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A cluster randomized, controlled trial of breast and cervix cancer screening in Mumbai, India: methodology and interim results after three rounds of screening

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Cervix and Breast cancers are the most common cancers among women worldwide and extract a large toll in developing countries. In May 1998, supported by a grant from the NCI (US), the Tata Memorial Hospital, Mumbai, India, started a cluster-randomized, controlled, screening-trial for cervix and breast cancer using trained primary health workers to provide health-education, visual-inspection of cervix (with 4% acetic acid-VIA) and clinical breast examination (CBE) in the screening arm, and only health education in the control arm. Four rounds of screening at 2-year intervals will be followed by 8 years of monitoring for incidence and mortality from cervix and breast cancers. The methodology and interim results after three rounds of screening are presented here. Good randomization was achieved between the screening (n = 75360) and control arms (n = 76178). In the screening arm we see: High screening participation rates; Low attrition; Good compliance to diagnostic confirmation; Significant downstaging; Excellent treatment completion rate; Improving case fatality ratios. The ever-screened and never-screened participants in the screening arm show significant differences with reference to the variables religion, language, age, education, occupation, income and health-seeking behavior for gynecological and breast-related complaints. During the same period, in the control arm we see excellent participation rate for health education; Low attrition and a good number of symptomatic referrals for both cervix and breast.

Epidemiology

Of the estimated 470,000 new cases of cervix cancer diagnosed each year worldwide, 80% occur in developing countries and around 27% occur in India from where 126,000 new cases are diagnosed annually and over 71,000 deaths because of cervix cancer are reported each year.[1,2] Nearly 70% of cervix cancer patients in India present at stages III and IV.[3] Around 20% of women who develop cervix cancer die within the first year of diagnosis and the 5-year relative survival rate is 50%.[4]

Breast cancer is the most common cancer among women worldwide and is also the leading cause of cancer deaths in women. Breast cancer is responsible for an estimated 189,000 and 184,000 deaths in developed and developing countries respectively thus accounting for 16% and 12% of all cancer deaths in women. Although the age-standardized incidence of breast cancer is generally lower in developing countries than in developed countries (23.1 vs. 63.2 per 100,000 women), incidence rates are seen to vary widely between and within countries. Breast cancer is already more common than cervix cancer in a number of developing countries.[5] Data from developing countries suggests that age-standardized incidence rates of breast cancer are rising rapidly in low-incidence regions such as Africa and Asia.[6]

There are no organized screening programmes for cervix and breast cancers in India. Cervix Cytology and Mammography based screening programmes are difficult to organize in India because of issues related to absence of trained manpower, infrastructure, logistics, quality assurance, frequency of screening and costs involved. Simple tests like visual inspection of the cervix after application of 4–5% acetic acid (VIA) and Clinical Breast Examination (CBE) have generated considerable interest in several developing countries. VIA has been shown to have a sensitivity ranging from 67% to 90%.[7–11] Much of what we know about the benefit of the CBE is derived from indirect evidence. The sensitivity of CBE

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in picking up breast cancers in women who have not had much screening has been found to be much better than in those that have had regular screening.[12–16] Both VIA and CBE are inexpensive, do not require hi-tech equipment, and can be performed at the grass-root level by primary health workers.[17,18] Screening for cervix and breast cancers by VIA and CBE rather than Cytology and Mammography may therefore be a more appropriate strategy for resource poor settings.

The undisputable proof of the efficacy of screening tests for cervix and breast cancers would be their ability to reduce the cervix cancer incidence and mortality and breast cancer deaths when implemented in a program setting. Whether a screening program using VIA and CBE will be followed by a reduction in disease burden and mortality, and the cost effectiveness of this approach based on real program information remains to be established.

To determine the efficacy and cost-effectiveness of well planned health education programs along with screening for cervix and breast cancers using VIA and CBE, provided by trained primary health workers, in reducing the incidence of cervix cancer and mortality because of cervix and breast cancers, a Cluster-Randomized, Controlled, Trial was initiated in May 1998, by investigators from the Tata Memorial Hospital, in a low socioeconomic, previously unscreened population, in Mumbai, India. We present here for the first time the methodology, baseline information and the interim results after three screening rounds. At this stage of the trial the length and lead-time biases would affect the survival (case fatality). Both VIA and CBE being clinical examination tests, the over-diagnosis bias if any would be minimal [CBE unlike Mammography does not detect nonpalpable ductal carcinoma-*in-situ*. VIA does not detect HPV infections that are unlikely to progress to CIN, which would be otherwise detected by most HPV screening tests and to some extent by conventional cytology]. Findings of this stage of the trial will be as valuable, as that after the completion of four screens and the following four monitoring rounds, for planning appropriate low cost strategies for cervix and breast cancer screening in resource constrained populations.

The trial when completed is expected to provide valuable information on the utility of VIA and CBE as cost effective tools for reducing cervix and breast cancer mortality in resource constrained settings.

Material and Methods

Design

This is a cluster randomized, controlled, trial that compares the efficacy of health education, VIA and CBE, performed by trained primary health workers, in reducing the incidence of cervix cancer and mortality due to cervix and breast cancers among women aged 35–64, living in the slums of Mumbai, India.

Twenty slum clusters were selected by single stage, simple random sampling technique. These 20 clusters were then randomly assigned to the screening and control (health education) arms. We have therefore 10 clusters in the screening arm and 10 clusters in the control.

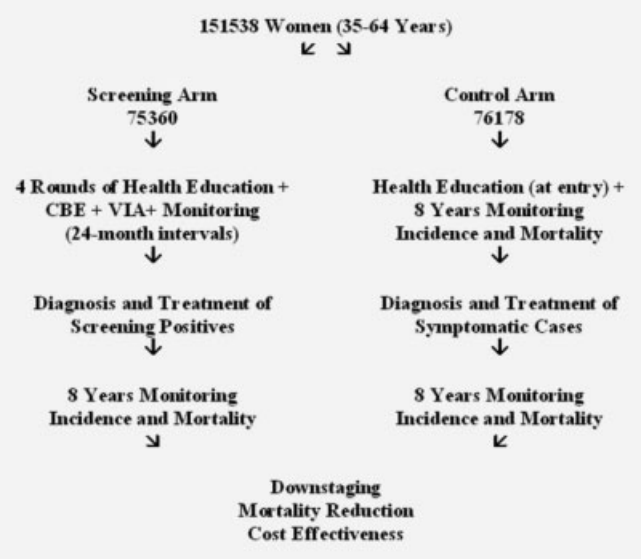

Figure 1. Screening trial schema.

The complete trial will include four rounds of health education, VIA and CBE at 24-month intervals, followed by 8 years of active monitoring for cervix cancer incidence and cervix and breast cancer mortality in the screening arm and one round of health education at entry, followed by active monitoring for self-reported cases and deaths due to breast and cervix cancers in the control arm. The schema of the trial is presented in Figure 1.

Incidence and mortality is monitored by:

a. Door-to-door survey by trained social workers
b. Data matching with the "Mumbai Municipal Death Records"
c. Data matching with the population-based "Mumbai Cancer Registry".

Sample size

We have recruited 75,360 and 76,178 eligible women in the screening and control arms respectively. After adjusting for intracluster correlation (intracluster correlation and design effect is 0.000085477 and 1.647 for cervix cancer variables and 0.00013758 and 2.0408 for breast cancer variables), with an alpha 0.05, the trial has 80% power to detect a 25% reduction in the cervix cancer incidence and a 40% reduction in the cervix cancer mortality. The trial also has 80% power to detect a 25% reduction in breast cancer mortality.

Training

Women with 10th grade education having good communication skills and preferably living in the selected clusters were recruited and trained for 4 weeks, to perform a speculum

examination of the cervix and identify VIA positive cases following application of 4% acetic acid and using halogen lamp illumination (the IARC manual for VIA was used for this training).[19] The same women were also trained to perform CBE using a modified version of the "Canadian National Breast Screening Study Protocol". Women with a graduate degree in Medical Social Work were recruited and trained for 4 weeks, for delivering a standard health education program for breast and cervix cancer, for conducting household surveys, introducing the consent forms, pre- and post-screening counseling and for follow-up communication. The primary health workers and the medical social workers are given 1-week annual refresher training.

Recruitment and informed consent

The trial is approved by the Scientific and Human Ethics Committees of the Tata Memorial Hospital. Technical and financial reports are submitted annually to these committees and the sponsor (National Cancer Institute, Bethesda, MD). The Tata Memorial Hospital has an internal data monitoring committee that monitors the trial, besides, there is an external data safety and monitoring board that meets at least once a year to review the trial.

Community rapport was first developed, followed by a baseline household survey for the enlistment and a brief sensitization of eligible women. Group health education programs using standard audio-visual kits were carried out next, in both the screening and control arms. In the screening arm the women were invited to participate in the cervix cancer screening (VIA) and breast cancer screening (CBE) program.

Inclusion criteria

Women between the ages of 35 and 64 years, living in the selected clusters for more than 1 year, were included in the trial. Women who had previous history of cervix and breast cancer (as evidenced by documented proof of histological diagnosis) were excluded from the trial.

Informed consent was taken after counseling by a medical social worker and a signature (or left hand thumb impression for illiterate women) was obtained on the consent letter that is printed in the local language. Another woman from the same community was invited to witness the procedure of informed consent and was then requested to sign on the consent form as a witness. All participating women received identity cards. Trained primary health workers then performed the VIA test and CBE. VIA and/or CBE positive women were referred to the "Preventive Oncology Clinic" at the Tata Memorial Hospital. A trained medical officer (expert) blinded to the primary health workers findings, rescreened (using the same VIA and CBE screening techniques and criteria) 5% of all the screened women, selected by simple random sampling, as part of a quality assurance program. At the Tata Memorial Hospital, the VIA positive referrals underwent colposcopy, conventional cytology and biopsies (in cases of positive colposcopic findings). Histologically confirmed CIN II and above lesions and invasive cancers were treated as per the existing treatment protocols at the Tata Memorial Hospital. The CBE positive referrals underwent a CBE by a surgeon specialized in the management of breast cancer, mammography, sonography, core needle biopsy or a simple excision biopsy of the lump. Histologically confirmed cases of breast cancer were treated as per the existing treatment protocols at the Tata Memorial Hospital.

The same procedures of community rapport building, baseline survey and health education were followed in the control arm. The eligible women from the control arm, however, were not invited for screening. These women were provided an identity card and information about the availability of screening and treatment services for cervix and breast cancers at the Tata Memorial Hospital. Women from the control arm who approached the Preventive Oncology Clinic at the Tata Memorial Hospital, through symptomatic referral, seeking screening or treatment for cervix or breast cancers, were offered the same diagnostic and treatment services as that received by women from the screening arm.

Data recording, management and analysis

Sociodemographic and risk factor information was manually recorded by medical social workers prior to the screening. The primary health worker records the clinical findings during screening. Referred women have medical case history sheets, investigation and treatment procedures recorded in the hospital files. All the above information is transferred to an electronic database. Data analysis is carried out in STATA^{tm} 8.2. The "Intracluster Correlation" and "Design Effect" was calculated using MLWIN software. Analysis is on intention-to-treat basis.

Results

The trial began recruiting in May 1998. Three rounds of screening were completed in May 2005.

Socio-demographic characteristics

At the baseline, a comparison of the important socio-demographic variables showed a good equivalence of the subjects in the screening and control arms. In both arms, the women had a mean age of 45 years, mean age at menarche was 14 years, 54% were pre-menopausal, 2% peri-menopausal and 44% post-menopausal. Mean age at menopause for the post-menopausal women was 43 years. The women were mostly married (83%), mean age at marriage was 18 years. The women had on an average four children, the mean age at first childbirth was 21 years, and around 10% had consulted a health care provider previously for gynecological complaints. Over 98% had breastfed their children, less than 1% had a family history of breast cancer and a little over 1% had consulted a health care provider previously for breast-related symptoms. In both arms, around 35% of the women had no formal schooling, around 89–92% were homemakers, around

45–47% lived below the poverty line and were mostly Hindus (78–79%) (Table 1).

Participation, compliance, downstaging and mortality reduction

Significant differences were seen between the ever-screened and the never-screened participants in the screening arm, with reference to important variables like age ($p < 0.001$), education ($p < 0.001$), occupation ($p = 0.002$), income ($p < 0.001$), language ($p < 0.001$), previous history of gynecologic consultation ($p < 0.001$), previous history of consultation for breast-related complaints ($p = 0.004$) and family history of breast cancer ($p = 0.057$) (Table 2).

Cervix cancer screening

Out of 75,360 eligible women listed in the screening arm 51,145 (67.87%), 41,354 (57.84%) and 36,643 (54.26%) women participated in the first, second and third screening rounds for cervix cancer.

The screening positivity rates for VIA were 0.89%, 1.11% and 0.95% during the first, second and third rounds. Compliance rates for diagnostic confirmation following a positive VIA test were 75.15%, 78.51% and 83.49% during the first, second and third rounds of screening. (Table 3). Cohen's kappa for the agreement rates for VIA between the expert and the primary health workers was 0.893.Histologically confirmed cases of cervix cancer were 20, 12 and 17 (around 0.03%, 0.02% and 0.03% of the eligible women) during the first, second and third rounds of screening. Interval cervix cancers between rounds one-two and two-three were 4 and 22 cases (Table 3). HSIL and LSIL cases were 18 and 62 in the first round, 8 and 49 in the second round, and 18 and 24 in the third round. The mean age at detection for the screening detected cervix cancer cases was 47.41 years. The mean age at diagnosis for interval cervix cancers was 50 years. Till the time of completion of three rounds of screening 18 deaths out of the total 85 cervix cancer cases were recorded (case fatality rate 21.18%).

In the control arm, we had an unusually high participation rate of 90.88% for the health education at entry. Even during the second and third rounds, that had only door-to-door surveillance for cervix and breast cancer morbidity and mortality, there was a participation rate of 86.98% and 88%. An overall attrition of 11.18% is seen at the end of the third round. During the corresponding period, there were a good number of symptomatic referrals from the control arm. For cervix we had 43 symptomatic referrals with eight histologically confirmed cases at round one, 51 symptomatic referrals with 28 histologically confirmed cases at round two, and 48 symptomatic referrals with 14 histologically confirmed cases at round three (Table 4). For the women in the control arm the mean age at detection of cervix cancer was 50.34 years. During this period 15 deaths out of the 50 reported cervix cancer cases were recorded (case fatality 30%).

Out of the 20 cases of cervix cancer detected during the first round of screening 16 (80%) were detected in early stages of the disease (stages 0/I/II) and 4 (20%) were detected in advanced stages (stages III/IV). Out of the 12 cases of cervix cancer detected during the second round 10 (88.33%) of the cases were detected in early stages and 2 (16.67%) in advanced stages. Of the 14 interval cervix cancers detected between rounds one and two, disease-staging information was unavailable for two cases, seven (58.33%) were diagnosed in early stages and five (41.67%) were diagnosed in advanced stages. All 17 cases of cervix cancer detected during the third round were detected in early stages (100%). Of the 22 interval cervix cancers detected between rounds two and three, staging information was unavailable for 2 cases, 12 (60%) were diagnosed in early stages and 8 (40%) were diagnosed in advanced stages (Table 5).

In the control arm (during the period corresponding to the first round of screening in the screening arm) eight cases of cervix cancer were diagnosed, staging information was unavailable for one case, one (14.29%) was diagnosed in early stages and six (85.71%) were diagnosed in advanced stages of the disease. During the second round 28 cases of cervix cancers were diagnosed, staging information was unavailable for 4 cases, 9 (37.50%) were diagnosed in early stages and 15 (62.50%) in advanced stages of the disease. During the third round 14 cases of cervix cancers were diagnosed, staging information was unavailable for two cases, four (33.33%) were diagnosed in early stages and eight (66.67%) in advanced stages of the disease (Table 6).

Breast cancer screening

Out of 75,360 eligible women listed in the screening arm 69,227 (90.88%), 62,755 (86.98%) and 59,543 (88.00%) women participated in the first, second and third screening rounds for breast cancer. The screening positivity rates for CBE were 0.46%, 0.77% and 0.94% during the first, second and third rounds. Compliance rates for diagnostic confirmation following a positive CBE were 68%, 70.60% and 78.06% during the first, second and third rounds of screening (Table 7). Histologically confirmed cases of breast cancer were 32, 24 and 25 (around 0.04%, 0.03% and 0.04%) during the first, second and third rounds of screening. Interval cancers between rounds one-two and two-three for breast cancer were 27 and 17 (Table 7). The mean age at detection for the screening detected breast cancer cases was 49.80 years. The mean age at diagnosis for interval breast cancers was 47.07 years. Till the time of completion of three rounds of screening, 22 deaths out of the total 125 breast cancer cases were recorded (case fatality rate 17.6%).

During the corresponding period, in the control arm, there were a good number of symptomatic referrals for breast cancer too, we had 18 symptomatic referrals with three histologically confirmed cases at round one, 61 symptomatic referrals with 39 histologically confirmed cases at round two, and 76 symptomatic referrals with 45 histologically confirmed

Table 1. Distribution by important socio-demographic variables at entry

Variables		Screening arm (n =75360) column %	Control arm (n = 76178) column %
Age Groups	35–39	30.22	30.00
	40–44	23.03	22.66
	45–49	18.86	18.54
	50–54	12.53	12.57
	55–59	08.05	08.05
	60–64	07.31	08.17
Mean age (SD)		44.84 (07.86)	44.92 (08.01)
Education	Literate	04.14	04.82
	Illiterate	35.18	35.73
	School	56.23	54.44
	High School +	04.45	05.01
Income per month	<Rs. 500	47.19	45.40
	Rs. 501–1000	46.59	48.93
	>Rs.1000	06.22	05.67
Occupation	Housewife	88.60	91.93
	Service	02.81	02.58
	Manual labour	06.29	04.06
	Self-employed	02.30	01.43
Religion	Hindu	77.89	79.02
	Muslim	12.99	11.39
	Others	09.12	09.59
Language	Marathi	56.87	53.35
	Hindi	17.15	20.06
	Others	25.98	26.58
Marital status	Unmarried	00.40	00.60
	Married	82.59	82.62
	Widowed	16.48	16.38
	Divorced	00.53	00.40
Menstrual status	Premenopausal	53.78	53.85
	Postmenopausal	43.76	44.04
	Perimenopausal	02.46	02.11
Mean age at menarche (SD)		13.79 (01.26)	13.85 (01.24)
Mean age at menopause (SD)		43.36 (04.96)	43.62 (04.87)
Mean age at marriage (SD)		17.99 (03.89)	17.85 (03.82)
Mean age at first child birth (SD)		20.82 (03.70)	20.74 (03.61)
Average number of children (SD)		3.58 (01.61)	3.56 (01.61)
Previous consultation for gynecologic complaints	Yes	10.70	09.87
	No	89.30	90.13
Previous consultation for breast related complaints	Yes	01.21	01.06
	No	98.79	98.94
Family history of breast cancer	Yes	00.70	00.68
	No	99.30	99.32

Table 2. Distribution of screening participants and non-participants, in the screening arm, by important socio-demographic variables

Variables	Ever-screened N: 63061 (row %)	Never-screened N: 12299 (row %)	
Age group			
35–44	56.08	38.48	$p < 0.001$
45–59	37.58	49.16	
60–64	06.34	12.36	
Mean age (SD)	44.32 (07.68)	47.54 (8.24)	
Religion			
Hindu	78.44	75.00	$p < 0.001$
Muslim	12.52	15.44	
Christian	03.29	03.58	
Buddhist	03.58	03.08	
Others	02.17	02.90	
Occupation			
Housewife	88.45	89.35	$p = 0.002$
White-collar worker	02.89	02.42	
Manual labour	06.38	05.82	
Self employed (small business)	02.28	02.41	
Education			
Literate	04.05	04.59	$p < 0.001$
Illiterate	33.97	41.60	
School	57.43	49.92	
High school	03.52	02.84	
Graduates	01.03	01.05	
Income			
Less than Rs. 500 p.m.	47.51	45.47	$p < 0.001$
Rs. 501–1000 p.m.	46.27	48.28	
Over Rs. 1000 p.m.	06.22	06.25	
Language			
Marathi	57.98	51.06	$p < 0.001$
Hindi	17.21	16.84	
Gujarati	06.53	10.46	
Others	18.28	21.64	
Any previous consultation for Gynaec related complaints			
Yes	04.67	42.03	$p < 0.001$
No	95.33	57.97	
Any previous consultation for breast-related complaints			
Yes	01.24	00.75	$p = 0.004$
No	98.76	99.25	
Family history of breast cancer			
Yes	00.69	00.93	$p = 0.057$
No	99.31	99.07	

cases at round three (Table 8). For the women in the control arm the mean age at detection of breast cancer was 49.79 years. During this period 10 deaths out of the 87 reported breast cancer cases were recorded (case fatality rate 11.49%). Cohen's kappa for the agreement rates for CBE between the expert and the primary health workers was 0.849.

Out of the 32 cases of breast cancer detected during the first round of screening disease-staging information was unavailable for two cases, 21 (70%) were detected in early stages (stages 0/I/II) and 9 (30%) in advanced stages of the disease (stages III/IV). Out of the 24 cases of breast cancer detected during the second round staging information was unavailable for two cases, 15 (68.18%) cases were detected in early stages and seven (31.82%) in advanced stages. Of the 27 interval breast cancers reported between screening rounds one and two, staging information was unavailable for four cases, 17 (73.91%) were diagnosed in early stages and six (29.09%) in advanced stages. Out of the 25 breast cancer cases detected during the third screening round, staging information was unavailable for four cases, 12 (57.14%) cases were detected in early stages and nine (42.86%) in advanced stages. Of the 17 interval breast cancers reported between rounds two and three, staging information was unavailable for three cases, 13 (92.86%) were diagnosed in early stages and one (7.14%) in advanced stage (Table 9). In the control arm during first round three cases of breast cancer were diagnosed, two (67%) were diagnosed in early stages and one (33%) in advanced stage of the disease. During the second round, 39 breast cancer cases were diagnosed, staging information was unavailable for six cases, 18 (54.55%) were diagnosed in early stages and 15 (45.45%) in advanced stages of the disease. During the third round, 45 breast cancer cases were diagnosed, staging information was unavailable for six cases, 18 (46.15%) were diagnosed in early stages and 21 (53.85%) in advanced stages of the disease (Table 10).

Discussion

Screening for cervix and breast cancers in resource poor settings presented a great challenge, particularly when the population did not perceive this as a priority. Adhering to the rigors of a randomized controlled trial presented further hardships in a population that was probably being screened for the first time. Although some amount of information was available through the electoral rolls and census data, we found the information inadequate and the basic demographic information of the selected population had to be collected on first-hand basis.

A good equivalence of the participants in the screening and control arms is seen. The mean age at menarche (14 years) and at menopause (43 years) is typical of women from low-nutritional settings. Marriage is universal with an average of four children and breastfeeding is the norm (theoretically all the above variables are protective against breast cancers).

Table 3. (Cervix): screening participation and diagnosis in the screening arm

Screening round	Eligible women	Screened (% of eligible)	Screen positive (% of eligible)	Compliance-to-diagnosis (% of screen +ve)	Histologically confirmed (% of eligible)
One	75,360	51,145 (67.87%)	672 (0.89)	505 (75.15%)	20 (0.03%)
Interval					4
Two	71,500 (attrition 5.12%)	41,354 (57.84%)	791 (1.11%)	621 (78.51%)	12 (0.02%)
Interval					22
Three	67,530 (overall attrition 10.39%)	36,643 (54.26%)	642 (0.95%)	536 (83.49%)	17 (0.03%)

Table 4. (Cervix): participation in health education/monitoring and symptomatic referrals in the control arm

Health education/ monitoring round	Eligible women	Compliance to health education/monitoring (% of eligible)	Symptomatic referrals	Histologically confirmed (% of eligible)
One	76,178	69,227 (90.88%)	43	8 (0.01%)
Two	72,145 (attrition 5.29%)	62,755 (86.98%)	51	28 (0.04%)
Three	67,664 (overall attrition 11.18%)	59,543 (88.00%)	48	14 (0.02%)

Table 5. Staging at diagnosis (cervix-screening arm)

Screening round	Early stage (0 + I + II)	Late stage (III + IV)	Staging not available	Total
One	16 (80.00%)	4 (20.00%)	0	20
Interval cancers	7 (58.33%)	5 (41.67%)	2	14
Two	10 (88.33%)	2 (16.67%)	0	12
Interval cancers	12 (60.00%)	8 (40.00%)	2	22
Three	17 (100.00%)	0	0	17

Table 6. Staging of symptomatic referrals at diagnosis (cervix-control arm)

HE/monitoring rounds	Early stage (0 + I + II)	Late stage (III + IV)	Staging not available	Total
One	1 (14.29%)	6 (85.71%)	1	8
Two	9 (37.50%)	15 (62.50%)	4	28
Three	4 (33.33%)	8 (66.67%)	2	14

The consistently high participation rates for both cervix and breast cancer screening are very good considering that over 35% were illiterate and were exposed to cervix and breast cancer education and screening for the first time. VIA screening was done at least once for 83.68%, twice for 57.68% and thrice for 30% women. CBE screening was done at least once for 93.75%, twice for 70.35% and thrice for 39.09% women. The only other trial that compared breast cancer screening by CBE with no screening was conducted in Philippines and had a 91.5% participation rate in the first round of screening. The Philippines trial that was planned for five annual examinations however ceased after the first round because of very low compliance with clinical follow-up.[12]

Low overall attrition 10.39% (screening arm) and 11.18% (control arm) are good for long-term retaining and follow-up of the cohort. For VIA, which is a visual test, the screening positivity rates have remained steady through the three screening rounds, whereas for CBE, which is a tactile test, the screening positivity rates increased significantly after the first round. It is probably easier to adapt with visual learning skills when compared with tactile learning skills. The increased CBE positivity rates could also be partly attributed to the emergence of masses, including some cancers, over time. The VIA positivity rates are very low when compared with rural studies in India but are close to the rates for urban Mumbai.[7–11] The CBE positivity rates in our trial are lower than the Philippines trial.

The success of a screening program ultimately lies in the number of screen positives successfully treated and the deaths prevented, which is directly dependent on the percentage of screen-detected cases that actually seek further diagnostic and treatment services. In this trial the average compliance rates for diagnostic confirmation for cervix (78.95%) and breast (73.01%) and for treatment completion for cervix (94%) and for breast (92%) in the screen-detected cases is very good considering the educational and socioeconomic background of the women screened. The mean age at detection for breast cancer (48.5 years for the screen detected and 49.5 years for the symptomatic referrals from the control arm) is almost 5–7 years earlier than what is typically seen in mammography based screening programs in richer countries.[20] This despite the presence of a number of protective factors is puzzling

Table 7. (Breast): screening participation and diagnosis in the screening arm

Screening round	Eligible women	Screened (% of eligible)	Screen positive (% of eligible)	Compliance- to-diagnosis (% of screen +ve)	Histologically confirmed (% of eligible)
One	75,360	56,985 (75.62%)	350 (0.46%)	238 (68.00%)	32 (0.04%)
Interval					27
Two	71,500	49,012 (68.55%)	551 (0.77%)	389 (70.60%)	24 (0.03%)
Interval					17
Three	67,530	47,133 (69.80%)	638 (0.94%)	498 (78.06%)	25 (0.04%)

Table 8. (Breast): participation in health education/monitoring and symptomatic referrals in the control arm

Health education/ monitoring round	Eligible women	Compliance to health education/ monitoring (% of eligible)	Symptomatic referrals	Histologically confirmed (% of eligible)
One	76,178	69,227 (90.88%)	18	3 (0.004)
Two	72,145	62,755 (86.98%)	61	39 (0.05)
Three	67,664	59,543 (88.00%)	76	45 (0.07%)

Table 9. Staging at diagnosis (breast-screening arm)

Screening round	Early stage (0 + I + II)	Late stage (III + IV)	Staging not available	Total
One	21 (70.00%)	9 (30.00%)	2	32
Interval Cancers	17 (73.91%)	6 (26.09%)	4	27
Two	15 (68.18%)	7 (31.82%)	2	24
Interval	13 (92.86%)	1 (7.14%)	3	17
Three	12 (57.14%)	9 (42.86%)	4	25

Table 10. Staging of symptomatic referrals at diagnosis (breast-control arm)

HE/monitoring rounds	Early stage (0 + I + II)	Late stage (III + IV)	Staging not available	Total
One	2 (66.67%)	1 (33.33%)	0	3
Two	18 (54.55%)	15 (45.45%)	6	39
Three	18 (46.15%)	21 (53.85%	6	45

and requires further study of the possibility of the presence of other risk factors.

Significant differences are seen, between the ever-screened and the never-screened participants in the screening arm, with reference to the variables like age, religion, language, income, education, occupation, family history of breast cancer and health seeking behavior for gynecological and breast-related complaints. This information would be very valuable for planning cervix and breast cancer screening programs in other similar communities.

Using a Two-tailed "Fisher's Exact Test" we can see that the intermediate end point, i.e., significant downstaging for cervix cancer, is seen right from the first round ($p = 0.008$) and remains significant through rounds two ($p = 0.022$) and three ($p < 0.001$). Downstaging for breast cancer is not evident in the first ($p = 1.00$) and second ($p = 0.467$) rounds but reaches significant levels in the third round ($p = 0.004$). We should expect this to improve as the trial progresses. The case fatality risk ratio for cervix cancer is 0.71 and for breast cancer is 1.53 at this stage. The difference in mortality between the screening and control arms for cervix cancer ($p = 0.344$) and breast cancer ($p = 0.304$) has not reached levels of statistical significance. We expect to see a significant improvement in the case fatality ratios too as the trial progresses.

The control arm that received only one round of health education has also seen a fair number of symptomatic referrals, suggesting that, for very low resource settings where population based screening, even with VIA and CBE by primary health workers is not feasible, health education combined with access to screening and treatment services, may be a simple and feasible strategy for reduction in cervix and breast cancer mortality.

The excellent agreement between expert and the primary health workers is a real achievement for resource poor settings where we expect that a vast majority of the population would have to depend on primary health workers for their routine health care needs.

On the basis of the findings of the interim analysis we conclude that this trial, that has been planned for four screening rounds and monitoring for another 8 years thereafter, is progressing as per plan and is expected to provide further clues to the feasibility and efficacy of VIA and CBE based cervix and breast cancer screening in low resource settings as it progresses.

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