancer (stage IIB or higher) were 19.6 and 21.7 per 100000 women, respectively.

Implication

Only further follow-up will clarify whether earlier detection of breast cancer because of CBE screening results in reduction in mortality.

Limitations

Mortality data will only be available after completion of three rounds of screening. Further follow-up will clarify whether earlier detection in the intervention group represents overdiagnosis or a lead time bias.

From the Editors

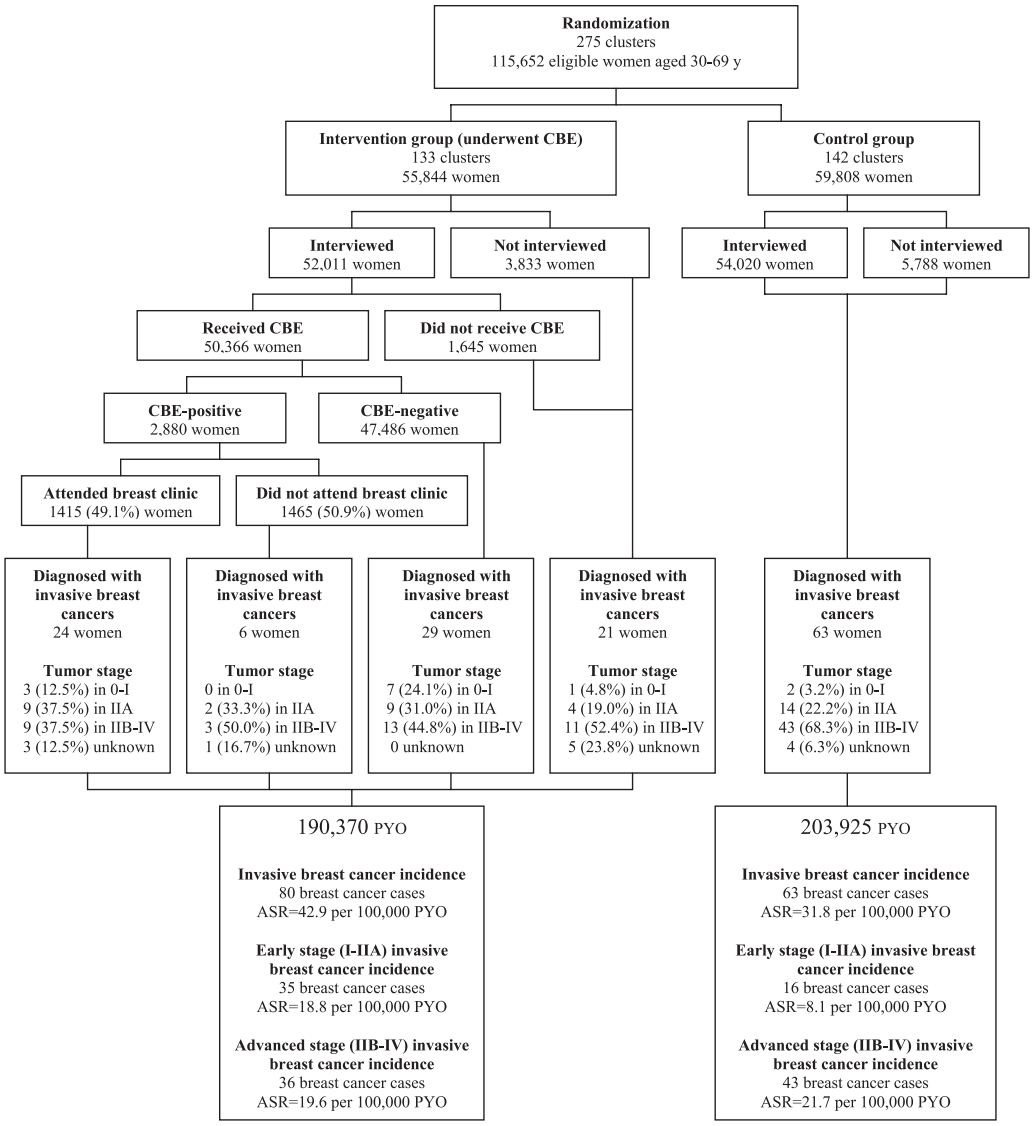

Figure 1. Enrollment of participants in the trial and outcomes. Eligible women were apparently healthy women aged 30–69 years, with intact breasts and no history of breast cancer. Women were interviewed for sociodemographic and reproductive history. Some of the eligible women were not interviewed or did not undergo clinical breast examination (CBE) (in intervention group) either because they were not present at the time when the female health workers visited their homes or did not attend a nearby health center or a makeshift clinic in the locality. Tumor staging was done based on Union for International Cancer Control TNM stage groupings (15). Age-standardized incidence rates per 100 000 person-years were calculated using the direct standardization method with the world standard population as a reference population (2,3). ASR = age-standardized rate; PYO = person-years of observation.

10.0%) (P = .019), respectively (Table 2). Intermediate outcomes and treatment modalities that showed non-statistically significant differences are also shown in Table 2 The age-standardized incidence rates of early-stage breast cancer were 18.8 and 8.1 per 100 000 women in the intervention and control groups, respectively; the corresponding rates of advanced breast cancer (stage IIB or higher) were 19.6 and 21.7 per 100 000 women, respectively (Figure 1).

In this study, we detected substantially higher numbers of early-stage breast cancers in the intervention group compared with the control group. An improvement in stage at diagnosis following CBE was reported both in the Philippines and Mumbai trials (21,22). A high frequency of early stages was observed in CBE-negative women, similar to that of CBE-positive women, in our study (Figure 1). It is worthwhile to investigate if a high degree of breast awareness among screened women, following health education and the tactile perception of normal breast and lumps using silicone breast models by women themselves during CBE contributed to the early detection, as opposed to low frequency of early disease among control women and nonparticipants in the intervention group (Figure 1). This underscores the need to assess whether creating breast awareness alone could achieve an equivalent impact to that of CBE on early detection and breast cancer mortality, with more favorable trade-off between benefits and harms.

We chose cluster randomization to avoid contamination between study groups; however, increased awareness among control group women because of sporadic messages in the media could not be ruled out. We included women as young as age 30 years because one-fifth of breast cancer

Table 1. Performance characteristics of clinical breast examination*

Characteristic	Performance values	95% CI
Intervention group†, No.	55844	—
Women screened, No.	50366	—
CBE positive, No.	2880	—
Screen-positivity rate (per 100 women screened)	5.7	5.5 to 5.9
Breast cancer detection rate (per 1000 women screened)	0.6	0.4 to 0.8
Screen-detected cancers (true-positive cancers), No.	30	—
Interval cancers (false-negative cancers), No.	28	—
False-positive rate (per 100)‡, %	5.7	5.5 to 5.9
Sensitivity§, %	51.7	38.2 to 65.0
Specificity‖, %	94.3	94.1 to 94.5
PPV¶, %	1.0	0.7 to 1.5
NPV#, %	99.9	99.9 to 100.0

* CI = confidence interval; CBE = clinical breast examination; PPV = positive predictive value; NPV = negative predictive value; — = not applicable.

† Apparently, healthy women aged 30–69 years were eligible for inclusion in the intervention group to undergo clinical breast examination.

‡ False-positive results included women who did not have breast cancer diagnosed within 3 years from a positive CBE. False-positive rate was defined as the proportion of women without breast cancer who had a CBE-positive screening test.

§ Sensitivity was calculated by dividing true positives by the sum of true positives plus false negatives.

‖ Specificity was defined as the proportion of women without cancer who were CBE negative after screening and was calculated by dividing true negatives by the sum of true negatives plus false positives.

¶ Positive predictive value was the proportion of screen-detected cancers among CBE-positive screens.

Negative predictive value was proportion of CBE negative with no breast cancer among the CBE-negative women.

cases occur between 30 and 40 years of age in low- and middle-income countries (3,11,12); CBE may detect early breast cancers, which may otherwise manifest clinically as late stages as women become older. Triennial screening was chosen for logistic convenience, and such an interval is used in the British screening program; shortening the interval to less than 3 years was predicted to have a relatively small effect on breast cancer mortality (23). A recent model-based cost-effectiveness study in India indicated that, even with an interval of 5 years, CBE may lead to considerable reductions in mortality and high numbers of life-years gained (24). The participation for CBE was high in our study because screening was provided in women's homes or nearby health centers. However, only half of the CBE-positive women subsequently attended the breast clinic in the project office, and it is worth investigating the reasons for low adherence to referral.

A major limitation of the study is only intermediate outcomes are reported, and the mortality data are not available at the moment. It remains to be seen whether the observed early detection during the prevalence round in our study, although encouraging, will be followed by decreased incidence of advanced cancers and statistically significantly reduced breast cancer mortality. Although no substantial declines in advanced disease following widespread mammography screening has consistently been reported in studies (25–27), such a reduction may be observed following CBE screening if clinically significant palpable cancers are detected early by CBE. Further follow-up will clarify this. Further follow-up will also clarify whether the earlier detection associated with CBE represents overdiagnosis or lead time or will lead to a reduction in advanced stages and in mortality. Both improved early detection and optimized and/or improved treatment incorporating advances in breast cancer

Table 2. Comparison of intermediate outcome measures and treatment modalities in the study groups*

Intermediate outcomes and treatment modalities	Intervention group		Control group		P†
	No.	% (95% CI)	No.	% (95% CI)	
Breast cancers	80‡		63		
Size of tumor, ≤2 cm	15	18.8 (10.2 to 27.3)	4	6.3 (0.3 to 12.4)	.030
Negative pathological node	40	50.0 (39.0 to 61.0)	22	34.9 (23.1 to 46.7)	.071
Early-stage breast cancers§	35	43.8 (32.9 to 54.6)	16	25.4 (14.6 to 36.1)	.023
Advanced-stage breast cancers‖	36	45.0 (34.1 to 55.9)	43	68.3 (56.8 to 79.7)	.005
Estrogen receptor–positive breast cancers	28	35.0 (24.5 to 45.5)	23	36.5 (24.6 to 48.4)	.85
Treatment received					
Surgery	61	76.3 (66.9 to 85.6)	50	79.4 (69.4 to 89.4)	.66
Radiotherapy	39	48.8 (37.8 to 59.7)	27	42.9 (30.6 to 55.1)	.48
Chemotherapy	61	76.3 (66.9 to 85.6)	46	73.0 (62.1 to 84.0)	.66
Hormone therapy	24	30.0 (20.0 to 40.0)	20	31.7 (20.3 to 43.2)	.82
Breast conservative surgery	14	17.5 (9.2 to 25.8)	3	4.8 (−0.5 to 10.0)	.019
Deaths	3	3.8 (−0.4 to 7.9)	6	9.5 (−2.3 to 16.8)	.16

* The outcome information was collected by Trivandrum population-based cancer registry staff from hospital medical records. An intention-to-treat analysis was performed to assess the differences in outcomes between the intervention and control groups.

† *P* values were calculated using a two-sided test on the equality of proportions using large sample statistics, which also gives exact *P* values.

‡ Thirty breast cancers were detected by clinical breast examination.

§ Early-stage included stage 0–IIA breast cancers. Staging was based on Union for International Cancer Control TNM stage groupings (15).

‖ Advanced-stage included Union for International Cancer Control stage IIB–IV breast cancers.

therapy (because of better awareness of breast cancer and its signs among women, early diagnosis and improved accessibility to diagnosis, and treatment because of health service reorganization) have contributed to improved survival and reduction or stabilization of breast cancer death rates even before widespread screening in several high- to moderate-resource countries (4,8,25–31). Our study will eventually provide important evidence on whether CBE is effective or not in reducing breast cancer mortality, thereby contributing to the formulation of public health policies for the early detection and control of breast cancer in low- and middle-income countries.

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Affiliations of authors: Screening Group, Early Detection and Prevention Section, International Agency for Research on Cancer, Lyon, France (RS, RM); Division of Radiotherapy (KR, GA, BSM), Division of Pathology (ST), Division of Surgical Oncology (JP, PA), and Division of Imageology (MV), Regional Cancer Center, Trivandrum, Kerala, India.