



C I R C U L A R

Imphal, the 14th October, 2026

No. 216/RIMS-MRU/2026: It is to notify that, the 17th **Research Masterclasses 2026**, of the Department of Health Research, Ministry of Health and Family Welfare, Government of India, will be conducted virtually, on **30th October, 2026 (Friday)**.

2. All the faculties (RIMS, Dental College and College of Nursing), members of EC, LRAC of MRU, Principal Investigators undertaking MRU funding projects (including under process projects) and residents are invited to attend the session at **Sushruta Hall, RIMS, Imphal**.

Date: 30.10.2026 (Friday)

Time: 3:00 PM onwards

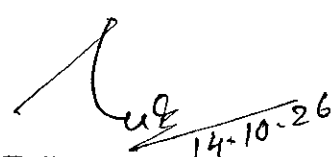
Venue: Sushruta Hall, RIMS, Imphal

Event Name: Research Masterclass under DHR-ICMR Research Grand Rounds

Speaker Name: Dr. Rajendra A. Badwe, Hon. Professor Emeritus, Ex-Director, Tata Memorial Centre, Mumbai

3. The **research paper** to be discussed during the Masterclass will be uploaded on the **RIMS website** and circulated to the concerned Departments / Colleges through official email.

4. As per the directives issued by the DHR, **maximum participation** from our institute is highly encouraged.


(Prof. T. Jeetenkumar Singh)
Nodal Officer
MRU, RIMS, Imphal

Copy to:

1. The P.S. to Director, RIMS, Imphal for kind information of Director
2. The P.A. to Medical Superintendent, RIMSH, Imphal for kind information
3. The Dean (Academic), RIMS, Imphal for kind information.
4. The Principal, Dental College, RIMS, Imphal
5. The Principal, College of Nursing, RIMS, Imphal
6. All Heads of Departments, RIMS, RIMS, Imphal
7. The Chairperson/Co-Chairperson, LRAC, MRU, RIMS, Imphal
8. The Internal Member, LRAC, MRU, RIMS, Imphal
9. The Member, EC, MRU, RIMS, Imphal
10. The Principal Investigator, MRU, RIMS, Imphal
- ✓ 11. The IT Cell, RIMS, Imphal – with a request for uploading the notice in the website & technical support on 30.10.26
12. Asst. Engineer (Elect. /Civil), RIMS, Imphal - with a request for ensuring uninterrupted power supply & optimum AC functioning.
13. The Care Taker, Sushruta Hall, RIMS, Imphal - for proper upkeep of the venue & accompanying facilities.
14. Guard file.

No. R.11016/03/2025-HR
भारत सरकार/Government of India
स्वास्थ्य एवं परिवार कल्याण मंत्रालय/Ministry of Health & Family Welfare
स्वास्थ्य अनुसंधान विभाग/Department of Health Research

2nd Floor, IRCS Building
Red Cross Road, New Delhi – 110001
Dated 12.10.2026

To
The Dean/ Principal/ Director of Medical Colleges/ Institutes

Subject: Request to attend Research Masterclasses for MRU network– reg.

Sir/Madam,

DHR-ICMR has initiated a dedicated platform to conduct Research Grand Rounds to strengthen the National research ecosystem through sustained collaboration and knowledge exchange. The objectives of the Research Grand Rounds are as follows:

- I. To deliberate on research methodologies, analytical tools, and emerging scientific approaches
- II. To strengthen the methodological understanding amongst researchers needed to implement different kinds of research.
- III. To foster collaboration and connectivity across research institutions

2. These Research Grand Rounds will be organized as monthly webinars entitled 'Research Masterclass' proposed around the last Friday of each month. The speakers for these Research Masterclasses will be eminent research scientists in the country who will be discussing their original research work in details from methodological point of view.

3. The next Research Masterclass is scheduled for **30.10.2026 (Friday) at 3:00 PM**. The speaker is **Dr. Rajendra A. Badwe, Hon. Professor Emeritus**, Ex - Director, Tata Memorial Centre, Mumbai. The research paper to be discussed during the research masterclass is enclosed. The link for the research masterclass will be shared shortly.

4. Accordingly, it is requested to kindly disseminate the information in your institution and ensure maximum participation in Research Masterclass. Your institute is requested to share at least two questions related to research paper attached on the following email: **dhr-mru@gov.in** latest by 27.10.2026. These questions will be discussed with the speaker during masterclass.

Encls: As above

Yours faithfully,



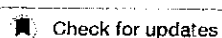
(Dharkat R. Luikang)

Deputy Secretary to the Government of India

Copy to: The Nodal Officer of Multi-Disciplinary Research Units (MRUs)



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Effect of screening by clinical breast examination on breast cancer incidence and mortality after 20 years: prospective, cluster randomised controlled trial in Mumbai

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Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2021;372:n256
<http://dx.doi.org/10.1136/bmj.n256>

Accepted: 19 January 2021

ABSTRACT OBJECTIVE

To test the efficacy of screening by clinical breast examination in downstaging breast cancer at diagnosis and in reducing mortality from the disease, when compared with no screening.

DESIGN

Prospective, cluster randomised controlled trial.

SETTING

20 geographically distinct clusters located in Mumbai, India, randomly allocated to 10 screening and 10 control clusters; total trial duration was 20 years (recruitment began in May 1998; database locked in March 2019 for analysis).

PARTICIPANTS

151 538 women aged 35-64 with no history of breast cancer.

INTERVENTIONS

Women in the screening arm (n=75 360) received four screening rounds of clinical breast examination (conducted by trained female primary health workers) and cancer awareness every two years, followed by five rounds of active surveillance every two years. Women in the control arm (n=76 178) received one round of cancer awareness followed by eight rounds of active surveillance every two years.

MAIN OUTCOME MEASURES

Downstaging of breast cancer at diagnosis and reduction in mortality from breast cancer.

RESULTS

Breast cancer was detected at an earlier age in the screening group than in the control group (age 55.18 (standard deviation 9.10) v 56.50 (9.10); $P=0.01$), with a significant reduction in the proportion of women with stage III or IV disease (37% (n=220) v 47% (n=271), $P=0.001$). A non-significant 15% reduction in breast cancer mortality was observed in the screening arm versus control arm in the overall study population (age 35-64; 20.82 deaths per 100 000 person years (95% confidence interval 18.25 to 23.97) v 24.62 (21.71 to 28.04); rate ratio 0.85 (95% confidence interval 0.71 to 1.01); $P=0.07$). However, a post hoc subset analysis showed nearly 30% relative reduction in breast cancer mortality in women aged 50 and older (24.62 (20.62 to 29.76) v 34.68 (27.54 to 44.37); 0.71 (0.54 to 0.94); $P=0.02$), but no significant reduction in women younger than 50 (19.53 (17.24 to 22.29) v 21.03 (18.97 to 23.44); 0.93 (0.79 to 1.09); $P=0.37$). A 5% reduction in all cause mortality was seen in the screening arm versus the control arm, but it was not statistically significant (rate ratio 0.95 (95% confidence interval 0.81 to 1.10); $P=0.49$).

CONCLUSIONS

These results indicate that clinical breast examination conducted every two years by primary health workers significantly downstaged breast cancer at diagnosis and led to a non-significant 15% reduction in breast cancer mortality overall (but a significant reduction of nearly 30% in mortality in women aged ≥ 50). No significant reduction in mortality was seen in women younger than 50 years. Clinical breast examination should be considered for breast cancer screening in low and middle income countries.

TRIAL REGISTRATION

Clinical Trials Registry of India
CTRI/2010/091/001205; ClinicalTrials.gov
NCT00632047.

Introduction

The incidence of breast cancer is rising in all countries of the world,¹ but particularly so in low and middle income countries.² For example, in Mumbai, India, the incidence of breast cancer has risen by nearly 40% between 1992 and 2016,³ and breast cancer is the leading cause of death from cancer in women in most states of India.⁴ Breast cancers in low and middle income countries are frequently detected in advanced stages, and consequently, more than half the global deaths from breast cancer occur in these countries.⁵

WHAT IS ALREADY KNOWN ON THIS TOPIC

Breast cancer screening by mammography reduces mortality in women aged 50 and older, but its effectiveness in women younger than 50 is questionable. Breast self-examination has not been proven to be an effective method for early detection of breast cancer. Whether screening by clinical breast examination can reduce mortality from breast cancer is not known.

WHAT THIS STUDY ADDS

In a 20 year study, clinical breast examination conducted by trained female health workers in Mumbai led to a downstaging of breast cancer at diagnosis and reduced mortality from the disease by nearly 30% in women aged 50 and older, but with no mortality reduction seen in women younger than 50. A 5% reduction in all cause mortality was seen in the screening arm compared with the control arm, but was not statistically significant. Clinical breast examination should be considered for breast cancer screening in low and middle income countries.

While mammography is the established screening tool in developed countries, the screening modality that is appropriate for India and other low and middle income countries remains undetermined.⁶⁻⁷ Breast self-examination might not be useful as a general strategy,⁸⁻⁹ largely because it is not feasible to ensure women perform it well. However, a case-control study based on data from the Canadian National Breast Screening Study showed that in a controlled setting, where the quality of breast self-examination was carefully evaluated, women who conducted the procedure benefitted well.¹⁰ Mammography, which is widely practiced in Western countries, might not be an appropriate approach in low and middle income countries because of its cost and complexity.⁶⁻¹¹ Furthermore, most women in low and middle income countries are younger than 50, and mammography is less effective in this age group.¹²⁻¹⁵

Clinical breast examination (CBE) is an alternative screening method, and was one of the components of screening in two important randomised trials.¹⁶⁻¹⁸ The Health Insurance Plan Study was conducted in greater New York, USA, in the 1960s during which 62 000 women aged 40-64 were randomised to receive yearly CBE plus mammography or no screening.¹⁴ During the 1960s, mammography was in its early stages of development, and a disproportionately large number of breast cancers were detected by CBE. An estimated two thirds of the reduction in breast cancer mortality in the Health Insurance Plan study could be attributed to CBE.¹⁶

To determine the relative contributions of mammography and CBE in the reduction of breast cancer mortality, the Canadian National Breast Screening Study was initiated in the early 1980s. In one of two parts of the study, women aged 50-59 were randomly allocated to receive either yearly CBE plus mammography or yearly CBE alone.¹⁵ The trial had the potential to determine whether mammography provided any added benefit in terms of mortality reduction in addition to that provided by CBE. After 13 years of follow-up and five rounds of screening, deaths from breast cancer in the two arms were almost identical.¹⁵ These results remained unchanged after 25 years of follow-up.¹⁷ The findings of the Health Insurance Plan Study and Canadian National Breast Screening Study provided a strong argument for a randomised trial to compare CBE with no screening,¹⁸⁻¹⁹ and formed the basis for the Mumbai study.²⁰ This study aimed to determine whether CBE plus provision of cancer awareness would downstage breast cancer at diagnosis and reduce mortality from the disease, compared with no screening.

Methods

The Mumbai study had two components: screening for cervix cancer by visual inspection and screening for breast cancer by CBE. The results of the cervical cancer component have been reported, as well as details of methodology to include design, mechanisms of community outreach, recruitment and informed

consent, training of primary health workers and medical social workers, sample size estimation, adherence to screening (after three rounds), and mechanism of referral and treatment.²⁰⁻²² The above methodological aspects are summarised in this paper.

Definition of a cluster

A cluster comprised of many closely situated dwellings in congested slum areas, defined by geographical boundaries such as railway lines, water pipelines, highways, roads, public parks, and canals. Each cluster had 9000 to 10000 dwellings with a population of 50 000-65 000, of which about 7500 women were aged 35-64. Transfer between control and intervention clusters was unlikely because the clusters were geographically separate, and because virtually none of the participants underwent breast screening outside the trial. The standard of care in our study population was no screening.

Randomisation method

Randomisation was by cluster, where groups rather than individuals were chosen as units of randomisation. Twenty independent clusters were numbered 1-20 and randomly allocated to screening or control groups by a draw of lots. With this procedure, 10 clusters were assigned as screening clusters and 10 as control clusters.

Trial participants and intervention

The current study, a cluster randomised controlled trial, recruited 151 538 women aged 35-64 from 20 clusters in Mumbai. Women in the screening arm ($n=75\,360$) received four rounds of CBE conducted by trained female primary health workers and cancer awareness information every two years, followed by five rounds of active surveillance by way of home visits every two years. Women in the control arm ($n=76\,178$) received one round of cancer awareness followed by eight rounds of active surveillance every two years. Participants in both arms were eligible for free diagnostic evaluation and treatment at the Tata Memorial Hospital; women in both groups were provided with identical identity cards to obtain free treatment at the hospital. Recruitment started in May 1998 and was completed in April 2002. Four rounds of CBE were concluded in December 2007 and follow-up continued until May 2018. The database was locked in March 2019 for analysis.

Sample size considerations

We based sample size calculations primarily on expected incidence and mortality data from breast and cervical cancer over the long duration of the study. Intracluster correlation was estimated using age, education status, and religion of women in the study. The computation was done using MLWin Software. For estimation of sample size, we considered two primary outcomes—breast and cervical cancer mortality. Sample size derived was 150 000 women, which was calculated to detect 25% reduction in mortality from

breast cancer with 80% power and 5% type I error, after adjusting for intraclass correlation and design effect (0.00013758 and 2.0408, respectively). With these considerations, 230 deaths from breast cancer in the control group were required for mortality analysis to be recommended. The smaller design effect observed in the study indicated that the sample size was adequate to estimate reduction in mortality with anticipated power.

Three way data linkage

To capture information on death from any cause, the trial had a three way data linkage system. Primary collection of data was done by trained medical social workers by home visits. Data were matched with those of Mumbai Municipal Death Records²³ and with the Mumbai Cancer Registry.²⁴ More information about the linkage systems and process has been provided in the supplementary material.

Breast cancer deaths

Breast cancer as the cause of death among women who were diagnosed with breast cancer was blindly ascertained by two independent experts. If there was a discrepancy between the two experts, the records were blindly reviewed by a third independent reviewer. Cause of death was assigned to breast cancer when at least two of the three reviewers concurred. Cause of death could not be ascertained in 40 women.

Statistical analysis

We calculated incidence rates in both arms by taking into account the number of person years determined

from the date of entry into the trial to the date of diagnosis. The number of person years for calculating mortality rates was determined from the date of entry in the trial to the date of death. Data were censored during analysis for women who had migrated or were lost to follow-up, or who had died from other causes. All deaths in both arms were included for all cause mortality estimates. We used a Poisson regression model to estimate incidence and mortality rate ratios and their 95% confidence intervals. Adjustments were made for design effect. All statistical tests were two sided, and $P < 0.05$ was considered to be statistically significant. The data were analysed on the basis of intention to screen (all women, irrespective of compliance), and when the predefined number of events (230 deaths) were documented in the control arm. All analyses were carried out in Stata software version 12 (Stata, College Station, TX).²⁵

The study underwent several protocol amendments during its long course, particularly in the initial years. The amendments were suggested by consultants or the data safety monitoring committee from time to time and were duly approved by the institutional review board. These amendments were also approved by the funding agency (US National Cancer Institute). All interpretations in the manuscript are aligned with the finally amended protocol.

Patient and public involvement

Patients and public were not involved in setting the research question, outcome measures, design, interpretation, or writing of the results. However, involvement of local community leaders was sought

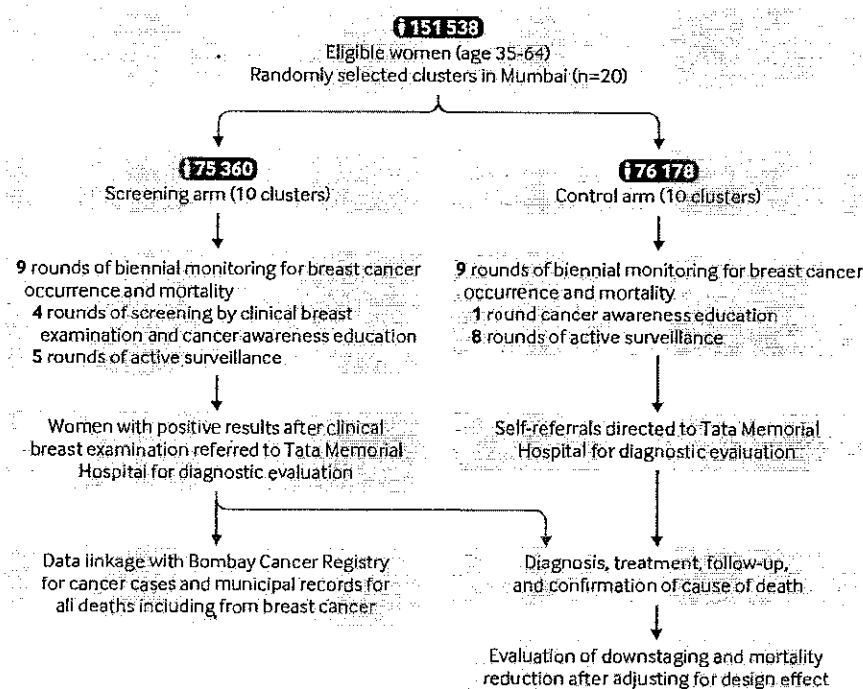


Fig 1 | Trial flow diagram

table 5). After nine rounds of active surveillance, 655 breast cancer cases were recorded in the control arm (supplementary table 5). Progressively more breast cancers were detected in each round as the women aged. Mean adherence of these women to treatment was 97.63%.

Age at enrolment and age at diagnosis of breast cancer

Mean age at diagnosis of breast cancer in women in the screening arm was 55.18 (standard deviation 9.10 (95% confidence interval 54.47 to 55.88)). Mean age at diagnosis in the control arm was 56.50 (9.10 (55.80 to 57.20)). This difference indicated that screening had brought forward breast cancer diagnosis by 16 months ($P=0.01$; table 1). At the time of recruitment, over 70% women in both the screening and control arms were younger than 50, whereas at the time of breast cancer diagnosis, this proportion was reversed with nearly 75% of women aged 50 and older in both arms (table 1). These data implied that breast cancer was diagnosed predominantly in older women, or in younger women after they reached age 50. This finding formed the basis for us to analyse the subsequent data relating to breast cancer downstaging and mortality by using age 50 as the cutoff threshold, although this threshold was not prespecified in the protocol and should be considered a post hoc analysis.

Downstaging of breast cancer

Biennial CBE led to significant downstaging of breast cancer in all women ($P=0.001$; table 2), as well as in women younger than 50 ($P=0.005$) and in those aged 50 and older ($P=0.05$). Staging information was unavailable in 41 women in the screening arm and 73 women in the control arm. However, we saw no difference when comparing the survival of these women with missing information (supplementary figure 1).

Breast cancer incidence and absence of overdiagnosis

At the end of screening, we found 198 women with breast cancer in the screening arm and 151 in the control arm, which translated into a crude incidence rate of 60.57 and 45.30 per 100 000 women years, respectively (rate ratio 1.34 (95% confidence interval 1.05 to 1.71); $P=0.02$; table 3). We saw an excess of

Arm	Age at enrolment (for all trial participants)					Age at diagnosis (for participants with breast cancer only)						
	Total No	No of women aged <50 (%)	No of women aged ≥50 (%)	P value	Mean age (SD (95% CI))	Difference (95% CI)	Total No	No of women aged <50 (%)	No of women aged ≥50 (%)	P value	Mean age (SD (95% CI))	Difference (95% CI)
Screening	75 177*	54 212 (72.11)	20 965 (27.89)	0.06	44.84 (7.90) (44.78 to 44.90)	0.078 (-0.002 to 0.158)	640†	161 (25.16)	479 (74.84)	0.01	55.18 (9.10) (54.47 to 55.88)	1.321 (0.330 to 2.312)
Control	76 097*	54 188 (71.21)	21 909 (28.79)		655		147 (22.44)	508 (77.56)	56.50 (9.10) (55.80 to 57.20)			

*Information on age was not available for 183 women in the screening arm and 83 women in the control arm among the total women enrolled for the 643 women with breast cancer in the screening arm, one had bilateral breast cancer, who was considered only once.

Table 2 | Staging of breast cancer at diagnosis

Age group	Randomised group	Stages I or II (No (%))	Stages III or IV (No (%))	Total No	Pearson χ^2	Difference (%) in stages III+IV between screening and control arms (95% CI)
All women*	Screening arm	379 (63)	220 (37)	599	11.757 (P=0.001)	9.83 (4.208 to 15.368)
	Control arm	311 (53)	271 (47)	582		
<50†	Screening arm	271 (63)	161 (37)	432	8.034 (P=0.005)	9.77 (3.008 to 16.423)
	Control arm	206 (53)	183 (47)	389		
≥50‡	Screening arm	108 (65)	59 (35)	167	3.906 (P=0.05)	10.27 (0.094 to 20.092)
	Control arm	105 (54)	88 (46)	193		

*Staging information unavailable from 41 women in the screening arm and 73 women in the control arm.

†Staging information unavailable from six women in the screening arm and 12 women in the control arm.

‡Staging information unavailable from 35 women in the screening arm and 61 women in the control arm.

47 diagnoses of breast cancer in the screening arm compared with the control arm (table 3). After a median follow-up of 18 years, the screening and control arms had 640 and 655 cases of breast cancer, respectively, which translated into a crude incidence rate of 62.76 and 64.43 per 100 000 women years, respectively (0.97 (0.87 to 1.09), P=0.66; table 3). Supplementary table 7 shows that although, as expected, a higher incidence of breast cancer was seen in the screening group than in the control group up to study year 10 (that is, until the end of screening round 4), this difference reduced gradually from study year 12 onwards (starting surveillance round 1) and disappeared completely by study year 18 (surveillance round 5).

Breast cancer mortality

We recorded 213 breast cancer deaths in the screening arm and 251 deaths in the control arm (rate ratio 0.85 (95% confidence interval 0.71 to 1.01), P=0.07; table 3). Thus, overall, a 15% non-significant reduction in mortality was seen when women of all ages were considered. Among women younger than 50, 149 breast cancer deaths were recorded in the screening arm and 158 deaths in the control arm (0.93 (0.79 to 1.09), P=0.37). Among women aged 50 and older, 64

breast cancer deaths were recorded in the screening arm and 93 deaths in the control arm (0.71 (0.54 to 0.94), P=0.02; table 3). This subset analysis based on the age 50 threshold was not stipulated in the protocol and was a post hoc analysis. The cumulative breast cancer mortality in the screening and control arms over 20 years is shown in figure 2. An excess of breast cancer deaths in the screened population was seen in both age subgroups (age <50 and ≥50) in the early years after randomisation (fig 2), which lasted for about 14 years in women younger than 50 and about six years in those aged 50 and older.

When breast cancer mortality data were analysed on the basis of attendance to the number of CBE screening rounds, we found that even women younger than 50 who attended all four rounds of screening benefitted significantly in terms of mortality reduction (rate ratio 0.66 (95% confidence interval 0.53 to 0.83), P<0.001). But this benefit did not exist if these women attended only three rounds (0.88 (0.60 to 1.27), P=0.48). Women aged 50 and older, however, benefitted from attending both three as well as four rounds of screening (attendance to all four rounds (0.64 (0.45 to 0.93), P=0.02); attendance to three rounds (0.66 (0.44 to 1.00), P=0.05); supplementary table 8).

Table 3 | Breast cancer incidence, breast cancer mortality, and all cause mortality after 20 years since commencement of study

	Screening arm				Control arm				Rate ratio (95% CI) ^t	P value
	Total No of women	No of diagnoses or deaths	No of person years	Crude rate per 100 000 person years (95% CI)	Total No of women	No of diagnoses or deaths	No of person years	Crude rate per 100 000 person year (95% CI)		
Breast cancer incidence										
Completion of active screening	75 360	198	326 891.2	60.57 (49.87 to 74.62)	76 178	151	333 346.7	45.30 (38.51 to 53.64)	1.34 (1.05 to 1.71)	0.02
Completion of 20 years of study	75 360	640	1 019 761	62.76 (57.02 to 69.35)	76 178	655	1 016 616	64.43 (60.43 to 68.90)	0.97 (0.87 to 1.09)	0.66
Breast cancer mortality										
All ages*	75 360	213	1 023 097	20.82 (18.25 to 23.97)	76 178	251	1 019 500	24.62 (21.71 to 28.04)	0.85 (0.71 to 1.01)	0.07
Age <50	54 212	149	763 141.8	19.53 (17.24 to 22.29)	54 188	158	751 367.0	21.03 (18.97 to 23.44)	0.93 (0.79 to 1.09)	0.37
Age ≥50	20 965	64	259 955.2	24.62 (20.62 to 29.76)	21 909	93	268 133.1	34.68 (27.54 to 44.37)	0.71 (0.54 to 0.94)	0.02
All cause mortality										
All ages*	75 360	11 261	1 023 180	1100.59 (989.98 to 1224.58)	76 178	11 853	1 019 831	1162.25 (1037.16 to 1303.45)	0.95 (0.81 to 1.10)	0.49
Age <50	54 212	4450	763 177.7	583.09 (539.66 to 629.69)	54 188	4708	751 508.2	626.47 (572.73 to 684.32)	0.931 (0.829 to 1.045)	0.23
Age ≥50	20 965	6811	260 001.8	2619.6 (2456.3 to 2796.9)	21 909	7145	268 323.2	2662.8 (2498.2 to 2835.8)	0.984 (0.902 to 1.073)	0.71

*Information on age not available for 183 women in the screening arm and 81 women in the control arm among study participants of all ages.

†Rate ratio calculated by Poisson regression model after adjusting for cluster design.

All cause mortality

When we considered all cause mortality during the 20 year period, we saw a non-significant reduction of 5% in the screening arm. All cause mortality rates were 1100.59 and 1162.25 per 100 000 women years in the screened and controls arms, respectively (rate ratio 0.95 (95% confidence interval 0.81 to 1.10); $P=0.49$). The subdivision of all cause mortality by age (<50 and ≥50) is also represented (table 3). Breast cancer deaths comprise less than 3% of deaths from all causes in women in India; and hence a reduction in all cause mortality was not expected. The cumulative all cause mortality in the screening and control arms over 20 years is shown in supplementary figure 2.

Discussion

Statement of principal findings

We report here results of our randomised trial that compared CBE screening with no screening. We showed that biennial CBE performed by trained female primary health workers significantly advanced breast cancer diagnosis by 16 months, and also downstaged

the disease with fewer stage III or IV cancers in screened women. Overall, CBE led to a non-significant 15% reduction in breast cancer mortality; however, a significant reduction of nearly 30% was observed in women aged 50 and older. In women younger than 50, despite successful downstaging, no mortality reduction was observed. Lack of mortality reduction in younger women is consistent with data reported in some mammography trials,¹⁶ and could point to undetermined biological factors.

Participant attendance to the number of screening rounds also appeared to be important in breast cancer mortality reduction for women younger than 50. We found a 34% mortality reduction in this age group if the women attended all four rounds of screening ($P<0.001$). This benefit, however, disappeared if they attended only three rounds (mortality reduction 13%, $P=0.48$). For women aged 50 and older, however, we observed mortality reduction after attendance to three and four rounds of screening (34%, $P=0.05$ and 36%, $P=0.02$, respectively; supplementary table 8).

Strengths and weaknesses in relation to other studies

Two other randomised trials have compared CBE screening with no screening.^{26 27} A cluster randomised controlled trial was initiated in Kerala, India, in 2006 where three rounds of CBE every three years was planned to evaluate whether CBE can reduce incidence of advanced breast cancers and mortality from the disease.²⁶ Early results have shown a higher proportion of early stage breast cancers in the intervention arm than in the control arm.²⁶ Another trial comparing CBE screening with no screening in the Philippines could not be satisfactorily concluded because of unacceptably low levels of adherence,²⁷ possibly because of external investigators not fully anticipating cultural and psychosocial barriers.

In our study, an excess mortality from breast cancer was seen in the screening arm during the first few years of screening for the total study population as well as when stratified by age groups. Such an excess mortality was also seen in the cervical cancer component of this trial.²⁸ A meta-analysis of seven breast cancer screening trials²⁹ suggested an excess breast cancer mortality up to the fifth year of screening in women younger than 50 and in the first year in older women. This excess was, however, not apparent in a combined analysis of Swedish trials.³⁰ The possible finding of early excess cancer mortality needs exploring. The theory of biological predeterminism (pre-existing micrometastases before diagnosis and surgery) fails to explain this excess mortality but could point towards an impact of events at the time of diagnosis and surgery on mortality.³¹

Strengths and weaknesses of this study

One crucial element of our study that led to its successful completion was that it was entirely indigenous. The trial was conceived, designed and

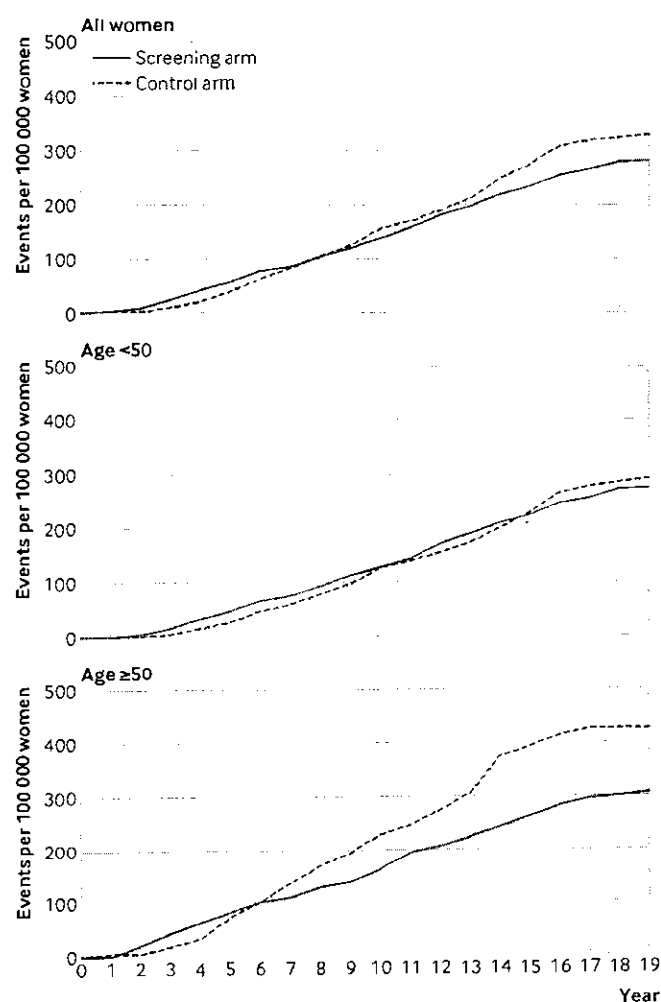


Fig 2 | Cumulative breast cancer mortality during 20 years of study

implemented by a team based in Mumbai and had full understanding of the psychosocial, geopolitical, and geographical ground realities that influence the conduct of complex, public health randomised trials in low and middle income countries. Our study was conducted in slum areas largely inhabited by socioeconomically disadvantaged women who often moved residence requiring our medical social workers to trace their new abodes, sometimes in far flung parts of the city. Owing to our medical social workers making innumerable home visits to a population that was often mobile, we were able to achieve a satisfactory compliance at all levels of screening. The quality of CBE performed by our primary health workers was also of high standard, which was confirmed by comparing the screening findings with a specialist breast clinician. We were also able to capture death records of a high proportion of cases because of the three way data linkage system. Finally, our study included near perfect randomisation for a cluster randomised controlled trial; all demographic and breast risk factors were equally distributed in the screening and control arms. Provision of timely treatment could have helped to improve quality of life in screened women by preventing advanced stage disease, including local recurrence.

Our study also had some limitations. Cancer staging data were unavailable from 41 women in the screening arm and 73 women in the control arm. This limitation probably did not affect the study results because the survival curves of patients with missing staging information were similar in the screening and control arms (supplementary figure 1). However, a sensitivity analysis of patients with missing staging information, in which all 41 women from the screening arm were assigned cancer stages III or IV and all 73 women from the control arm were assigned to cancer stages I or II, led to loss of statistical significance in the downstaging effect of screening. Another study limitation was that cause of death information was not available through death certificates and the available documents for some women. To overcome this limitation, three independent experts reviewed the records of all women with breast cancer who had died. Breast cancer was assigned as a cause of death only when at least two reviewers concurred (213 (83%) of 258 in the screening arm and 251 (90%) of 278 in the control arm).

Our blinded review process for assigning cause of death was based on similar mechanisms used in other screening trials.^{32 33} However, the possibility of some residual uncertainty cannot be excluded; some degree of variability is inevitable in screening trials when death certificates are often modestly accurate and medical records often incomplete.

We did not observe a significant reduction in all cause mortality. But because breast cancer deaths comprise less than 3% of all deaths in women in India, we did not expect a reduction in all cause mortality in our study.

Meaning of the study—possible explanations and implications for clinicians and policymakers

Our study validates CBE as an alternative modality of breast screening. It demonstrates that CBE screening is effective in reducing breast cancer mortality in Indian women aged 50 and older without any overdiagnosis. In our trial, we were able to use a vertical programme with dedicated staff that was centrally controlled. Furthermore, women in India and in many other low and middle income countries are relatively lean and have smaller breasts than women in Western countries. The health workers who screened women with CBE in this trial had passed 10th grade education and could be trained to perform CBE within a minimal training period (about four weeks). We believe that CBE screening by primary health workers is replicable in the general population, and CBE has already been implemented in other parts of India as pilot schemes. Our study suggests that implementation of population screening by CBE in low and middle income countries is feasible, provided that adequate training of screening providers, careful monitoring, and quality of performance are assured.

Whether the use of CBE in low and middle income countries at the community level can lead to a reduction in breast cancer mortality is still unknown. Its success can only be ascertained several years after CBE has been implemented as public health programme.

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We thank AB Miller for constructive suggestions made during the design stage of the study; EE Daniel, Porin Notani, and KA Dinshaw for their contributions in the formative stages of this study; Shalini Singh for establishing the community framework of the study in its initial stage; Vani Parmar, Rajendra Kerkar, Meenakshi Thakur, Subhash Ramani, and Balasubramanian Ganesh, who served as consultants to the study; Vinay Deshmone, Rucha Kaushik, and Amruta Beke for independently reviewing the patients files to ascertain the cause of death; all the current members of our data safety and monitoring board (2016 to present): Ian Tannock (chairperson), Phillippe Autier, Prakash C Gupta, Prabhat Jha, and Valerie Berak; and previous members of our data safety and monitoring board (2004-15): R Sankaranarayanan (chairperson), Prakash C Gupta, and V Gajalakshmi. This study is dedicated to the selfless contributions made by the many primary health workers and medical social workers who were key to the success of the study.

Contributors: IM was responsible for the conceptualisation, study design, intellectual content, community organisation, supervision of community activities, data collection, data analysis, statistical analysis, data interpretation, literature search, writing, editing, and review of the manuscript. GAM was responsible for the community organisation, monitoring and supervision of community activities,

data collection, data analysis, statistical analysis, literature search, manuscript editing, and review of the manuscript. RPD was responsible for the data analysis, statistical analysis, manuscript editing, and review of the manuscript. SG was responsible for the data analysis, statistical analysis, and review of the manuscript. VVK and HKAS were responsible for the monitoring of the field work, data collection, and review of the manuscript. SSS was responsible for the community organisation, overall supervision of the field work, monitoring of the study, data collection, data analysis, and review of the manuscript. RH was responsible for data analysis, statistical analysis, manuscript editing, and review of the manuscript. SG and CSP were responsible for data analysis, manuscript editing, and review of the manuscript. RAB was responsible for concepts, study design, intellectual content, overall supervision of the field work, monitoring of the study, data collection, data analysis, statistical analysis, literature search, manuscript preparation, manuscript editing, and review of the manuscript. IM and RAB are the study guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: The trial was funded by a US National Institutes of Health RO1 grant (RO1CA074801) for 1997-2000, 2000-03, 2005-10, and 2010-15. The trial was also supported in 2003-04 and 2016-19 by Intramural funding from the Tata Memorial Centre. The study was also supported by Sir Dorabji Tata Trusts, M K Tata Trusts, and the Department of Atomic Energy, Government of India. Treatment costs were supported by the Women's Cancer Initiative, India. Funders had no role in study design, in collection, analysis, and interpretation of data, in writing the report, and in decision to submit the paper for publication. The principal investigator had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support from the US National Institutes of Health, Tata Memorial Centre, Sir Dorabji Tata Trusts, M K Tata Trusts, Department of Atomic Energy Clinical Trial Centre (Government of India), and the Women's Cancer Initiative, India for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The study was approved by the institutional ethics committees of the Tata Memorial Centre. In addition to the internal data safety and monitoring committee of Tata Memorial Centre, an independent data safety and monitoring board comprising international experts reviewed the trial annually.

Data sharing: The data generated by our research and those used in this article will be made available, wherever legally and ethically required.

IM and RAB confirm that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as originally planned have been explained.

Dissemination to participants and related patient and public communities: Study results will be disseminated through scientific publications, presentations at scientific meetings, press release, social media platforms, articles in lay press, and patient and public engagement events organised by our centre.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Web appendix: Supplementary material

Supplementary Table 1:

Distribution of participants by demographic and breast cancer risk factors

Variables		Screening arm N=75360 (%)	Control arm N=76178(%)
Age groups	35-39	22718 (30.22)	22832 (30.00)
	40-44	17311 (23.03)	17245 (22.66)
	45-49	14183 (18.86)	14111 (18.54)
	50-54	9422 (12.53)	9564 (12.57)
	55-59	6049 (08.05)	6127 (08.05)
	60-64	5494 (07.31)	6218 (08.17)
Mean age (SD)		44.84 (07.86)	44.92 (08.01)
Median (IQR)		43 (Q1 38, Q3 50, IQR 12)	43 (Q1 38, Q3 50, IQR 12)
Marital status	Unmarried	295 (00.40)	454 (00.60)
	Married	61584 (82.60)	62048 (82.62)
	Widowed	12289 (16.48)	12301 (16.38)
	Divorced	393 (00.53)	302 (00.40)
Menstrual status	Premenopausal	40361 (53.78)	40913 (53.85)
	Postmenopausal	32845 (43.77)	33456 (44.04)
	Perimenopausal	1842 (02.45)	1601 (02.11)
Mean age at menarche (S.D)		13.79 (01.26)	13.85 (01.24)
Mean age at menopause (S.D)		43.36 (04.96)	43.62 (04.87)
Mean age at marriage (S.D)		17.99 (03.89)	17.85 (03.82)
Mean age at first child birth (S.D)		20.82 (03.70)	20.74 (03.61)
Average number of children (S.D)		3.58 (01.61)	3.56 (01.61)
Breast feeding (%)	Yes	70002(98.85)	70389 (98.64)
	No	811 (01.15)	971 (01.36)
Family history of breast cancer (%)	Yes	517 (00.70)	504 (00.68)
	No	73312 (99.30)	74050 (99.32)
Previous consultation for breast-related complaints (%)	Yes	882 (01.21)	785 (01.06)
	No	72105 (98.79)	73142 (98.94)

Supplementary Table 2:

Compliance to screening, referral and breast cancer cases detected till round 4 in screening arm

Screening Round	Eligible Women	Women Examined	Compliance to Screening (%)	Screen +ve cases N (%)	Compliance of screen +ve cases to referral N (%)	Breast Cancers Confirmed
One	75360	56985	75.62	350 (0.61)	239 (68.29)	32
Two	74922	49012	65.42	552 (1.13)	393 (71.20)	55
Three	74211	47133	63.51	638 (1.35)	503 (78.84)	42
Four	73241	46554	63.52	1024 (2.20)	819 (79.98)	70
Total &/ or Mean	74433	49921	67.07	1.28	76.21	199

*One participant was considered twice because of bilateral breast cancer

Supplementary Table 3:

Breast cancers detected during 4 rounds of screening

Round One	Screen detected	32
	Interval cancers	26
	Non- Compliers	04
Round Two	Screen detected	25
	Interval cancers	14
	Non- Compliers	01
Round Three	Screen detected	27
	Interval cancers	37
	Non- Compliers	03
Round Four	Screen detected	30
Total		199

*One participant was considered twice because of bilateral breast cancer

Supplementary Table 4:

Compliance to active surveillance and breast cancer cases recorded during rounds 5 – 9 in screening arm

Round	Eligible Women	Compliance to Surveillance (%)	Breast Cancers
Five	71886	57549 (80.06)	74
Six	70455	55310 (78.50)	75
Seven	69006	53732 (77.87)	74
Eight	67437	51951 (77.04)	67
Nine	64099	47705 (74.42)	152
Total breast cancers			442

Supplementary Table 5:

Compliance to active surveillance and breast cancer cases recorded from round 1- 9 in control arm

Round	Eligible women	Compliance to surveillance (%)	Breast cancers
One	76178	69227 (90.88)	2
Two	75654	62763 (82.96)	38
Three	74842	59541 (79.56)	51
Four	73768	59303 (80.39)	60
Sub-total after 4 rounds of active surveillance			151
Five	72341	56689 (78.36)	74
Six	70914	54576 (76.96)	87
Seven	69381	53158 (76.62)	83
Eight	67784	51427 (75.87)	81
Nine	64325	47143 (73.29)	179
Sub-total in rounds 5-9 of active surveillance			504
Total breast cancers			655

Supplementary Table 6

Women availing breast cancer treatment at TMH and Other Hospitals

Treatment Taken	Screening Arm (%)	Control Arm (%)	Pearson χ^2 P-value
TMH as well as other hospitals	413 (64.53)	399 (60.91)	$\chi^2 = 1.717$ $p = 0.190$
Other hospitals only	227 (35.47)	255 (38.93)	
No information	-	1(0.15)	
Total	640	655	

Supplementary Table 7:**Cumulative breast cancer cases in Screening and Control Arm during successive rounds**

Screening arm		Control arm	
Screening Round 1	32	Active Surveillance Round 1	2
Screening Round 2	87	Active Surveillance Round 2	40
Screening Round 3	129	Active Surveillance Round 3	91
Screening Round 4	199	Active Surveillance Round 4	151
Active Surveillance Round 1	273	Active Surveillance Round 5	225
Active Surveillance Round 2	348	Active Surveillance Round 6	312
Active Surveillance Round 3	422	Active Surveillance Round 7	395
Active Surveillance Round 4	489	Active Surveillance Round 8	476
Active Surveillance Round 5	641	Active Surveillance Round 9	655

Supplementary Table 8:

Breast cancer mortality on the basis of attendance to number of screening rounds (3 or 4)

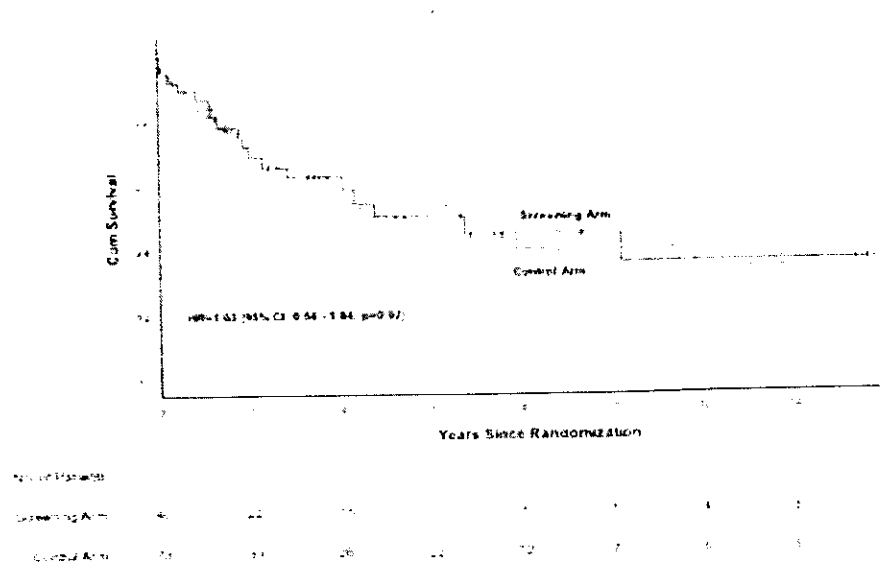
	Screening arm				Control arm				Rate ratio (95% CI)	P- Value
	No. of women	No. of breast cancer deaths	Person years	**Crude rate (95% CI)	No. of women	No. of breast cancer deaths	Person years	**Crude rate (95% CI)		
Breast cancer mortality: Screened in all 4 screening rounds										
Age*	24984	62	394239.1	15.726 (13.57 to 18.43)	76178	251	1019500	24.620 (21.71 to 28.04)	0.639 (0.526 – 0.776)	<0.001
< 50	19296	43	309187.8	13.907 (11.41 to 17.16)	54188	158	751367	21.028 (18.97 to 23.44)	0.661 (0.527 – 0.830)	<0.001
≥ 50	5688	19	85051.27	22.339 (16.52 to 30.46)	21909	93	268133.1	34.684 (27.54 to 44.37)	0.644 (0.445 – 0.931)	0.02
	Screening arm				Control arm				Rate ratio (95% CI)	P- Value
	No. of women	No. of breast cancer deaths	Person years	**Crude rate (95% CI)	No. of women	No. of breast cancer deaths	Person years	**Crude rate (95% CI)		
Breast cancer mortality: Screened in 3 screening rounds										
Age*	19825	57	291331.5	19.565 (14.69 to 26.76)	76178	251	1019500	24.620 (21.71 to 28.04)	0.795 (0.578 – 1.092)	0.16
< 50	14482	40	217467.3	18.394	54188	158	751367	21.028	0.875	0.48

				(12.88 to 27.67)				(18.97 to 23.44)	(0.603 – 1.269)	
≥ 50	5342	17	73864.24	23.015 (16.14 to 33.39)	21909	93	268133.1	34.684 (27.54 to 44.37)	0.664 (0.439 – 1.002)	0.05

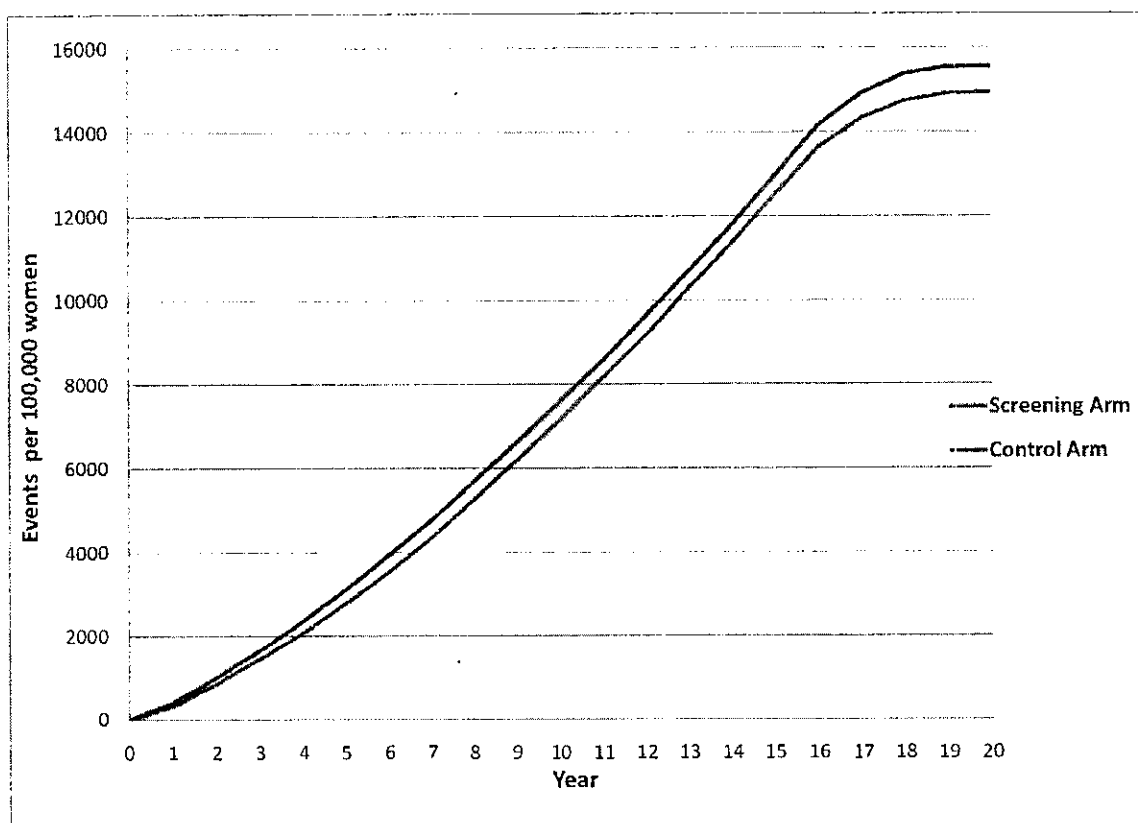
*Information on age was not available for 183 women in screening arm and 81 women in control arm among the total women enrolled

**Crude rate per 100000 person years. #Rate Ratio = Rate Ratio calculated by 'Poisson regression model 'after adjusting for 'cluster design'.

Supplementary Figure 1: Survival of women in whom staging information was unavailable; 41 cases in screening and 73 cases in control arms.



Supplementary Figure 2: Cumulative all-cause mortality over twenty years.



Information about the linkage systems and process:

The primary collection of follow up data was done through individual household visits by our Medical Social Workers who collected information on ~85% of incident and death cases in the study. The rest of the data were collected through linkages with Municipal Corporation of Greater Mumbai (MCGM) and Mumbai Cancer Registry.

The vital statistics division of the Municipal Corporation of Greater Mumbai (MCGM) has one of the most advanced birth and death record registries in India. Records have been validated through independent audits to be 95% complete. Records of MCGM are computerized and available within six months of an event of birth or death. The municipal death records were obtained every six months and were matched with the primary trial data mentioned above. Finally, our Medical Social Workers made individual home visits to corroborate details of women in study which were matched with the MCGM data.

The Bombay Cancer Registry, established in 1963, is the oldest population based cancer registry to be set up in India. This registry was started with inputs from the NIH and the Descriptive Epidemiology Unit of IARC. Subsequently, the registry staff were further trained at the University of Tampere, Finland under the guidance of Prof. Matti Hakama. The Registry collects cancer related information from all major hospitals and private nursing homes. The major cancer hospitals are visited daily, while other hospitals and nursing homes are visited once a week. The maximum time lag between a diagnosed case of cancer and the availability of this information at the Bombay Cancer Registry is one week. It however takes three years for the registry to collate, quality check and publish the data. A quality control survey conducted by Indian Council of Medical Research (ICMR) to assess the quality and completeness of the Bombay Cancer Registry records shows a completeness of 95.4%.

Reference:

Yeole BB. An assessment of improvement in reliability and completeness of Mumbai cancer registry data from 1964-1997. *Asian Pac J Cancer Prev.* 2001;2(3):225-32.